Essentials in Lung Transplantation

Allan R. Glanville
Editor

Springer

Essentials in Lung Transplantation

A L G r a w a n y

Allan R. Glanville
Editor

Essentials in Lung Transplantation

Springer

Editor
Allan R. Glanville
The Lung Transplant Unit
Department of Thoracic Medicine
St Vincent's Hospital
Sydney
NSW
Australia

ISBN 978-3-319-90932-5 ISBN 978-3-319-90933-2 (eBook)
https://doi.org/10.1007/978-3-319-90933-2

Library of Congress Control Number: 2018949948

This Springer imprint is published by Springer Nature, under the registered company Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

This work is dedicated to our patients, their carers and our colleagues who, by working together, honour the greatest gift, organ donation, and thereby sustain life and hope.

Preface

This work presents a comprehensive summary of the basic tenets of lung transplantation with an update on recent developments in the field. The emphasis is to provide an approachable and easily digested product that relies heavily on teaching through visual images. Each of the authors is an Australian and many are recognised experts in the area. Lung transplantation is now a core activity in each state of Australia with almost 3000 transplants performed throughout Australia. With the growth of donor resources which have doubled over the last 10 years, patients with life-threatening advanced lung diseases can look forward with some security to improvements in survival and quality of life. This work examines the operational principles which underpin that success and show how an evidenced-based approach combined with wisdom born of experience leads to better outcomes in day-to-day management.

Unlike other books in the field, this work focuses on simplicity and elegance of style with ample visual images to demonstrate the core messages. Importantly this work provides a unique Australian viewpoint and discusses the relevance of international trends and strategies in the context of the local environment.

Sydney, NSW, Australia — Allan R. Glanville

Contents

Chapter 1
Who and When to Transplant: What Has Changed?

Isuru N. S. Seneviratne and Peter Hopkins

1.1 Introduction

Lung transplantation needs to be considered for all patients with advanced lung disease whose clinical condition continues to deteriorate despite maximal medical or surgical therapy [1].

It is generally accepted that referral for lung transplantation should typically occur early in patients who have a lung disease that is amenable to transplantation. Such patients will have an impaired ability to perform activities of daily living and a reduced life expectancy over the next 2 years. It is important to note that referral to a transplant centre may not mean that the patient will necessarily be listed for transplant. Early referral may however, allow identification and management of modifiable risk factors to facilitate progression to lung transplantation. For example, a patient with class I obesity or a patient with physical deconditioning could be supported to optimise weight loss or enrol in pulmonary rehabilitation respectively, to improve their functional status before listing for transplantation.

Following lung transplant evaluation, a mutual decision in favour for transplantation needs to occur between the patient, patient's family and transplant specialists before a patient is placed on the transplant list.

Chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), cystic fibrosis (CF) are the three most common indications for transplant [2] and account for approximately 80% of all procedures performed worldwide (Fig. 1.1) [3].

I. N. S. Seneviratne (✉) · P. Hopkins
Queensland Lung Transplant Service, The Prince Charles Hospital, Brisbane, QLD, Australia

Queensland Health, Brisbane, QLD, Australia
e-mail: peter.hopkins@health.qld.gov.au

A. R. Glanville (ed.), *Essentials in Lung Transplantation*,
https://doi.org/10.1007/978-3-319-90933-2_1

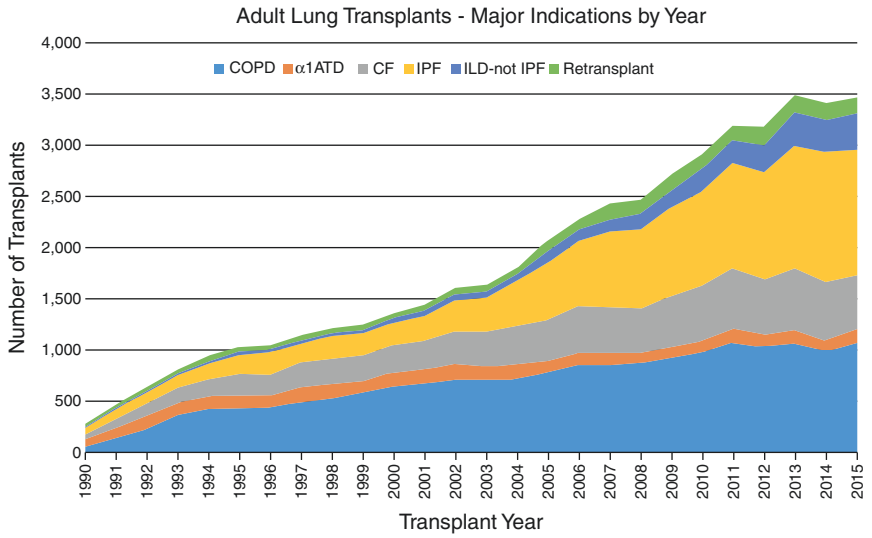


Fig. 1.1 Adult lung transplants—major indications by year

1.2 General Inclusion and Exclusion Criteria for Lung Transplantation

General criteria for recipient selection have been developed by the International Society for Heart and Lung Transplantation (ISHLT) [1] and include:

1. A risk of death from lung disease within 2 years if lung transplantation is not performed in excess of 50%
2. A high (>80%) likelihood of surviving at least 90 days after lung transplantation
3. A high (>80%) likelihood of 5-year post-transplant survival from a general medical perspective provided that there is adequate graft function

In addition to these General criteria, disease specific criteria also exist to better stratify/quantify patients' disease burden and the need for lung transplantation (see Sect. 1.4 and Table 1.1).

International consensus guidelines [1] for absolute and relative exclusion criteria for lung transplantation are detailed in Table 1.2. It is important to recognise that these criteria serve only as a guideline. As clinical experience grows with lung transplantation and with the development of new treatments and improvements in existing therapeutic techniques (for lung transplantation and overall general health and disease management) these criteria as continuously being tested and new boundaries are being established. Examples of this include the approach to pre-transplant malignancy, in an era where we are seeing more people being cured of their malignancy with very little long term complications from the cancer or treatment undertaken; an age value as a contraindication to proceeding with

Table 1.1 Quick reference guide of specific clinical condition criteria for transplant

• *COPD* that is progressive despite smoking cessation, optimization of medications, pulmonary rehabilitation, and supplemental oxygen, a BODE index [4] of 5–6; $PaCO_2$ >50 mmHg (6.6 kPa) and/or PaO_2 < 60 mmHg (8 kPa), or FEV_1 <25% of predicted
• At the time of a confident radiographic diagnosis of *idiopathic pulmonary fibrosis* (IPF) or a histologic diagnosis of IPF or *fibrosing nonspecific interstitial pneumonia* (NSIP), regardless of lung function
• *Interstitial lung disease* (ILD) associated with rheumatic disease, sarcoidosis, or pulmonary Langerhans cell histiocytosis and New York Heart Association (NYHA) functional class III or IV (ie, symptoms with minimal exertion or severe limitation with symptoms at rest) or rapidly progressive respiratory impairment
• *ILD* with forced vital capacity (FVC) <80% predicted, a diffusion capacity for carbon monoxide (DLCO) <40% predicted, or the requirement for supplemental oxygen, at rest or with exertion
• *Pulmonary vascular disease* and NYHA functional class III or IV; during escalation of therapy e.g. incorporation of intravenous prostaglandin therapy
• Patients with *pulmonary veno-occlusive disease* (PVOD) or *pulmonary capillary hemangiomatosis* should be evaluated at the time of diagnosis
• *Cystic fibrosis* patients with an FEV_1 <30% of predicted, a six-minute walk distance <400 m, development of pulmonary hypertension, and/or life-threatening haemoptysis despite bronchial embolization

Table 1.2 Absolute and relative exclusion criteria for lung transplantation

Absolute exclusion criteria
1. Recent history of malignancy: A minimum of 2-years (ideally 5-years) disease-free interval combined with a low predicted risk of recurrence after lung transplantation (please see special considerations for lung transplantation)
2. Untreatable significant dysfunction of another major organ system (e.g., heart, liver, kidney, or brain) unless combined organ transplantation is considered
3. Uncorrected atherosclerotic disease with suspected or confirmed end-organ ischemia or dysfunction and/or coronary artery disease not amenable to revascularisation
4. Acute medical instability, including, but not limited to, acute sepsis, myocardial infarction, and liver failure
5. A bleeding diathesis that cannot be corrected
6. Chronic infection with highly virulent and/or resistant microbes that are poorly controlled pre-transplant
7. Evidence of active Mycobacterium tuberculosis infection
8. Significant chest wall or spinal deformity expected to cause severe restriction after transplantation
9. Class II or III obesity (body mass index [BMI] ≥35.0 kg/m^2)
10. Current non-adherence to medical therapy or a history of repeated or prolonged episodes of non-adherence to medical therapy that are perceived to increase the risk of non-adherence after transplantation
11. Psychiatric or psychologic conditions associated with the inability to cooperate with the medical/allied health care team and/or adhere with complex medical therapy
12. Absence of an adequate or reliable social support system

(continued)

Table 1.2 (continued)

13. Severely limited functional status with poor rehabilitation potential.
14. Substance abuse or dependence (e.g., alcohol, tobacco, marijuana, or other illicit substances). Convincing evidence of risk reduction behaviours (e.g. active long-term participation in therapy for substance abuse and/or dependence) should be required before offering lung transplantation. Ongoing abstinence should be verified with serial blood and urine testing of substances that are of concern
Relative exclusion criteria
1. Age >65 years in association with low physiologic reserve and/or other relative contraindications (please see special consideration for lung transplant)
2. Class I obesity (BMI 30.0–34.9 kg/m^2), particularly truncal (central) obesity
3. Progressive or severe malnutrition
4. Severe, symptomatic osteoporosis
5. Extensive prior chest surgery with lung resection
6. Mechanical ventilation and/or extracorporeal life support (ECLS). However, carefully selected candidates without other acute or chronic organ dysfunction may be successfully transplanted
7. Colonization or infection with highly resistant or highly virulent bacteria, fungi, and certain strains of mycobacteria (e.g., chronic extrapulmonary infection expected to worsen after transplantation)
8. For patients infected with hepatitis B and/or C, a lung transplant can be considered in patients without significant clinical, radiologic, or biochemical signs of cirrhosis or portal hypertension and who are stable on appropriate therapy. Lung transplantation in candidates with hepatitis B and/or C should be performed in centres with experienced hepatology units
9. For patients infected with human immunodeficiency virus (HIV), a lung transplant can be considered in those with controlled disease with undetectable HIV-RNA, and compliant on combined anti-retroviral therapy. Lung transplantation in HIV-positive candidates should be performed in centres with expertise in the care of HIV-positive patients
10. Infection with Burkholderia cenocepacia, Burkholderia gladioli, and multi-drug resistant Mycobacterium abscesses. For patients with these infections to be considered suitable transplant candidates, the patients should be evaluated by centres with significant experience managing these infections in the transplant setting, and patients should be aware of the increased risk of transplant because of these infections
11. Atherosclerotic disease burden sufficient to put the candidate at risk for end-organ disease after lung transplantation. With regard to coronary artery disease, some patients will be candidates for percutaneous coronary intervention or coronary artery bypass graft (CABG) preoperatively or, in some instances, combined lung transplant and CABG
12. Other medical conditions that have not resulted in end-stage organ damage, such as diabetes mellitus, systemic hypertension, epilepsy, central venous obstruction, peptic ulcer disease, or gastroesophageal reflux, should be optimally treated before transplantation
13. Extensive prior thoracic surgery with lung resection

Adapted from Weill D et al. A consensus document for the selection of lung transplant candidates [1]

transplant in a generation where people are living longer and remaining healthier for a longer period.

Because of this changing dynamic of health and medicine, it is important that all patients that meet inclusion criteria for lung transplantation be referred for transplantation discussion and/or evaluation to allow a detailed review of possible contraindications and to assess the actual impact these will have on achieving a favourable outcome following lung transplantation.

1.3 Special Considerations for Lung Transplantation

1.3.1 Nutritional Status

It is now well established that nutritional status can adversely affect post-transplant survival. Given this the ISHLT consensus guidelines state that class I obesity (BMI 30–34.9 kg per m^2) is a relative contraindication for lung transplantation, while class II or III obesity (BMI ≥35 kg per m^2) is an absolute contraindication [1].

In addition to obesity, there is strong data surrounding poor post-transplant outcomes, in particular primary graft dysfunction, in malnourished candidates [2, 5]. This appears to be especially the case in those individuals with COPD and CF [4, 6, 7]. As such, it is now clear that these individuals should be as vigorously evaluated as those individuals with an elevated BMI and aggressive attempts to improve the nutritional status prior to lung transplant are warranted.

1.3.2 Frailty and Sarcopaenia

Frailty and sarcopaenia are characterised by loss of physiologic and cognitive reserves that predispose to adverse outcomes from acute stressors [8]. Though frailty correlates with increasing age, it is not an inevitable consequence of ageing. It is important to note that frailty is a dynamic condition, and is potentially reversible.

Two major frailty models have been described—the frailty phenotype and the frailty index [8]:

1. The frailty phenotype defines frailty as a distinct clinical syndrome meeting three or more of five phenotypic criteria: weakness, slowness, low level of physical activity, self-reported exhaustion, and unintentional weight loss (see Table 1.3).
2. The frailty index defines frailty as cumulative deficits identified in a comprehensive geriatric assessment.

Table 1.3 Frailty phenotype [9]

Criteria
1. Decreased grip strength
2. Self-reported exhaustion
3. Unintentional weight loss of more than 4.5 kg over the past year
4. Slow walking speed
5. Low physical activity
Definition
– Positive for frail phenotype: ≥3 criteria present
– Intermediate/pre-frail: one or two criteria present
– Non-frail: no criteria present

Data shows that approximately one third of lung transplant candidates are frail [10] and a large proportion of these individuals are over the age of 50 years [11]. Recent data has shown that pre-transplant frailty was independently associated with decreased survival after lung transplantation [12]. This result builds on the information of previously published data, which has shown a clear link between 6-min walk distance (which assesses aspects of the frailty phenotype) and lung transplant outcomes [13, 14]. Frailty assessment should therefore be an integral part of transplant assessment, not just to improve post-transplant outcomes but also because it may represent an important area for intervention to improve candidate selection and lung transplant outcomes.

1.3.3 Malignancy

Until recently, malignancy within the prior 5 years has been considered a contraindication for transplantation given the potential for immunosuppressive agents to accelerate malignant potential. Advances in cancer therapeutics have enabled many patients to achieve complete cure of their underlying malignancy and then progress onto the need for lung transplantation for their underlying lung disease. This waiting period of 5 years has the potential to impact adversely on patient outcomes as they wait for this period to lapse prior to formal listing for lung transplantation. It is clear that the disease-free pre-transplant interval has the largest effect on mortality and post-transplant recurrence [15]. However additional factors including cancer type (e.g. haematological malignancy versus prostate cancer [whereby pre-transplant haematological malignancy has the worst prognosis post transplantation [15, 16]]), histological subtype and tumour size are important considerations in the risk stratification process with regard to disease-free survival post-transplant. The changing oncological landscape has challenged the dogma of considering cancer-survivors for transplant and now an individualised approach that includes shared-decision making with oncologists is needed to determine the actual risk of recurrence within the context of the post-transplant risk factors.

With vastly expanding oncological treatment modalities, comes the increase in treatment-related lung injury. This lung injury maybe severe enough to necessitate the need for lung transplantation and examples include bleomycin-induced lung fibrosis and more recently obliterative bronchiolitis following stem cell transplant for haematological malignancy. These cases add an increased degree of complexity to the malignancy scenario due to the potential multi-system complications of the inciting treatment and adverse effects of the medical treatments utilised to manage the initial adverse event (e.g. steroids for pneumonitis with the seqela of osteoporosis, diabetes, etc.). The ever-increasing cohort of case reports and case series demonstrates that these patients can be successfully transplanted with good outcomes but require meticulous management and discussion in the per-transplant and post-transplant phases through a mutli-specialty, multi-disciplinary approach.

1.3.4 Mechanical Bridge to Transplantation Including Extracorporeal Life Support (ECLS)

The use of strategies to support an acutely decompensated patient until a suitable organ becomes available has increased in recent years. With advancements in technology and clinical expertise with these mechanical strategies, we are now seeing improved outcomes for these patients.

Of these strategies mechanical ventilation is still the most common bridge used [1] but there is increased interest in the use of ECLS as a bridge to transplant. Both of these strategies require patients to be bed-bound and often sedated. This reduces their ability to participate actively in physiotherapy and can lead to severe deconditioning and may compromise their suitability for transplantation. It is generally accepted that post-transplant mortality increases proportionately to time mechanical support is required and caution should be exercised in transplanting candidates who have prolonged need for mechanical support. Thus, there is always a dilemma with regards to timing of transplantation between ensuring clinical stability following the initial insult and preventing the deleterious effects of prolonged mechanical support.

In an ideal situation patients that a bridged to transplant with mechanical support would have undergone a comprehensive transplant assessment and all medical and psychosocial risk factors identified before bridge therapy is initiated. However, the reality is that of an unexpected and abrupt deterioration compelling the need for mechanical support. Knowing this it is important to recognise that outcomes are generally poorer in patients who are initiated on a mechanical support without warning for respiratory failure. This is in part due to the inability to complete a detailed medical and psychological evaluation from a medical perspective but also as it does not allow the patient and family time to fully considered lung transplantation and the implications for the long term.

Current International consensus guidelines are unable to provide clear indications and contraindications to the use of mechanical support, in particular ECLS as a bridge to transplant due to the paucity of published data. Regardless, it is well accepted by centres that the use of mechanical support is an integral part of pre-transplantation medicine and is a situation that undoubted will become more common in the future and is an area in need of further study and development to improve outcomes further.

1.3.5 Pulmonary Artery Hypertension (PAH)

Typically patients with PAH in addition to their lung vasculature abnormality have a failing right ventricle at the time of referral for transplant assessment. In the past, these patients have commonly been managed with a combined Heart-Lung transplantation due to the concerns regarding myocardial dysfunction, in particular the right ventricle in the post-transplant period.

It is now clear that PAH represents a heterogeneous population not only due to the underlying primary mechanism but also the consequences on right and/or left ventricular function [17]. In line with this, it is now known that some patients will have a more favourable outcome with Heart-Lung transplantation while others will have comparable outcomes with isolated bilateral lung transplantation. The rational for this that even though the right ventricle may be dysfunctional pre-transplant it has the ability to remodel after lung transplantation and return to normal/near-normal function.

A recent review article [17] recommends that patients with congenital heart disease and Eisenmenger's syndrome, severe right ventricular dysfunction (ejection fraction 10–25%) and/or left ventricular dysfunction (ejection fraction 32–55%) should undergo Heart-Lung transplantation. It is recommended that all other PAH patients should be managed with bilateral lung transplantation. This approach in addition to decreasing waiting list times has the added advantage of enhancing organ utilisation for other recipients.

1.4 Specific Clinical Condition Criteria

1.4.1 Chronic Obstructive Pulmonary Disease

Individuals with COPD should be referred for transplant assessment when the patient continues to deteriorated despite maximal treatment including medication, pulmonary rehabilitation, and oxygen therapy [1].

Other specific indication for referral for transplant assessment include [1]:

1. BODE index of 5–6.
2. $PaCO_2$ >50 mmHg or 6.6 kPa and/or PaO_2 <60 mmHg or 8 kPa.
3. FEV1 <25% predicted.

Prior to or concurrently with the lung transplant assessment, evaluation for lung volume reduction should be undertaken as this can delay the need for lung transplant by almost 3 years [18, 19]. Lung transplantation surgery can be performed following lung volume reduction surgery and carries little additional risk [20, 21]. With the emergence of bronchoscopic procedures for lung volume reduction in individuals with heterogeneous emphysema, this may provide a less invasive and hazardous therapy to improve symptoms and quality of life compared with lung transplant and lung volume reduction surgery. It is important to note that successful lung volume reduction may result in significant improvements in functional and nutritional status and in many instances can improve the patient's suitability as a transplant candidate and outcomes following lung transplantation [19].

The clinical course of individuals with COPD is typically very protracted and survival outcomes with advanced stage disease is typically better than other respiratory diseases for which lung transplant is undertaken. With this, it is an ongoing challenge to determining the right time to list these individuals for lung transplantation.

Indication for listing as per international consensus guidelines [1] include:

1. Significant deterioration in quality of life
2. BODE index >7
3. FEV1 15–20% predicted
4. Three or more severe exacerbations during the preceding year
5. One severe exacerbation with acute hypercapnic respiratory failure
6. Moderate to severe pulmonary hypertension
7. Recipient characteristic which would make procurement of an appropriate organ difficult e.g. Patient height, blood group, highly sensitised (i.e. a patient that has a large number of antibodies [that may have occurred through previous pregnancy, previous blood transfusion] present to various HLA antigens that would likely cause antibody mediated rejection of the transplanted organ)

1.4.2 Interstitial Lung Disease (ILD)

It is well described in respiratory literature that ILD, and in particular idiopathic pulmonary fibrosis (IPF), has a worse prognosis with respect to other lung conditions that require lung transplantation. The propensity of these individuals to deteriorate rapidly underpins the need for early referral for transplant assessment. The most recent American Thoracic Society consensus document highlights that transplantation and supplemental oxygen were the only treatments strongly recommended for patients with IPF, and a transplant discussion was recommended at the time of diagnosis [22].

Other recommendations for referral for transplant assessment include [1]:

1. Histopathologic or radiographic evidence of usual interstitial pneumonitis (UIP) or fibrosing non-specific interstitial pneumonitis (NSIP), regardless of lung function.
2. Abnormal lung function: forced vital capacity (FVC) <80% predicted or diffusion capacity of the lung for carbon monoxide (DLCO) <40% predicted.
3. Any dyspnoea or functional limitation attributable to lung disease.
4. Any oxygen requirement, even if only during exertion.
5. For inflammatory ILD, failure to improve dyspnoea, oxygen requirement, and/or lung function after a clinically indicated trial of medical therapy.

Timing of listing of individuals with IPF has become more challenging in recent years due to the availability of anti-fibrotic agents (pirfenidone, nintedanib) which have been shown to reduce disease progression and improve survival [23, 24]. While these therapies have the potential to delay the need for lung transplantation, long term data is still lacking. Studies of anti-fibrotic agents have primarily been limited to IPF, but work is now underway to examine their utility in other types of ILD.

Indication for listing patients with ILD as per international consensus guidelines include [1]:

1. Decline in FVC ≥10% during 6 months of follow-up (note: a 5% decline is associated with a poorer prognosis and may warrant listing).
2. Decline in DLCO ≥15% during 6 months of follow-up.
3. Desaturation to <88% or distance <250 m on 6-min walk test or >50 m decline in 6-min-walk distance over a 6-month period.
4. Pulmonary hypertension.
5. Hospitalization because of respiratory decline, pneumothorax, or acute exacerbation.

1.4.2.1 Special Considerations

- *Single vs Bilateral Lung Transplantation*

  Although single lung transplantation is regularly done for individuals with ILD, studies have shown that bilateral lung transplant may result in improved long-term survival [25–29]. In addition to the demonstrated survival benefits of bilateral lung transplantation, bilateral lung transplantation is preferred in the setting of structural lung abnormalities such as cysts, bullae, and bronchiectasis which can develop in the advanced staged of ILD and can act as a nidus for infection. In addition, there is also the risk of malignancy developing in the native lung.
- *Telomerase associated Idiopathic pulmonary fibrosis and telomerase mutations*
  Telomeres are a functional complex at the end of linear eukaryotic chromosomes. They are essential for maintaining the integrity and stability of linear eukaryotic genomes. Telomere length regulation and maintenance contribute to normal human cellular aging and human diseases [30]. It is now known that mutations in the telomeres are associated with IPF and also with hematologic manifestations, such as myelodysplasia. Individuals with telomerase mutations appear to have increased rates of haematological, liver and arthritic complications post-transplant and these may necessitate the need for adjustment of the immunosuppressive regimen [31, 32]. Despite these risks, long-term survival is possible, but requires a cautious approach when considering these patients for transplant with heightened vigilance to monitor for other complications associated with telomere mutation.

- *Collagen vascular disorder associated ILD*

  ILD is commonly associated with collagen vascular disorders such as scleroderma and rheumatoid arthritis. In some instances, the ILD is the prominent process and hence may warrant transplantation. The multi-system nature of collagen vascular disorders requires a thorough evaluation of extra pulmonary manifestations that may impact transplant eligibility.

  As an example, many centres regard systemic sclerosis (SSc) as a relative, and in some instances as an absolute contraindication to lung transplantation because of concerns about oesophageal dysmotility and gastroparesis increasing the risk of aspiration. Data does however suggest that outcomes post-transplantation may be similar to other patients with ILD. Thus carefully selected patients with SSc can undergo lung transplantation with good outcomes utilising specific medical and surgical interventions to control oesophageal dysmotility and gastroparesis post-transplant.

1.4.3 Cystic Fibrosis (CF)

Predicting survival in individuals with cystic fibrosis is challenging as there are no variables that consistently and accurately predictive poor outcome. Transplantation should be considered in CF patients who have a 2-year predicted survival of <50% and who have functional limitations classified as New York Heart Association Class III or IV [1].

Other variables that should prompt a transplant assessment as per international consensus guidelines include [1]:

1. A FEV1 that has fallen to 30% or a patient with advanced disease and a rapidly falling FEV1 despite optimal therapy (particularly in a female patient), infected with non-tuberculous mycobacterial (NTM) disease or B cepacia complex (see section below) and/or with diabetes.
2. A 6-min walk distance of less than 400 m.
3. Development of pulmonary hypertension in the absence of a hypoxic exacerbation (as defined by a systolic pulmonary arterial pressure (PAP) >35 mmHg on echocardiography or mean PAP >25 mmHg measured by right heart catheterization).
4. Clinical decline characterised by increasing frequency of exacerbations associated with any of the following:
   (a) An episode of acute respiratory failure requiring non-invasive ventilation.
   (b) Increasing antibiotic resistance and poor clinical recovery from exacerbations.
   (c) Worsening nutritional status despite supplementation.

(d) Pneumothorax.
(e) Life-threatening haemoptysis despite bronchial embolisation.

Indications for listing [1]:

1. Chronic respiratory failure with:
   (a) hypoxia alone (partial pressure of oxygen [PaO_2] <8 kPa or < 60 mmHg).
   (b) Hypercapnia (partial pressure of carbon dioxide [$PaCO_2$] >6.6 kPa or >50 mmHg).
2. Long-term non-invasive ventilation therapy.
3. Pulmonary hypertension.
4. Frequent hospitalization.
5. Rapid lung function decline.
6. World Health Organization Functional Class IV.

1.4.3.1 Specific Considerations

- *Non-tuberculous Mycobacteria (NTM) disease*

  In recent years there has been increased rates of NTM isolation in patients with CF. CF patients with nontuberculous mycobacteria cultured from sputum prior to transplantation are at increased risk of post-transplant infection. With increasing clinical experience with these pathogens it has been established that specific NTM are more pathogenic and have a greater impact post-transplant than others. The highest risk is seen in those infected with *Mycobacterium abscessus* [33] whereas species such as *Mycobacterium avium* complex (MAC—comprising of *M. avium, M. intracellulare and M. chimera*) only have a marginal impact on outcomes post lung transplant. Recommendations from ISHLT, based on case series and expert opinions, suggest the following:

  1. All patients with CF who are referred for transplantation should be evaluated for NTM pulmonary disease.
  2. Patients with NTM disease who are being evaluated for transplantation should have the organism confirmed according to microbiology guidelines and begin treatment before transplant listing.
  3. Treatment should be performed by, or in collaboration with, a physician experienced in the management of such patients.
  4. Progressive pulmonary or extrapulmonary disease secondary to NTM despite optimal therapy or an inability to tolerate optimal therapy is a contraindication for transplant listing.

- *Burkholderia cepacia complex (Bcc)*

  Patients with CF who are infected with Bcc have been shown to have a more rapid progression of respiratory disease and thus are more likely to require lung transplantation but have poorer outcomes after transplantation. However, it is now known that certain genomovars, or subspecies, may have greater virulence than others and thus

impact transplant outcomes [34, 35]. The Bcc subspecies *Burkholderia cenocepacia* in particular have a significantly worse survival after transplantation compared to uninfected patients with CF, and the increased mortality is directly attributable to Bcc infection. Hence Infection with Bcc is considered a relative contraindication to lung transplantation. Taking this into account the following recommendations are made [1]:

1. All patients with CF referred for transplantation should be evaluated for the presence of Bcc.
2. Patients with species other than *B. cenocepacia* do not constitute an increased risk for mortality after transplantation and can be listed, provided that other criteria are met.
3. Patients with *B cenocepacia* have an increased risk of mortality secondary to recurrent disease after transplantation. It is recommended that centres continuing to accept such patients should have an active research program assessing novel approaches to prevent and control recurrent disease and should be experienced in management of these patients.

1.4.4 Pulmonary Vascular Diseases

With the developments of targeted therapies for the treatment of pulmonary hypertension, the timing of referral for transplant for pulmonary vascular disease is less clear. Medical therapies (e.g. prostanoids, endothelin receptor antagonists, and phosphodiesterase inhibitors) now have the ability to stabilise patients whom in the past would certainly have died unless they proceeded to lung transplantation. Additionally, the advent of novel therapies (such as selexipag, riociguat) may continue to change this landscape.

Recommendation for referral for transplant assessment [1]:

1. NYHA Functional Class III or IV symptoms during escalating therapy.
2. Rapidly progressive disease (assuming weight and rehabilitation concerns not present).
3. Use of parenteral targeted pulmonary arterial hypertension (PAH) therapy regardless of symptoms or NYHA Functional Class.
4. Known or suspected pulmonary veno-occlusive disease (PVOD) or pulmonary capillary hemangiomatosis.

Timing of transplant listing:

1. NYHA Functional Class III or IV despite a trial of at least 3 months of combination therapy including prostanoids.
2. Cardiac index of <2 l/min/m^2.
3. Mean right atrial pressure of >15 mmHg.
4. 6-min walk test of <350 m.
5. Development of significant haemoptysis, pericardial effusion, or signs of progressive right heart failure (renal insufficiency, increasing bilirubin, brain natriuretic peptide, or recurrent ascites).

1.5 Lung Retransplantation

Lung retransplantation represents only a small proportion of those that undergo lung transplantation. ISHLT registry data shows that since 1995 lung retransplantation accounted for 4% of all lung transplants undertaken and for the 2015 year just under 8% of all lung transplants were retransplantation. However, with improvements in the overall health status of post-transplant patients has seen an increase in the frequency of repeat transplant in recent years.

In general, the same clinical criteria used for selection for the initial lung transplantation should be adopted with particular emphasis on the presence of significant renal dysfunction. This and other co-morbidities significantly increase the risk of mortality in retransplant candidates.

As with the initial lung transplantation a bilateral or single lung transplant can be undertaken. As mentioned previously single lung transplant can increase the risk of the remaining 'native' lung acting as a nidus for infection. The failed allograft may also represent a source of ongoing immune stimulation, and its removal would offer intuitive advantages [1]. Given these reasons, complete removal of a failed allograft is advisable.

Specific prognostic factors that have been identified include [1]:

1. Patients retransplanted for bronchiolitis obliterans syndrome (BOS) have better survival than those transplanted for primary graft dysfunction or airway complications.
2. Patients who are >2 years out from initial transplantation have better outcomes than patients retransplanted earlier.
3. Patients retransplanted for BOS have been seen to have more rapid declines in airflow than patients transplanted for other indications.
4. Patients retransplanted in <2 years after the initial transplantation also have an even greater risk of developing BOS.

Despite improving survival rates of retransplant candidates, overall survival remains inferior to survival seen after initial transplantation. With this is mind consideration must be given to the ethical issues surrounding lung allocation to retransplantation candidates i.e. allocation of a lung to a patient who has already received a lung transplant versus an individual who has not. Another factor to consider is that it is generally accepted that priority is given to younger patients regarding retransplantation; however at the same time categorically placing older patients at a disadvantage is inappropriate. These aspects, in addition to the medical issues surrounding transplantation make this an ethically challenging area.

References

1. Weill D, Benden C, Corris PA, Dark JH, Davis RD, Keshavjee S, et al. A consensus document for the selection of lung transplant candidates: 2014—an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2015;34(1):1–15. [cited 2017 Oct 30]. http://www.ncbi.nlm.nih.gov/pubmed/25085497.

2. Yusen RD, Edwards LB, Kucheryavaya AY, Benden C, Dipchand AI, Goldfarb SB, et al. The Registry of the International Society for Heart and Lung Transplantation: thirty-second official adult lung and heart-lung transplantation report—2015; focus theme: early graft failure. J Heart Lung Transplant. 2015;34(10):1264–77. [cited 2017 Oct 30]. http://linkinghub.elsevier.com/retrieve/pii/S1053249815013893.
3. International Society for Heart and Lung Transplantation. Registries - heart/lung registries > slides. http://www.ishlt.org/registries/slides.asp?slides=heartLungRegistry.
4. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004;350(10):1005–12. [cited 2017 Oct 30]. http://www.nejm.org/doi/abs/10.1056/NEJMoa021322.
5. Madill J, Gutierrez C, Grossman J, Allard J, Chan C, Hutcheon M, et al. Nutritional assessment of the lung transplant patient: body mass index as a predictor of 90-day mortality following transplantation. J Heart Lung Transplant. 2001;20(3):288–96. [cited 2017 Nov 5]. http://www.ncbi.nlm.nih.gov/pubmed/11257554.
6. Lederer DJ, Wilt JS, D'Ovidio F, Bacchetta MD, Shah L, Ravichandran S, et al. Obesity and underweight are associated with an increased risk of death after lung transplantation. Am J Respir Crit Care Med. 2009;180(9):887–95. [cited 2017 Nov 5]. http://www.atsjournals.org/doi/abs/10.1164/rccm.200903-0425OC
7. Snell GI, Bennetts K, Bartolo J, Levvey B, Griffiths A, Williams T, et al. Body mass index as a predictor of survival in adults with cystic fibrosis referred for lung transplantation. J Heart Lung Transplant. 1998;17(11):1097–103. [cited 2017 Nov 5]. http://www.ncbi.nlm.nih.gov/pubmed/9855449.
8. Chen X, Mao G, Leng SX. Frailty syndrome: an overview. Clin Interv Aging. 2014;9:433–41. [cited 2017 Nov 5]. http://www.dovepress.com/frailty-syndrome-an-overview-peer-reviewed-article-CIA.
9. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146–56. [cited 2017 Nov 5]. http://www.ncbi.nlm.nih.gov/pubmed/11253156.
10. Singer JP, Katz PP, Dean MY, Chen J, Su B, Kern R, et al. Frailty Is common in lung transplant candidates and associated with poorer health-related quality of life. J Hear Lung Transplant. 2013;32(4):S43. [cited 2017 Nov 5]. http://linkinghub.elsevier.com/retrieve/pii/S105324981300925X.
11. Lederer DJ, Sonett JR, Philip NA, Larkin M, Peterson ER, Desai A, et al. Frailty and early mortality after lung transplantation: preliminary results. J Heart Lung Transplant. 2013;32(4):S119–20. [cited 2017 Nov 5]. http://linkinghub.elsevier.com/retrieve/pii/S1053249813002696.
12. Wilson ME, Vakil AP, Kandel P, Undavalli C, Dunlay SM, Kennedy CC. Pretransplant frailty is associated with decreased survival after lung transplantation. J Hear Lung Transplant. 2016;35(2):173–8. [cited 2017 Nov 5]. http://linkinghub.elsevier.com/retrieve/pii/S1053249815014758.
13. Tuppin MP, Paratz JD, Chang AT, Seale HE, Walsh JR, Kermeeen FD, et al. Predictive utility of the 6-minute walk distance on survival in patients awaiting lung transplantation. J Heart Lung Transplant. 2008;27(7):729–34. [cited 2017 Oct 30]. http://www.ncbi.nlm.nih.gov/pubmed/18582801.
14. Martinu T, Babyak MA, O'Connell CF, Carney RM, Trulock EP, Davis RD, et al. Baseline 6-min walk distance predicts survival in lung transplant candidates. Am J Transplant. 2008;8(7):1498–505. [cited 2017 Nov 5]. http://doi.wiley.com/10.1111/j.1600-6143.2008.02264.x.
15. Mistiaen WP. Heart transplantation in patients with previous malignancy. An overview. Acta Cardiol. 2015;70(2):123–30. [cited 2017 Nov 24]. http://www.ncbi.nlm.nih.gov/pubmed/26148371.
16. Beaty CA, George TJ, Kilic A, Conte JV, Shah AS. Pre-transplant malignancy: an analysis of outcomes after thoracic organ transplantation. J Heart Lung Transplant. 2013;32(2):202–11. [cited 2017 Nov 24]. http://www.ncbi.nlm.nih.gov/pubmed/23265911.
17. Olland A, Falcoz P, Canuet M, Massard G. Should we perform bilateral-lung or heart – lung transplantation for patients with pulmonary hypertension? Interact Cardiovasc Thorac Surg. 2017;17(1):166–70.

18. Burns KE, Keenan RJ, Grgurich WF, Manzetti JD, Zenati MA. Outcomes of lung volume reduction surgery followed by lung transplantation: a matched cohort study. Ann Thorac Surg. 2002;73(5):1587–93. [cited 2017 Nov 3]. http://linkinghub.elsevier.com/retrieve/pii/S0003497502034999.
19. Senbaklavaci O, Wisser W, özpeker C, Marta G, Jaksch P, Wolner E, et al. Successful lung volume reduction surgery brings patients into better condition for later lung transplantation. Eur J Cardiothorac Surg. 2002;22(3):363–7. [cited 2017 Nov 3]. https://academic.oup.com/ejcts/article-lookup/doi/10.1016/S1010-7940(02)00354-8.
20. Nathan SD, Edwards LB, Barnett SD, Ahmad S, Burton NA. Outcomes of COPD lung transplant recipients after lung volume reduction surgery. Chest. 2004;126(5):1569–74. [cited 2017 Nov 3]. http://linkinghub.elsevier.com/retrieve/pii/S0012369215313738.
21. Shitrit D, Fink G, Sahar G, Eidelman L, Saute M, Kramer MR. Successful lung transplantation following lung volume reduction surgery. Thorac Cardiovasc Surg. 2003;51(5):274–6. [cited 2017 Nov 3]. http://www.thieme-connect.de/DOI/DOI?10.1055/s-2003-43087.
22. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183(6):788–824. [cited 2017 Nov 3]. http://www.atsjournals.org/doi/abs/10.1164/rccm.2009-040GL.
23. King TE, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2083–92. [cited 2017 Nov 3]. http://www.nejm.org/doi/pdf/10.1056/NEJMoa1402582.
24. Richeldi L, Du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2071–82. [cited 2017 Nov 3]. http://www.nejm.org/doi/pdf/10.1056/NEJMoa1402584.
25. Christie JD, Edwards LB, Kucheryavaya AY, Benden C, Dipchand AI, Dobbels F, et al. The Registry of the International Society for Heart and Lung Transplantation: 29th adult lung and heart-lung transplant report-2012. J Heart Lung Transplant. 2012;31(10):1073–86. [cited 2017 Nov 4]. http://www.ncbi.nlm.nih.gov/pubmed/22975097.
26. Mason DP, Brizzio ME, Alster JM, McNeill AM, Murthy SC, Budev MM, et al. Lung transplantation for idiopathic pulmonary fibrosis. Ann Thorac Surg. 2007;84(4):1121–8. [cited 2017 Nov 4]. http://linkinghub.elsevier.com/retrieve/pii/S0003497507009460.
27. Toronto Lung Transplant Group. Unilateral lung transplantation for pulmonary fibrosis. N Engl J Med. 1986;314(18):1140–5. [cited 2017 Nov 4]. http://www.nejm.org/doi/abs/10.1056/NEJM198605013141802.
28. Neurohr C, Huppmann P, Thum D, Leuschner W, von Wulffen W, Meis T, et al. Potential functional and survival benefit of double over single lung transplantation for selected patients with idiopathic pulmonary fibrosis. Transpl Int. 2010;23(9):887–96. [cited 2017 Nov 4]. http://doi.wiley.com/10.1111/j.1432-2277.2010.01071.x.
29. Force SD, Kilgo P, Neujahr DC, Pelaez A, Pickens A, Fernandez FG, et al. Bilateral lung transplantation offers better long-term survival, compared with single-lung transplantation, for younger patients with idiopathic pulmonary fibrosis. Ann Thorac Surg. 2011;91(1):244–9. [cited 2017 Nov 4]. http://www.ncbi.nlm.nih.gov/pubmed/21172522.
30. Cong Y-S, Wright WE, Shay JW. Human telomerase and its regulation. Microbiol Mol Biol Rev. 2002;66(3):407–25. [cited 2017 Nov 4]. http://www.ncbi.nlm.nih.gov/pubmed/12208997.
31. Borie R, Kannengiesser C, Hirschi S, Le Pavec J, Mal H, Bergot E, et al. Severe hematologic complications after lung transplantation in patients with telomerase complex mutations. J Heart Lung Transplant. 2015;34(4):538–46. [cited 2017 Nov 4]. http://www.ncbi.nlm.nih.gov/pubmed/25612863.
32. Silhan LL, Shah PD, Chambers DC, Snyder LD, Riise GC, Wagner CL, et al. Lung transplantation in telomerase mutation carriers with pulmonary fibrosis. Eur Respir J. 2014;44(1):178–87. [cited 2017 Nov 4]. http://www.ncbi.nlm.nih.gov/pubmed/24833766.

33. Chalermskulrat W, Sood N, Neuringer IP, Hecker TM, Chang L, Rivera MP, et al. Non-tuberculous mycobacteria in end stage cystic fibrosis: implications for lung transplantation. Thorax. 2006;61(6):507–13. [cited 2017 Nov 4]. http://www.ncbi.nlm.nih.gov/pubmed/16601086.
34. Mahenthiralingam E, Vandamme P, Campbell ME, Henry DA, Gravelle AM, Wong LTK, et al. Infection with Burkholderia cepacia complex genomovars in patients with cystic fibrosis: virulent transmissible strains of genomovar III can replace Burkholderia multivorans. Clin Infect Dis. 2001;33(9):1469–75. [cited 2017 Nov 4]. https://academic.oup.com/cid/article-lookup/doi/10.1086/322684.
35. De Soyza A, Archer L, Wardle J, Parry G, Dark JH, Gould K, et al. Pulmonary transplantation for cystic fibrosis: pre-transplant recipient characteristics in patients dying of peri-operative sepsis. J Heart Lung Transplant. 2003;22(7):764–9. [cited 2017 Nov 4]. http://www.ncbi.nlm.nih.gov/pubmed/12873544.

Chapter 2
Surgical Approaches: Tricks of the Trade

Kumud Dhital and Yujiro Kawanishi

2.1 Introduction

Lung transplantation remains the most effective therapy for patients with limited life-expectancy resulting from end-stage non-malignant pulmonary pathology, and in whom the surgical procedure is not deemed to be futile. Over 4000 lung transplant procedures are performed annually, and in the past three decades, over 65,000 such procedures have been performed globally as registered with the International Society for Heart & Lung Transplantation (ISHLT), with >20,000 single lungs, >40,000 double lungs and >4500 heart-lung transplants [1]. The improved outcomes from bilateral sequential lung transplantation (BSLT) reflects an increasing use of this strategy, from 70% to >80% of the total lung transplant numbers over single lung transplantation which remains static at around 1000 cases per annum. The shift from heart-lung transplantation and domino heart donation for cystic fibrosis patients to a preference for BSLT after the early 1990s has resulted in fewer than 50 HL transplants being performed annually.

The continued shortage of ideal lung donors along with ongoing relaxation of acceptance criteria, in particular the removal of upper limits for recipient age and BMI as absolute contraindications, places greater responsibility on the transplant team to individualise the surgical procedure as well as the post-implant long-term management protocol to obtain the pre-requisite goal of improved quality of life and survival benefit. The sicker and measurably frail recipient with comorbidities poses the greatest challenge. Whilst frailty can be reversed with a successful transplant, the older patient requires careful assessment of the physiological reserve in withstanding a potentially prolonged post-operative course. The surgical considerations are therefore much broader than just the technical aspects of the peri-operative

K. Dhital (✉) · Y. Kawanishi
Lung Transplant Unit, St. Vincent's Hospital, Darlinghurst, NSW, Australia
e-mail: Kumud.Dhital@svha.org.au

A. R. Glanville (ed.), *Essentials in Lung Transplantation*,
https://doi.org/10.1007/978-3-319-90933-2_2

phase. Some of these are covered comprehensively in dedicated chapters in this book: including donor/recipient selection; the use of extra-corporeal membrane oxygenation (ECMO) as bridge to transplantation and for rescue therapy for post-transplant primary graft dysfunction (PGD); the use of donor organs from both donation after brain death (DBD) and donation after circulatory death (DCD) pathways, and the considered use of extra-corporeal lung perfusion (ECLP) for resuscitation and *ex* situ treatment of the donor lungs.

This chapter focuses on the remaining surgical issue of: the appropriate listing for a single, bilateral or heart-lung block transplantation; donor management and safe retrieval; surgical techniques including choice of incision, use of peri-operative extra-corporeal support and the management of lung, bronchial or vascular size mismatches. This chapter will not discuss the rarer procedure of living-related lobar lung transplantation that was initially championed over 2 decades ago by Vaughan Starnes in the USA [2] and subsequently remains limited to a few units in Japan where there is a significant shortage of organ donation [3].

2.2 Transplant Listing

A thorough surgical evaluation of the patient, together with a review of all the necessary pre-listing investigations is imperative. Notwithstanding the multidisciplinary teamwork involved in selecting and working-up a transplant recipient [4], the ultimate decision to accept a patient on the wait-list remains a surgical one. The important factors that may influence the choice of incision, the type of lung transplant, potential need for extra-corporeal support, anticipation of procedural complexity should all be highlighted at this stage and summarised on the wait-list. It is the responsibility of the surgeon carrying out this final patient assessment, that there are no surprises at the time of transplantation.

The primary decision on the type of transplant for a given recipient depends on a number of factors beyond the pathological diagnosis. These include: blood group, tissue typing, age, height, lung dimensions including the actual and predicted total lung capacity (TLC), previous thoracic interventions, cardiac morbidity, presence and nature of pulmonary hypertension, pre-existing renal dysfunction to tailor peri-operative immunosuppression regime, indication of pleural adhesions and/or presence of pleural based abscesses, frailty score, expected travel time and distance from the transplant centre and recipient consent for consideration of marginal donor lungs.

Single lung transplantation remains a very effective strategy for non-infective lung pathology particularly when the recipient starts to decline rapidly as is frequently the case in idiopathic pulmonary fibrosis (IPF), a diagnosis which continues to confer the highest wait-list and post-transplant mortality when compared to other pathologies. In order to limit wait-list attrition patients with IPF should be listed for BSLT with informed option of a SLT should the need arise. This requires careful pre-operative assessment of the comparative functions of right vs left lung to permit selection of the preferential side to be transplanted. Although the larger right lung is always preferable in the context of homogenous distribution of disease, consideration

should also be given where two IPF recipients with progressive decline in lung function may benefit from individual SLT from splitting the lung block from the same donor. SLT should also be offered to patients with homogenous emphysema with absence of significant contralateral bullous disease if their condition is declining to the point of considering withdrawal from the waiting list. SLT may also be offered in the context of primary pulmonary hypertension (PPH), but given their complex intra- and post-operative management, this option should be restricted to larger volume lung transplant centres with the necessary anaesthetic, cardiac surgical and intensive care skills.

Bilateral lung transplantation (BLT) is necessary for the infective conditions of cystic fibrosis (CF) and bronchiectasis. It is also preferable for PPH and emphysema with respect to survival advantage [5]. However, its superiority in patients with IPF is not evidenced on systematic review with adjustment for patient characteristics between the SLT vs BLT cohorts [6] and therefore questions the routine preference of BLT for this condition [7]. Heart-lung transplantation (HLT) remains the only option in the few selected cases with concomitant end-stage cardiac and pulmonary pathology. Typically, this occurs secondary to Eisenmenger's syndrome which arises from uncorrected congenital heart disease with chronic left-to-right shunt and subsequent onset of irreversible pulmonary hypertension. HLT may also be necessary in patients with PPH with secondary right ventricular (RV) dysfunction that is deemed too severe to reverse remodel with DLT alone.

2.3 Donor Management and Surgical Organ Retrieval

Careful adherence to guidelines for the management of the multi-organ donor remains the most important step in safeguarding a viable donor pool and in converting the donation to eventual retrieval of transplantable organs. Despite widely published guidelines [8–10] and the increasing number of dedicated donor management intensive care specialists, the lung donor utilization rate from multi-organ donors remains poor at <30% [11]. Poor haemodynamic management without central venous pressure monitoring, excess fluid administration, inadequate or excess tidal volume (ideally 6–8 ml/kg) and infrequent lung recruitment manoeuvres are often the avoidable causes of turn-down donor lungs. The surgical management of the donor lungs therefore starts with the consent for donation and a management protocol that ensures multi-organ protection. We accept donor lungs up to the age of 70 and will consider older donors on a case-by-case basis. A chest CT scan is mandatory in older donor with a smoking history to rule out malignancy and any significant emphysema. A history of trauma and the presence of intercostal drains in the donor should not preclude consideration of lung retrieval. The use of lungs from donation after circulatory death (DCD) is now common in many centres. Given the excellent medium to long-term outcomes [12–14], we treat these lungs similarly to those from the standard donation after brain death (DBD) pathway. We do not advocate the automatic use of extra-corporeal lung perfusion (ECLP) just on the basis of DCD origin.

The ratio of arterial oxygenation to fraction of inspired oxygen should ideally be >300 mmHg and this is typically measured at 100% inspired oxygen at a positive-end-expiratory-pressure (PEEP) of 5 mmHg. This and the standard chest radiograph are primary determinants of accepting the donor lungs. A good PF ratio which subsequently deteriorates often indicates segmental/lobar collapse or overzealous fluid administration with the development of pulmonary oedema. Partial deterioration of an acceptable PF ratio either immediately before or during the retrieval process should not preclude the use of these lungs, particularly if bronchoscopy is clear and the lungs appear normal on visual and manual examination. If the logistics of organ retrieval do not permit time for a diuretic driven recovery of lung function following excess fluid administration, then such lungs will benefit from a period of ECLP. Though expensive, this technique for resuscitation of pulmonary function through controlled recruitment, bronchial toileting and removal of excess interstitial pulmonary oedema, is likely to have a far greater role in permitting routine ex-situ therapeutic strategies in the future.

Beyond the basic immune compatibility of blood group and tissue typing, donor-recipient size matching is done on the basis of gender, height and the total lung capacity and the individual lung dimensions (apico-basal and maximum trans-thoracic) on the chest radiograph. A donor TLC range of 75–125% of the recipient is a common algorithm but which should be interpreted with caution particularly in avoiding oversizing bilateral lungs in a recipient with restrictive pulmonary fibrosis. On signs of significant deterioration on the waiting list, these PF patients should be considered for a single lung transplant, of the least functional side. In this case, a full sized single donor lung with a TLC equivalent to that expected in the recipient can be safely transplanted.

A pre-retrieval bronchoscopy is not mandatory if the PF ratio is acceptable with a normal chest radiograph. The actual retrieval procedure involves a standard mid-line sternotomy and wide opening into both pleural cavities. This is followed by close inspection of the lungs for any injury, bullous disease, palpation for surface and intra-parenchymal lesions, determination of lung expansion for all lobes, presence of significant oedema and a lung collapse test to rule out air-trapping or bronchial obstruction. Systemic heparin is administered before placement of purse strings on the ascending aorta (for cardiac procurement) and the main pulmonary artery (PA) just before its bifurcation. The aorta is separated from the PA. Ventilation is continued and once all teams are ready, the aorta and then the IVC are clamped, the left atrial appendage and IVC are transected (for cardiac retrieval) followed by simultaneous delivery of pneumoplegia +/− cardioplegia. Cold saline and ice slush is liberally poured over the lungs. On completion of pneumoplegia, ventilation is ceased and the SVC and aorta are sequentially transected. We take the aortic arch and at least 10 cm of the descending part in continuity from all DBD donors. This permits all options of distal aortic anastomosis in the recipient and if not required, the excess aortic tissue is processed for production of homograft conduit and cryo-preserved. Exceptionally, the aortic transection is at the level of the innominate artery take-off for our DCD heart program so that it can be rapidly connected to an ex situ perfusion device for reanimation, support and transportation. The main PA is only transected if the heart lung block is being split in the donor, which may be

necessary if two separate cardiac and thoracic teams are involved. The exception is for a rapid cardiac explant technique for our DCD heart transplant program. If such an in situ split is required then care must be taken to cut the PA at the bifurcation and not beyond. The left PA is shorter than the right and there is danger of inadequate length if the cut is made close to the pericardial reflection, particularly if there is excess traction on the proximal PA.

The left inferior pulmonary ligament is divided and the left lung brought out from the pleural cavity. The descending aorta is transected and held to allow separation of the lung keeping anterior to the oesophagus and behind the left atrium from the posterior mediastinum. The separation is carried cranially to the trachea. The left lung is allowed to fall back into its pleural cavity and the right lung freed in a similar fashion with division of the azygous vein. The endotracheal tube is partially withdrawn and the trachea stapled off after half expansion of the lungs. The entire heart-lung block is then taken to the back-table where it is triple bagged for transportation and any necessary separation of the block, including down-sizing of the lungs, takes place at our recipient hospital. In the event that the heart and lungs are going to separate transplant units, then the block is split on the back table at the donor hospital. This requires an incision between the base of the left atrial appendage and the left superior pulmonary vein which is then carried circumferentially in a clockwise fashion. There should be sufficient left atrial cuff beyond the pulmonary veins to permit a wide and unobstructed pulmonary venous anastomosis.

2.4 Recipient Surgery

2.4.1 Peri-operative Extracorporeal Support

While peri-operative extracorporeal support may be necessary in the presence of significant pulmonary hypertension, pre-existing cardiac dysfunction, need for a concomitant cardiac procedure, or inadequate oxygenation on single lung ventilation, the routine use of cardiopulmonary bypass (CPB) or extracorporeal membrane oxygenation (ECMO) during lung transplantation is largely determined by institutional or individual surgeon preference. The latter is also influenced by specialty surgical training and familiarity with circulatory support that varies across jurisdictions from a comprehensive cardiothoracic stream to that separated into distinct cardiovascular or thoracic pathways. Some units advocate the routine use of peri-procedural CPB [15] whilst others favour ECMO support not only during the procedure, but also post-operatively to mitigate against any significant cardio-pulmonary compromise from acute ischaemia-reperfusion injury [16, 17]. This conscious decision to leave the recipient on ECMO post-transplant creates difficulty in determining the presence of PGD. However, the ease of controlled reperfusion by avoiding excess cardiac output reaching the first lung, is a major advantage of extracorporeal support during lung transplantation. Except for a higher rate of blood product transfusion, the medium and long-term outcomes from both on and off-pump strategies are comparable. Our surgical preference is for single-lumen intubation and cardiopulmonary

bypass with central cannulation, reserving double lumen endo-tracheal tubes for those few off-pump cases in patients with large intra-thoracic cavities. As we transplant older recipients, the on-pump strategy also allows us to carry out concomitant cardiac surgical procedure.

2.4.2 Downsizing Lungs

Where the donor lungs are known to be significantly oversized with potential for cardiac and pulmonary tamponade, then it is best to perform a back-table lobectomy at the recipient hospital. Usually one or occasionally both lower lobes are formally sacrificed. If the size discrepancy is small to moderate, then the downsizing can be done after transplanting the lungs. Wedge resections of right middle lobe, the left lingual and/or the apical portions of the upper lobes can be performed with a linear stapler.

2.4.3 Bilateral Sequential Lung Transplantation

The first successful single and double lung transplants were performed by Joel Cooper from the Toronto group using the en bloc technique [18]. Airway complications led to further refinements with subsequent introduction of bilateral sequential lung transplantation [19–21]. Our preference is to have the patient supine, slight abduction at the shoulder with elbows winged-out to expose the axilla and a pad across the upper thoracic spine to elevate the chest (Fig. 2.1). This permits excellent

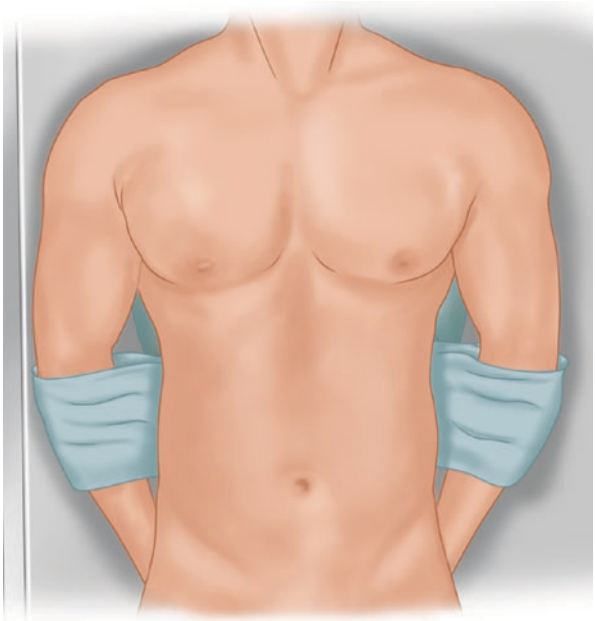


Fig. 2.1 Standard supine position with abduction at the shoulder and winged-out elbows

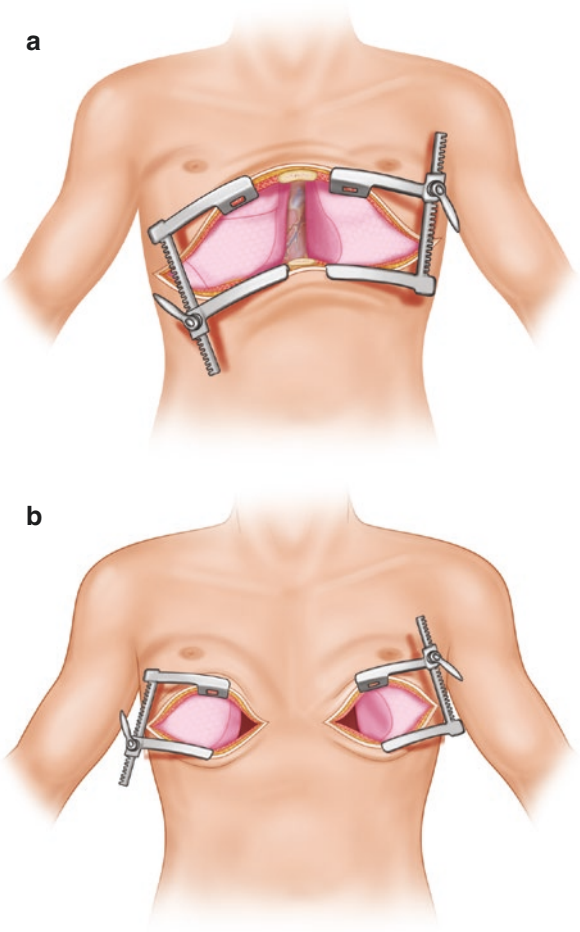


Fig. 2.2 (**a**) Trans-sternal clam-shell opening. (**b**) Bilateral antero-lateral thoracotomies

exposure for either bilateral anterolateral thoracotomies or a full clamshell as depicted in Fig. 2.2. The patient is prepped and draped leaving both groins exposed in the event that femoral cannulation for extracorporeal support is required. As a general rule, we perform the majority of BSLT through antero-lateral thoracotomies with the skin incision along the sub-mammary crease, and thoracic entry typically via the fourth or fifth intercostal space. Good exposure can be achieved without sacrificing the internal mammary artery by fully dividing the intercostal muscles all the way round to the posterior ends of the ribs if necessary. This also significantly reduces the risk of rib fractures in this vulnerable population. The exposure can be further improved with the placement of a pledgeted retraction suture on the diaphragm that is then brought out laterally through the chest wall. This is particularly helpful in IPF patients with limited space and may prevent the need to consider a conversion to a full clam-shell. The hole for this diaphragm retraction suture can be used for the basal intercostal drain at the end of the procedure.

In off-pump cases which require a double lumen intubation, the lung with the worst lung function is explanted first. In our predominantly on-pump practice with central cannulation and single lumen endotracheal intubation, we explant the right lung first. Following rib retraction and division of any anterior and medial adhesions, the first crucial step is in identifying and preserving the phrenic nerve. The phrenic and vagus nerves bilaterally, and the peculiar anatomic course of the left recurrent laryngeal nerve must be respected with continued vigilance for their preservation throughout the dissection phase. The potential complications of interrupted cough reflex, reduced gastric motility, diaphragmatic paralysis and vocal cord palsy can be devastating with prolonged ICU and hospital stay as well as poor quality of life following transplantation.

The pericardial fat above the phrenic nerve and some of the ipsilateral thymic fat is then removed before making a pericardial incision parallel to and 3–4 cm above the phrenic nerve to get exposure of the right atrium, the appendage, superior vena cava (SVC) and the ascending aorta. Pledgeted retraction sutures are placed inferiorly and superiorly along the pericardial edges to further improve the exposure before direct aortic cannulation. A 2-stage venous cannula is inserted through the right atrial appendage or a single-stage cannula directly into the inferior vena cava (IVC) before commencing CBP. We find it helpful to insert a second straight venous cannula up the SVC, via the body of the right atrium or directly into the SVC to eliminate the intermittent but significant rise in central venous pressure that is often seen with retraction of the hilar tissues particularly during the right pulmonary arterial anastomosis (Fig. 2.3). The blood vessels are dissected next and their anatomy

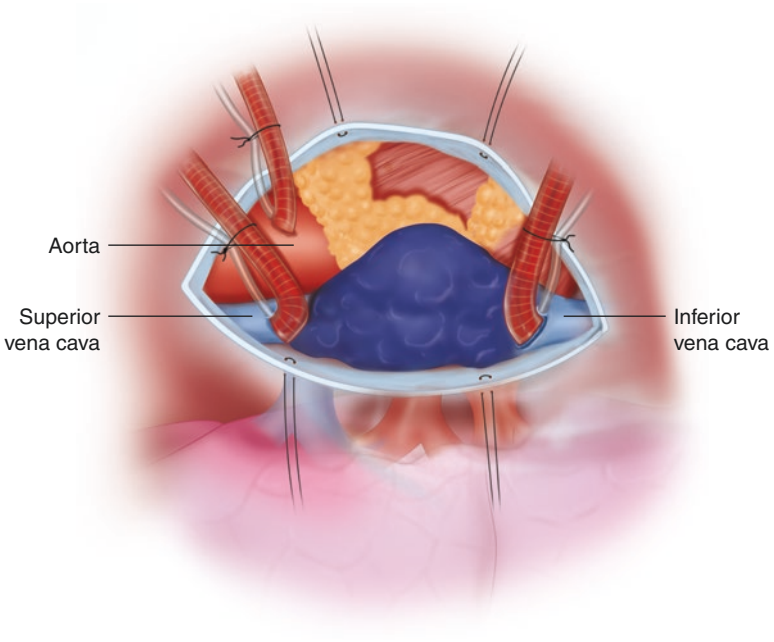


Fig. 2.3 Venous cannulations of both IVC and SVC with arterial return to the ascending aorta

facilitates dividing in order the superior pulmonary vein, the pulmonary artery and then the inferior pulmonary vein. The latter is easier after dividing the inferior pulmonary ligament. The pulmonary vessels are either divided between ties or with a vascular stapler. The posterior hilar tissues are separated with diathermy closer to the lung, with additional clips across any blood vessels to avoid any injury to the main vagus nerve and the oesophagus. Any remaining adhesions, particularly from previous pleurodesis, are then dissected before stapling off the bronchus and removing the explanted lung.

Lymph node clearance in CF and bronchiectatic patients can be time consuming but necessary to reduce bioburden and to guide antibiotic therapy. In these cases and particularly where there has been spillage from dissecting lung abscesses or lung tissue off the chest wall, we recommend a thorough irrigation of the pleural cavity with antiseptic solution. In non-infective cases, only the large and often calcified nodes that might impact on the anastomoses need be removed. Following meticulous haemostasis, the vascular and bronchial stumps are then prepared to facilitate the donor lung implantation. The two pulmonary venous stumps are grasped and a circumferential incision of the pericardium is made to expose their intra-pericardial origin. Infrequently, when there is insufficient common left atrial tissue for clamping and performing an anastomosis, careful dissection in Sondegard's inter-atrial groove will provide a deeper clamp placement. Similarly, the main PA stump is also pulled outwards and circumferentially freed. The right main bronchus is trimmed so as to leave a maximum of only two cartilaginous rings from the carina and making sure to leave the posterior membranous portion a little longer (Fig. 2.4). Care must be taken to achieve haemostasis, particularly with the bronchial arteries and the small vessels that supply the hilar tissues and lymph nodes.

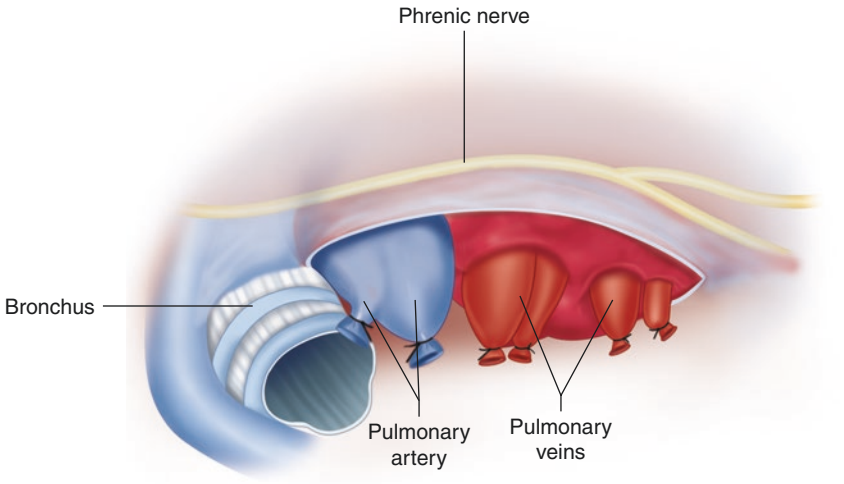


Fig. 2.4 Preservation of the phrenic nerve and the right main bronchus divided at a maximum of only 2 cartilaginous rings from the carina

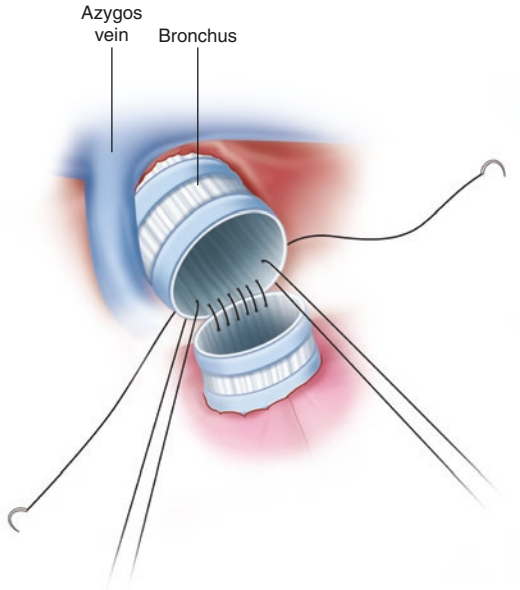


Fig. 2.5 Diagram illustrates the two retracting temporary stay sutures with completion of the membranous anastomosis first

The prepared donor lung is then orientated anatomically inside the chest cavity. Two 4/0 Prolene stay sutures are placed at the supero-posterior and infero-posterior edges (membrano-cartilaginous junctions) of the recipient bronchus and pulled out with a little traction. In the absence of a significant mismatch in bronchial sizes, we favour a continuous bronchial anastomosis with a double-armed 3/0 Prolene suture (Fig. 2.5). The membranous portion is joined first before completing the anastomosis with both needles bidirectionally so that the suture is tied down anteriorly. Where there is a mismatch in size, it is advisable to make a continuous suture of the membranous part and interrupted sutures along the cartilaginous segment that are placed sequentially to evenly distribute the tension of this telescoped anastomosis. Although not routinely necessary, the bronchial anastomosis should be covered with the loose peri-bronchial tissue with a few tacking sutures in cases that are at risk of poor bronchial healing such as recipients colonised with multi-resistant organisms or on chronic steroid therapy. Attention is then turned to anastomosing the left atrial cuff. Bearing in mind that the superior and inferior pulmonary veins are not on a horizontal plane, a Satinsky clamp is placed across the left atrium respecting this venous alignment to ensure that the anastomosis is free from any torsion. The pulmonary vein stumps are trimmed and the intervening left atrial wall is cut to produce a cuff that should have sufficient circumferential tissue for the anastomosis. A stay suture is placed across the infero-posterior margins of the recipient and donor inferior pulmonary veins before completing the anastomosis with an everting and running double-armed 4/0 Prolene suture making sure to appose the two atrial endothelial surfaces (Fig. 2.6). This prevents any muscle bulging into the left atrium and acting as a potential nidus for subsequent thrombus

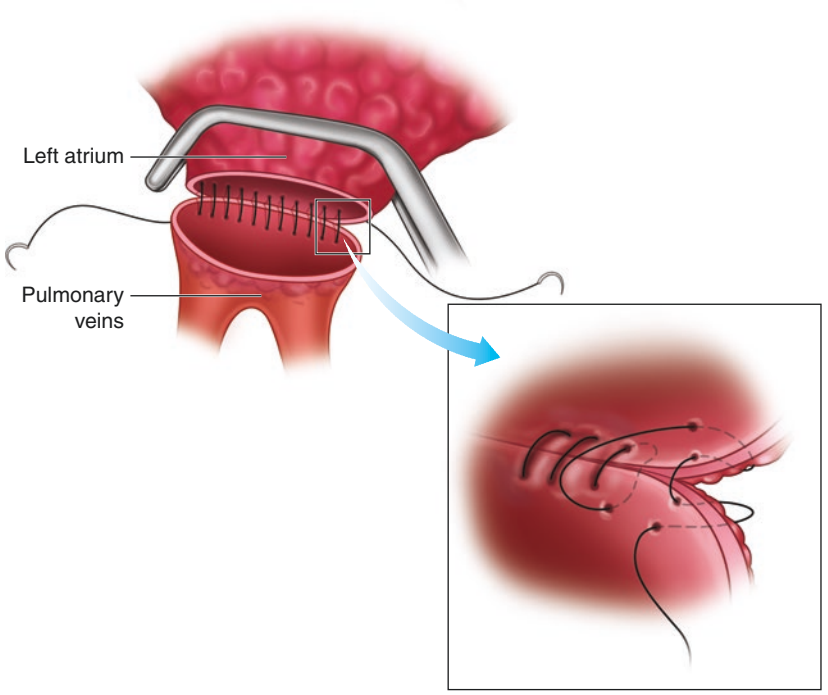


Fig. 2.6 Diagram shows the posterios wall of the left atrial anastomosis with everting sutures to ensure apposition of the endocardial layer with no protrusion of muscle or fat inside the left atrium

formation. The sutures are completed anteriorly and left untied with the left atrial clamp left in place.

Another Satinsky clamp is placed across the proximal right PA and the stump divided before the bifurcation of the upper lobe branch. Where there is significant size mismatch and the donor PA is much smaller, then the recipient PA is divided after the upper lobe branch. In either event, and given the greater compliance of the PA in comparison to the bronchus or left atrium, care must be taken to avoid leaving too much length particularly on the right PA that can result in an unacceptable kinking once blood flow is established. The PA is anastomosed with a continuous 5/0 Prolene suture and as with the left atrium, anastomotic torsion must be avoided. This suture is also left untied with the clamp on. Should there be concern about the lack of sufficient recipient PA or left atrial tissue to perform a safe anastomosis or there is a size mismatch that may not be resolved with circumferential plication, then being on CPB support allows the clamp/s to be removed altogether. This allows safe open anastomoses with a vent placed inside the left atrium and/or the recipient PA until the anastomosis is complete. An uncommon but recognised problem is that of inadequate donor left atrial tissue which typically results from poor division at the time of splitting the heart-lung block. In this situation, the adjacent donor pericardium can be usefully fashioned to circumferentially augment the size of the donor atrial cuff.

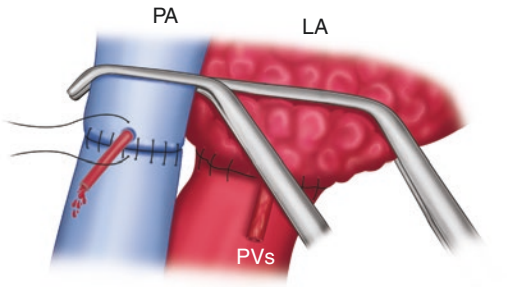


Fig. 2.7 De-airing of the pulmonary circulation with partial release of the left atrial clamp with retrograde flush out through the PA anastomosis. This is followed by partial release of the PA clamp and antegrade flush out from the LA anastomosis. In CPB cases, the heart is filled before partial unclamping of the LA clamp. In off-pump cases, it is imperative to release the PA clamp in a slow and controlled manner to avoid reperfusion injury

The final step is to ensure thorough de-airing of the donor pulmonary circulation and flushing out of any residual pneumoplegia. This is achieved by transient and partial release of the left atrial clamp thus allowing blood to flush out in a retrograde fashion from the PA suture line before tying down this anastomosis (Fig. 2.7). The PA clamp is then partially released in a similar fashion to allow the blood to flush out antegradely via the LA suture line before this too is tied down and both clamps then removed. Unlike the controlled reperfusion that can be achieved with cardiopulmonary bypass cases, it is imperative to prolong the gradual release of the PA clamp over 10–15 min in off-pump cases and to ensure that the anaesthetist is appropriately managing blood pressure to prevent over perfusion of the implanted donor lung. The same technique is used to explant the native left lung and implant the remaining donor lung. The only subtle difference is in the division of the left main bronchus. The left main bronchus is trimmed and pulled out with two temporary stay sutures placed at both membrano-cartilaginous junctions to facilitate the anastomosis. Once complete, the anastomosis will retract medially to lie just inside the hilar tissues and no extra tissue cover is required. Ventilation is recommenced and any air-leaks are secured at this stage. Intra-operative trans-oesophageal echocardiography is used routinely in our practice and this reveals inadequate de-airing of the left sided chambers then a root vent is placed. The cannulae are subsequently removed and the pericardium loosely tacked back together. Two fenestrated intercostal drains directed at the apex and the other basally are placed followed by careful attention to haemostatis. Excepting the anastomoses, the areas which often lead to unnecessary return to theatre for bleeding are the following: vessels in the inferior pulmonary ligament, small vessels in the hilar tissues and particularly associated with lymph node resection, sites of chest wall adhesion and the donor pericardial edge. The ribs are approximated with at least two figure-of-eight pericostal sutures with a check for any bleeding from the intercostal vessels before tying them down. Vicryl, ethylene or polydiaoxanone (PDS), are routinely used for the pericostal suture. A looped 1 PDS suture has the advantage of giving sufficient strength for costal approximation for up to 6 weeks and then permits some return of compliance at the intercostal space after complete resorption beyond

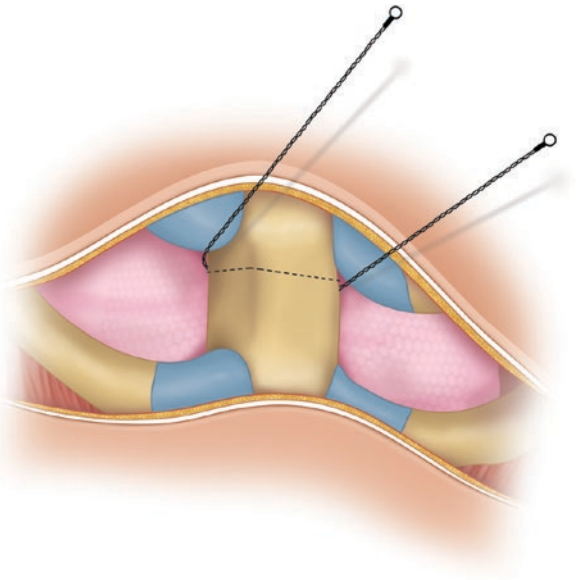


Fig. 2.8 The trans-sternal division with the Gigli saw is done obliquely to leave the posterior table longer and avoid post-operative over-ride of the superior sternum

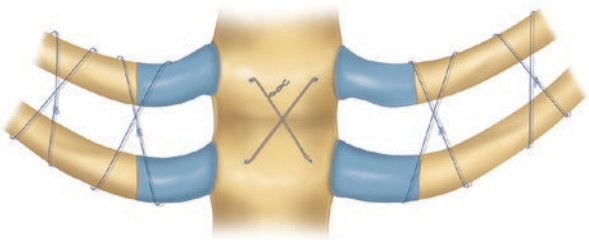


Fig. 2.9 Diagram illustrates the wire placements for closure of the clam-shell incision

6 months. This is followed by careful anatomical re-approximation of the muscle layers, an additional subcutaneous layer and completed with a final layer of continuous subcuticular suture.

If a full clam-shell incision is required, then this is done along the sub-mammary crease that is extended supero-medially to allow trans-sternotomy via the fourth or fifth intercostal space. The lateral extent of the incision does not have to go beyond the mid-axillary line. Although both internal mammary arteries require division between ties, this incision gives excellent exposure and permits easier institution of central CPB if required. The sternum is divided with a Gigli wire saw with a 45° antero-posterior bevel to prevent any subsequent over-riding of the superior sternum over the inferior part (Fig. 2.8). The remainder of the transplant operation is identical to that described above except for sternal closure. The sternum is brought together with a central figure-of-8 wire and the rib approximation is achieved with 2–3 figure-of-8 peri-costal sutures (Fig. 2.9).

Unacceptable lung function that usually manifests with high peak inspiratory pressures, poor arterial and mixed-venous saturations with requirement of high FiO_2, and obvious signs of pulmonary oedema despite lung protective anaesthetic

management, should prompt early ECMO rescue therapy [22, 23]. Depending on whether the cause is cardio-pulmonary or pulmonary alone, then appropriate veno-venous or veno-arterial configuration is instituted peripherally.

2.4.4 Single Lung Transplantation

A single lung transplant (SLT) requires intubation with a double-lumen endotracheal tube and surgery can be comfortably performed through a standard anterolateral approach via the fourth or fifth intercostal space as described above for BSLT except for a slight 30° upward tilt with the aid of a cushion or bean-bag (Fig. 2.10).

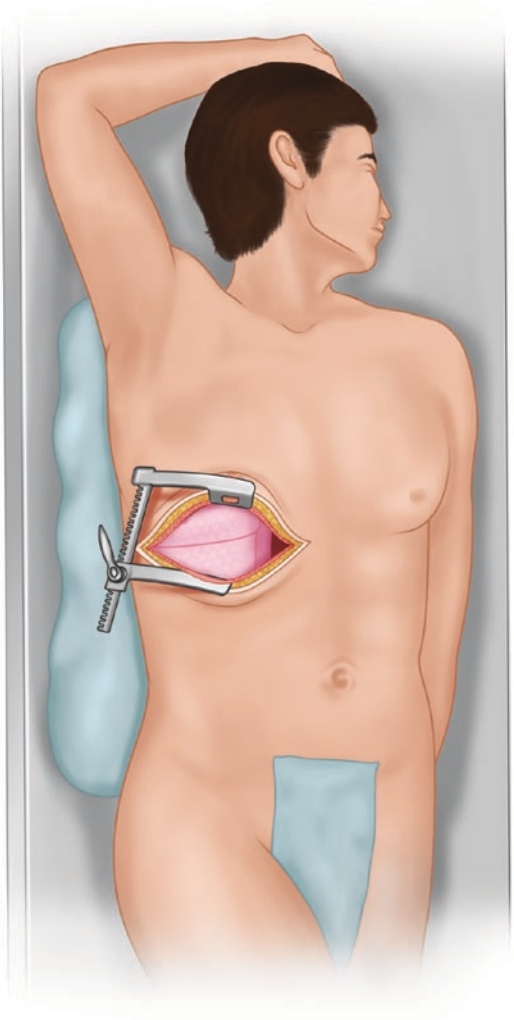


Fig. 2.10 Diagram illustrates patient positioning for single lung transplant with a slight raise (30°) on the operative side by a posterior cushion and leaving the groin clear for cannulation if required

The lower intercostal space is preferable for patients with a larger than predicted total lung capacity. The ipsilateral groin is also exposed in the infrequent event that cardio-pulmonary bypass is required from intolerance to single lung ventilation or in cases of significant pulmonary hypertension. The sequence of bronchial and vascular anastomosis remains as described above. As the majority of SLTs are done off-pump, it is imperative to control the reperfusion of the newly implanted lung with gradual release of the PA clamp over 10–15 min. Standard apical and basal drains are placed after achieving haemostasis and the chest closed as described above.

2.4.5 Heart-Lung Transplantation

The majority of heart—lung transplants (HLT) are performed in patients with Eisenmenger's Syndrome on the background of congenital heart disease and often, with multiple previous palliative procedures. These patients can be challenging due to cardio-pumonary adhesions and the presence of multiple large collateral vessels at the chest wall. In these cases, it is imperative to plan the recipient operation to allow sufficient time for the necessary dissection, excision of native heart-lung block and for achieving adequate haemostasis. Patients with significant pulmonary hypertension with irreversible right heart failure and others with cardiac pathologies that are not amenable to concomitant surgical management, such as coronary artery bypass and valve repair/replacement at the time of lung transplantation, may also be candidates for HLT. The practice of HLT for cystic fibrotic patients with subsequent domino heart donation has been long abandoned in favour of isolated DLT for this pathology.

The patient is positioned supine as for any major cardiac procedure with a standard median sternotomy. The pericardium is opened vertically in an inverted-T incision at the diaphragm. Both pleural cavities are opened widely and stay sutures placed on the pericardial edges. Majority of pleural adhesions, that are often highly vascular, should be divided with diathermy and surgical clips prior to systemic heparinization. CPB is established with bicaval cannulations with arterial return to the ascending aorta. After snaring the cavae and applying the aortic cross-clamp, a vent can be inserted directly into the LV for decompression thereby facilitating cardiac explant. The surgeon must at all times be vigilant in protecting the phrenic, the left recurrent laryngeal and vagal nerves.

The heart is explanted first in the standard manner (Fig. 2.11) starting with excision of the right atrial appendage (RAA) and carrying the incision anteriorly parallel to the right atrioventricular groove with extension directly into the coronary sinus and leaving a 1–2 cm margin from the inferior caval cannula. From the RAA, the incision is then carried into the roof of left atrium and extended along the atrial septum and ending to join the previous superior incision into the coronary sinus. The aorta is transected below the aortic cross-clamp leaving a 2 cm long cuff for subsequent anastomosis. The PA is transected at its bifurcation. The heart is retracted upwards and to the left so that the left atrial incision can be carried clockwise through the base of the left atrial appendage to above the left superior

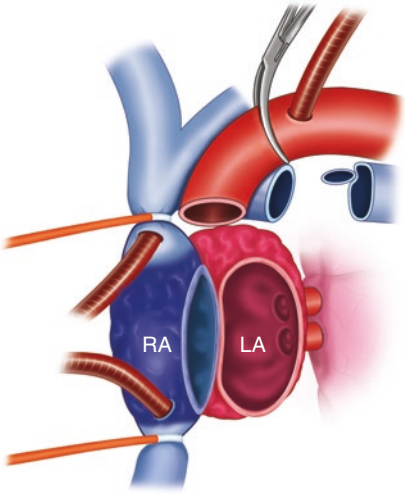


Fig. 2.11 Diagram illustrates the anatomy after cardiac explant. Note the small disc of left pulmonary artery tissue left intact to avoid damage to the recurrent laryngeal nerve. The stumps of both pulmonary arteries are just visible before subsequent removal of the lungs

pulmonary vein. The cardiectomy is completed by incising the remaining attachment along the left atrio-ventricular groove. Cranio-caudal pericardial incisions are made bilaterally at least 1 cm below the phrenic nerves over a distance enough to allow subsequent passages for the deflated lungs. The posterior wall of the left atrium is divided vertically to leave two separate LA cuffs that can be freed at the pericardial reflection and delivered into the chest cavity. On the right side, this requires dissecting the left atrial tissue from the inter-atrial septum. The main PA is divided at the carina and the right PA is freed and dissected laterally into the right chest cavity. In order to protect the left recurrent laryngeal nerve, a 1 cm disc of the left PA is left in-situ around an identifiable dimple from within the artery which marks the insertion point of the ligamentum arteriosum. Each lung is in-turn retracted up and medially to free any posterior adhesions and the pleural reflection up to the bronchi which are then stapled and transected just beyond the staple line before removing both lungs. The bronchial stumps are brought inside the pericardial space and gentle inferior traction lowers the tracheal carina which is partially opened transversely. This allows the placement of two traction sutures at the base of the cartilaginous rings to facilitate subsequent tracheal anastomosis before completing the tracheal transection. The soft tissues around the distal trachea must not be denuded so as to preserve the local blood supply. At this stage the right atrium is either removed entirely for a bi-caval anastomosis or just trimmed to allow bi-atrial connections. The chest wall and hilar tissues are examined thoroughly for haemostasis.

The prepared donor heart-lung block is lowered into the chest with the left lung being passed through the pericardial opening below the phrenic nerve. The right lung is either passed under the right atrial tissue or, in the case of a bi-caval anastomosis, it is passed through the previously made pericardial opening (Fig. 2.12). A continuous 3/0 Prolene suture is used for the tracheal anastomosis. The aorta is anastomosed next with placement of a vent on the ascending aorta before removal

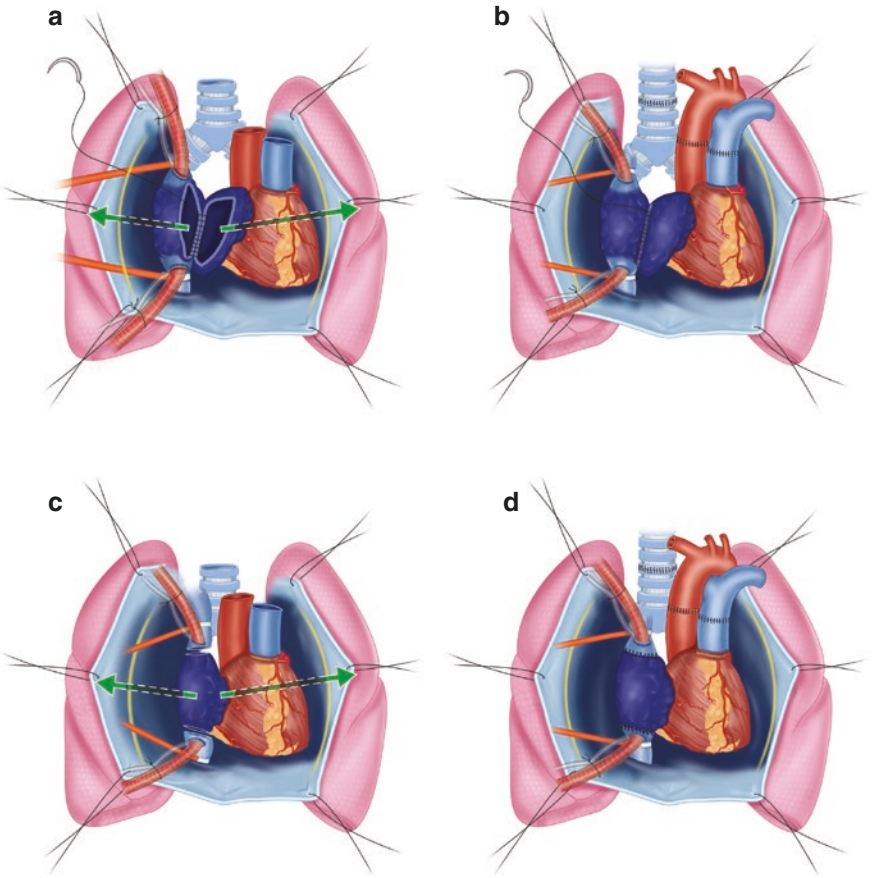


Fig. 2.12 The bi-atrial technique requiring passage of the right lung below the right atrium and through to the right pleural cavity is shown in (**a**) and the final result in (**b**). The bi-caval technique is demonstrated in figures (**c**) and (**d**)

of the cross-clamp. The right atrial or bi-caval anastomoses can be performed either before removal of the aortic cross-clamp, or safely on the reperfusing and/or beating donor heart. In this case a vent needs to be place into the mouth of the coronary sinus to limit the significant blood flow from it that can impair adequate visualization for completing the atrial or bi-caval anastomoses. Atrial and ventricular pacing wires are placed prior to inserting strategically directed fenestrated drains. One drain is placed in the inferior pericardial space and the other over the anterior surface of the heart. The apical pleural drain is inserted to course over the anterior aspect of the hilum and a basal drain pointed far down into the posterior cardio-phrenic angle. Unless the recipient has undergone previous cardiac procedure via a median sternotomy, it is possible to approximate the pericardial edges with a few tacking sutures. The sternum is then closed in routing fashion with interrupted wires.

2.5 Conclusion

Removal of an absolute recipient age barrier, the use of ever more marginal donor organs including those reconditioned with modern ECLP technology and improved post-operative management with good medium to long term survival has made lung and heart-lung transplantation more common and safer surgical therapies for patients with end-stage pulmonary or combined cardio-pulmonary pathology. Transplant volumes continue to rise with over 4000 cases performed annually in over 140 reporting centres for isolated lung transplantation and a 100 centres reporting HLT. DLT continues to be the most common form of lung replacement surgery with a decline in SLT from 37% to 27% over the past decade [1]. Despite these favourable statistics, there remains a significant shortfall of acceptable donor organs to serve the rising number of wait-listed patients. Rigorous adherence to donor management guidelines, novel bridge-to-transplant options, improved immune modulating therapies and increasing use of donor lung perfusion for both resuscitation and ex-situ therapies to promote better graft survival should all make the art of lung transplantation a more acceptable and widely adoptable therapy that currently remains unavailable in most regions of the world. As the number of lung programs grow to meet the rising demand from both primary recipients and those suitable for re-do lung transplantation, we need to address the significantly poor current conversion from multi-organ donation to subsequent lung retrieval. Increased utilisation of the marginal donor lung pool, particularly with lungs from DCD donors and increased but focused use of ECLP technology may significantly offset the marked discrepancy between supply and demand. Better utilisation of deceased donated organs will hopefully counter any desire to seek a wider adoption of living-related lobar transplantation. However in the absence of implantable and portable lung-replacement therapy, the latter may yet find a wider niche not only in jurisdictions and cultures where organ donation is not readily accepted, but also to mitigate against the unacceptable waitlist attrition of young patients with rapidly deteriorating end-stage pulmonary failure.

References

1. Chambers DC, Yusen RD, Cherikh WS, Goldfarb SB, Kucheryavaya AY, Khusch K, Levvey BJ, Lund LH, Meiser B, Rosanno JW, Stehlik J. The registry of the International Society for Heart and Lung Transplantation: thirty-fourth adult lung and heart-lung transplantation report – 2017. J Heart Lung Transplant. 2017;36(10):1047–59.
2. Starnes VA, Barr ML, Cohen RG, et al. Lobar transplantation: indications, technique and outcome. J Thorac Cardiovasc Surg. 1994;108:403–10.
3. Date H. Living-related lung transplantation. J Thorac Dis. 2017;9(9):3362–71.
4. Weill D, Benden C, Corris P, et al. A consensus document for the selection of lung transplant candidates: 2014 – an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2015;34(1):1–15.

5. Thabut G, Christie JD, Ravaud P, et al. Survival after bilateral versus single lung transplantation for patients with chronic obstructive pulmonary disease: a retrospective analysis of registry data. Lancet. 2008;371:744–51.
6. Kistler KD, Nalysnyk L, Rotella P, Esser D. Lung transplantation in idiopathic pulmonary fibrosis: a systematic review of the literature. BMC Pulm Med. 2014;14:139–50.
7. Meyer DM, Edwards LB, Torres F, Jessen ME, Novick RJ. Impact of recipient age and procedure type on survival after lung transplantation for pulmonary fibrosis. Ann Thorac Surg. 2005;79:950–7.
8. Kotloff RM, Blosser S, Fulda GJ, et al. Management of the potential organ donor in the ICU: Society of Critical Care Medicine/American College of Chest Physicians/Association of Organ Procurement Organizations Consensus Statement. Crit Care Med. 2015;43(6):1291–325.
9. Munshi L, Keshavjee S, Cypel M. Donor management and lung preservation for lung transplantation. Lancet Respir Med. 2013;1:318–28.
10. Courtwright A, Cantu E. Evaluation and management of the potential lung donor. Clin Chest Med. 2017;38:751–9.
11. Levin K, Kotecha S, Westall G, Snell G. How can we improve the quality of transplantable lungs? Expert Rev Respir Med. 2016;10(11):1155–61.
12. Levvey BJ, Harkess M, Hopkins P, et al. Excellent clinical outcomes from a national donation-after-determination-of-cardiac-death lung transplant collaborative. Am J Transplant. 2012;12(9):2406–13.
13. Cypel M, Levvey B, Van Raemdonck D, et al. International Society for Heart and Lung Transplantation donation after circulatory death registry report. J Heart Lung Transplant. 2015;34(10):1278–82.
14. Costa J, Shah L, Robbins H, et al. Use of lung allografts from donation after cardiac death donors: a single-Centre experience. Ann Thorac Surg. 2018;105:271–8.
15. Bates M, Factor M, Parrino PE, et al. Lung transplantation and the routine use of cardiopulmonary bypass and median sternotomy: experience at the Ochsner Multi-Organ Transplant Institute. Ochsner J. 2017;17:38–41.
16. Aigner C, Wisser W, Taghavi S, et al. Institutional experience with extracorporeal membrane oxygenation in lung transplantation. Eur J Cardiothorac Surg. 2007;31(3):46–473.
17. Machuca TN, Collaud S, Mercier O, et al. Outcomes of intraoperative extracorporeal membrane oxygenation versus cardiopulmonary bypass for lung transplantation. J Thorac Cardiovasc Surg. 2015;149(4):1152–7.
18. Cooper J, Pearson FG, Patterson GA. Technique of successful lung transplantation in humans. J Thorac Cardiovasc Surg. 1987;93:173–81.
19. Patterson GA, Cooper JD, Goldman B, Weisel RD, Pearson FG, Waters PF, Todd TR, Scully H, Goldberg M, Ginsberg RJ. Technique of successful clinical double lung transplantation. Ann Thorac Surg. 1988;45:626–33.
20. Venuta F, Van Raemodonck D. History of lung transplantation. J Thorac Dis. 2017;9(12):5458–71.
21. Taghavi S, Birsan T, Pereszlenyi A, et al. Bilateral lung transplantation via two sequential anterolateral thoracotomies. Eur J Cardiothorac Surg. 1999;15:658–62.
22. Wigfield CH, Lindsey JD, Steffens TG, et al. Early institution of extracorporeal membrane oxygenation for primary graft dysfunction after lung transplantation improves outcome. J Heart Lung Transplant. 2007;26(4):331–8.
23. Harting MG, Walczak R, Lin SS, Davis RD. Improved survival but marginal allograft function in patients treated with extracorporeal membrane oxygenation after lung transplantation. Ann Thorac Surg. 2012;93:366–71.

Chapter 3
Donation After Brain Death Versus Donation After Circulatory Death Donors in Lung Transplantation: Are They Different?

Gregory I. Snell and Bronwyn J. Levvey

3.1 Introduction

Successful lung transplantation (LTx) is facilitated by using quality donor lungs [1]. Historically, it has become evident that donor lungs can easily be damaged by pre-mortem disease states (eg smoking, asthma), the processes leading to death (eg trauma, drowning, aspiration), the processes of attempted medical resuscitation (eg fluid overload, ventilator-related pneumonia, atelectasis) and issues related to the actual surgical retrieval for transplant [2]. In particular, the latter includes lung ischaemia which is evident when the arterial/oxygenated blood supply to the donor lung is temporarily interrupted. This is clinically manifest as an acute lung inflammatory response known as ischemia-reperfusion injury, which occurs when the lung's arterial blood supply is reconnected to the new transplant recipient's circulation. These multidimensional processes place all LTx recipients at risk of significant morbidity and mortality from Primary Graft Dysfunction (PGD)- a clinical syndrome representing the sum of all these processes [3].

However, through a process of careful clinical evaluation, audit and evolution, it is has become increasing apparent that the lungs are actually more robust than first suspected- particularly in their tolerance of ischaemia. It is evident that the lung donor pool is not just limited to the traditional donation-after-brain death (DBD) donors with only brief ischaemic intervals (minutes) during retrieval process, but can now additionally safely include donation-after-circulatory death (DCD) donors, with protracted ischaemic intervals (up to hours) [4]. This chapter will contrast the main differences behind DBD and DCD donor LTx, while also acknowledging the essentially similar short and long-term outcomes.

G. I. Snell (✉) · B. J. Levvey
Lung Transplant Service, Alfred Hospital and Monash University, Alfred Hospital, Melbourne, VIC, Australia
e-mail: G.Snell@alfred.org.au

A. R. Glanville (ed.), *Essentials in Lung Transplantation*,
https://doi.org/10.1007/978-3-319-90933-2_3

3.2 The Key Features of DBD LTx

DBD donors have been the primary source of lung donors for the last 30 years. Brain death follows a severe brain insult which leads to brain swelling and raised intracranial pressure. Within the rigid confines of the skull, this raised pressure exceeds arterial pressure and actually completely stops intracranial blood flow and therefore the brain tissue's oxygen supply [5]. Irreversible loss of neurological function occurs subsequently (Table 3.1) and the patient can undergo a series of clinical and investigative tests to diagnose brain death. At this time the patient can be legally certified as deceased and thus can be considered as a potential organ donor (ie DBD) following consent being obtained from the next-of-kin (Fig. 3.1) [5, 6].

Despite the intensity of pre-retrieval physiological support, a hormonal storm related to acute brainstem compression can, at least temporarily, destabilise the donor. This cytokine inflammatory surge typically manifests as systemic hypertension and neurogenic pulmonary oedema, with resultant hypoxaemia [5]. Neurogenic pulmonary oedema can significantly compromise what was otherwise excellent donor lung function up to that point.

Table 3.1 Potential differences between donation after brain death and donation after circulatory death lung donors

	Donation after brain death	Donation after circulatory death
Current utilisation for transplant	Major source	Significant source
Potential to increase lung donor numbers further	Insignificant source	Major source
Consent for donation	After brain death certified	Before circulatory death occurs
Investigations needed from donor before death	Not usually required	May be required
Procedures needed on donor before death	Not required	May be required, eg bronchoscopy
Presence of brain death hormonal agonal 'storm'	Often	Rarely
Need to cease inotropes/ventilation before retrieval surgery	Never	Required
Likelihood of progression to become actual donor	95%	60–70%
Timing of lung retrieval	After brain death certified	After circulatory death certified
Potential for post-mortem pre-retrieval aspiration	Never	Rarely
Surgical technique	Standard	Standard
Duration of warm ischaemia	Short	Prolonged
Duration of cold ischaemia	Standard	Standard
Post- transplant management	Standard	Standard

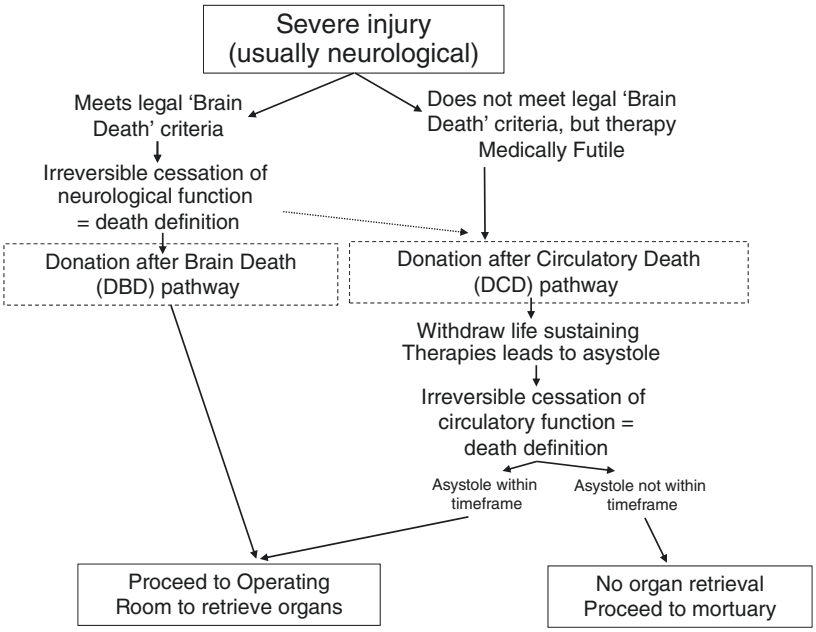


Fig. 3.1 A comparison of the donation after brain death and donation after circulatory death lung donation pathways. *OR* operating room

As the patient is now deceased, while remaining on ventilatory and circulatory support to ensure all organs remain perfused with oxygenated blood, it is possible to move the body carefully to the operating room to commence surgery to recover the donated lungs for the purposes of subsequent transplantation.

While the donor lung retrieval is underway, assisted ventilation (via a cuffed endotracheal tube) and maintenance of the circulation continues right up to the point of direct pulmonary arterial cold flush preservation of the lungs. The warm ischemic time in the DBD donor is defined as the time from pulmonary arterial cross-clamping by the surgeon, to attainment of a graft temperature of less than 10 °C via the pulmonary arterial flush, and is generally quite short (less than 15 min).

3.3 The Key Features of DCD LTx

DCD donors have really only been recognised as a novel yet significant source of transplantable lungs in the last 10 years [4, 7]. The concept of a definition of death based on irreversible loss of the circulation is one well understood by the general public and legal system. Indeed, the general community incorrectly believes most donors have died via just such a process, rather than appreciating that brain death is the most common donation pathway.

Table 3.2 Traditionally recognised categories of donation after circulatory death donors [8]

1. Death outside hospital
2. Unsuccessful resuscitation in hospital
3. Awaiting cardiac arrest after planned withdrawal of life-sustaining therapies
4. Awaiting cardiac arrest in known brain dead donor

Although there are a number of mechanisms by which lungs might theoretically be able to be recovered when the circulation ceases (Table 3.2), in the Australian context efforts have focussed on the so called Category 3 situation [4, 8]. Here, typically following a major neurological injury, careful medical assessment by several independent medical specialists confirms the medical futility of further life-sustaining therapy and withdrawal of such therapy is planned (Fig. 3.1). With the removal of these therapies (usually assisted ventilation and circulation supporting inotropes), the patient goes on to cardiac asystole. Death can then be legally confirmed, certified and the donation process and organ retrieval can proceed can proceed shortly thereafter. In contrast to the DBD donation scenario, consent for organ donation in the DCD pathway is sought from the donor next-of-kin before death, but only after the futility and withdrawal decisions have been made and discussed.

Rarely, the Category 4 (Table 3.2) situation arises [4, 8]. Typically this is where a family agree with the concept of lung donation, but not with the concept of brain death. In this circumstance, the DCD pathway can provide an acceptable alternative means of organ donation for them. In both cases the transplant team is not involved with decision making regarding the potential donor.

The timing of asystole following withdrawal of life-sustaining therapies is unpredictable. This is problematic as an operating room and surgical team need to be immediately available to facilitate the surgical retrieval of the donor lungs, noting in the DCD pathway that the warm ischemic time will always be significantly longer than in the DBD setting [9]. The warm ischaemic time in the DCD donor is most practically defined as the time from when the donor's systemic blood pressure falls below 50 mmHg to attainment of a graft temperature of less than 10 °C via the pulmonary arterial flush, and is generally around 45 min.

A prolonged warm ischaemic time has historically been considered by many to place the allograft at risk of severe PGD- with its known adverse short and long-term consequences [3]. From a practical point-of-view, and to minimise potential ischaemic lung damage, Australian lung transplant programs currently wait a maximum of 90 min from therapy withdrawal for asystole to occur (Fig. 3.1) [4]. If asystole occurs in this timeframe lungs are retrieved for transplantation, if not the transplant process is called off.

3.4 The Utility and Outcomes of DBD versus DCD LTx in Australia

The Australian and New Zealand Cardiothoracic Transplant Registry (ANZCOTR) officially records Australia's LTx activity [10]. From Fig. 3.2 it can be observed that DCD LTx numbers have steadily increased since 2006, while DBD numbers have

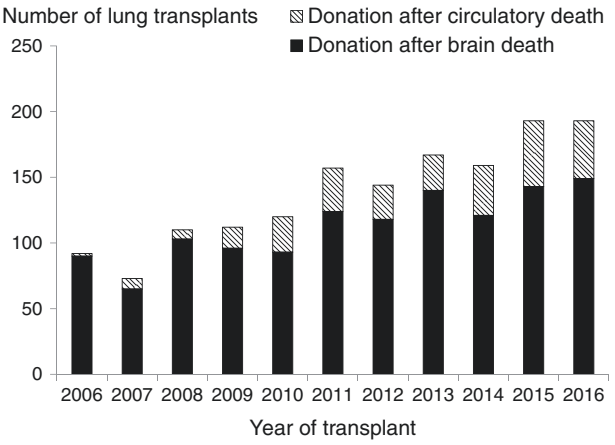


Fig. 3.2 Overall Australian experience in donation after brain death and donation after circulatory death lung donor lung transplants [23]

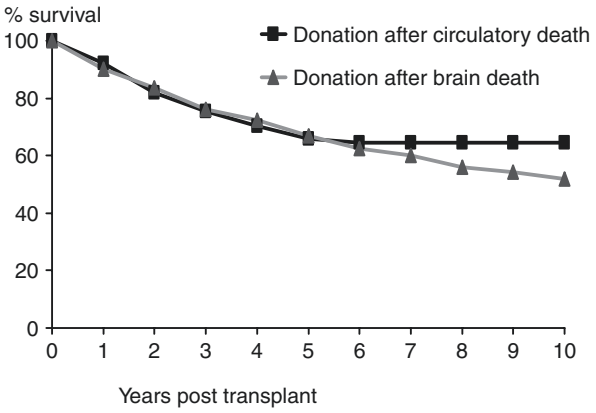


Fig. 3.3 A comparison of donation after brain death and donation after circulatory death lung donor lung transplant survival post-transplant-2006–2016 [10]

increased from 2009. Notably, in 2009 the Federal Government injected significant funds which have been successfully directed to facilitate increased numbers of DCD and DBD lung donors.

In parallel, an Australian National DCD LTx Collaborative was created in 2009 by Australia's 4 LTx programs to standardise DCD protocols, definitions and reporting [4]. The results of the Collaborative were first published in 2012, representing the largest and most successful record of DCD transplants up until this time. Short and long-term outcomes (including survival) were noted in this report to be essentially identical. The most recent ANZCOTR registry 2006–2016 data confirm this view (Fig. 3.3) [10].

Despite the previously noted concerns about the longer warm ischaemic times of DCD compared to DBD LTx [9], adverse long- term outcomes have simply not been seen [11]. The Collaborative has specifically analysed DCD ischaemic times versus survival and it is clear the 'standard' 90 min timeframe for standing down a team is definitely not the true clinical limit of warm ischaemic time [12]. Other Australian reports also note that DCD lungs are safe in high risk recipient situations, for example where pulmonary arterial hypertension is the disease indicating LTx [13] and for paediatric patients requiring LTx [14].

3.5 Potential for Increasing DBD LTx Donor Numbers

Australian audits of potential DBD LTx donors suggest relatively few unrecognised situations where additional quality donors are currently being missed although an updated analysis might prove informative [15, 16]. There are some gains to be made however by pushing age limits, using virally infected donors (particularly hepatitis C) or functionally 'extended' donor lungs [1]. In 3 of 4 Australian LTx programs, the use of ex-vivo perfusion (EVLP), where lungs can be perfused and ventilated for 6 hours outside the donor's body [17], does provide a vehicle to assess and potentially improve these extended lungs.

It is notable that some of the gains in DBD LTx numbers 2006–2016 (Fig. 3.2), have been achieved via donors being assessed through the DCD pathway and found unexpectedly to be progressing to brain death, and therefore manageable via the DBD pathway [18]. This makes little difference to the lung allograft, but this does facilitate significantly more heart and liver donors for transplantation.

3.6 Potential for Increasing DCD LTx Donor Numbers

In contrast to DBD LTx, a recent Australian audit of potential DCD LTx donors suggest a large pool of currently unrecognised Type 3 donors [19]. This pool included quality and extended lungs. In many cases the DCD pathway was simply not thought of when only the potential donor lungs, and no other organs, were suitable for transplantation.

DCD organs for transplantation are not just available from the current Category 3 situation (Table 3.2) we routinely consider in Australia. Rather there are other situations that could be considered and these are detailed in Table 3.3 [1, 20]. Indeed, DCD LTx can be undertaken utilising donors whose history is known and

Table 3.3 Sub-categorisation and modifications to the traditional categories of donation after circulatory death donors [1, 20]

1	(a) Death outside hospital, no witness
	(b) Death outside hospital, witnessed and attempted resuscitation
2	(a) Unsuccessful resuscitation in the intensive care unit, emergency room or operating room
	(b) Unsuccessful resuscitation in a hospital ward
3	(a) Awaiting cardiac arrest after planned withdrawal of life-sustaining therapies in the intensive care unit, emergency room or operating room
	(b) Awaiting cardiac arrest after planned withdrawal of life-sustaining therapies in a hospital ward
	(c) Spontaneous cardiac arrest occurring before planned withdrawal of life-sustaining therapies
4	(a) Spontaneous cardiac arrest in planned brain dead donor
	(b) Awaiting cardiac arrest in known brain dead donor
5	Medically assisted death (i.e. Euthanasia, assisted dying)

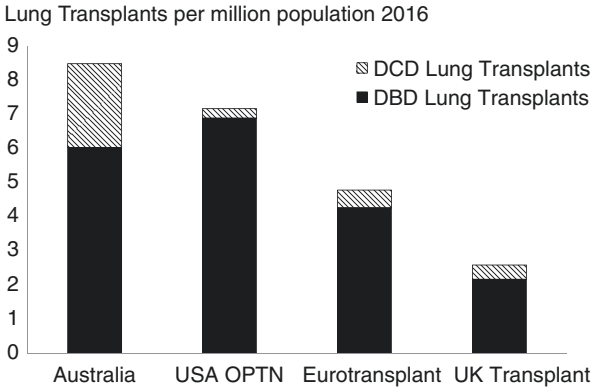


Fig. 3.4 Australian lung transplant experience [23] versus the United States of America OPTN (Organ Procurement and Transplantation Network) [21], Eurotransplant [24] and United Kingdom transplant registries [25] experience in 2016

who have an expected or even unexpected cardiac arrest in hospital. The use of the ward Medical Emergency Treatment (MET) call team and tight protocols are required to facilitate these approaches. EVLP may additionally provide a DCD lung assessment tool [17].

As noted above, the routine consideration of Category 3 DCD lungs for transplantation has made a significant contribution to Australian LTx numbers. This success has seen Australian LTx programs, via their involvement in the Australian National DCD Collaborative and the International Society for Heart and Lung Transplant DCD Registry, make a major impact on world DCD LTx numbers and strategies. Figure 3.4 shows these Australian successes, setting up a potential target for other national donor/transplant systems. The USA, in particular, is using just 10% of the DCD donor pool we do in Australia, despite their 500% higher waiting list mortality rate [21]. Adoption of Australia's proven approaches to DCD LTx can, and should, be able to be translated to very large numbers of DCD LTx worldwide [7, 22].

3.7 Conclusion

DCD lung donors are a realistic source of quality lungs for LTx. There are ethical, logistic and efficiency differences, but the outcomes are excellent and at least comparable to those of traditional DBD LTx. We need to continue to learn from our DCD experience applying lessons learnt to enhance the number and quality of all forms of lung donation. Australian LTx programs have much to contribute to global experience.

References

1. Snell GI, Paraskeva M, Westall GP. Donor selection and management. Semin Respir Crit Care Med. 2013;34(3):361–70.
2. Snell GI, Westall GP, Oto T. Donor risk prediction: how 'extended' is safe? Curr Opin Organ Transplant. 2013;18(5):507–12.

3. Snell G, Weill D, Strueber M, Garrity E, Reed A, et al. Report of the ISHLT Working Group on PGD: part 1, definition and grading; a 2017 Consensus Group statement. J Heart Lung Transplant. 2017;36:1097–103.
4. Levvey BJ, Harkess M, Hopkins P, Chambers D, Merry C, Glanville AR, et al. Excellent clinical outcomes from a national donation-after-determination-of-cardiac-death lung transplant collaborative. Am J Transplant. 2012;12(9):2406–13.
5. Australian and New Zealand Intensive Care Society. Death and organ donation. http://www.anzics.com.au/Pages/DaOD.aspx (2013).
6. National Council of Commissioners of Uniform State Laws. Uniform Determination of Death Act. http://pntb.org/wordpress/wp-content/uploads/Uniform-Determination-of-Death-1980_5c.pdf (1980).
7. Cypel M, Levvey B, Van Raemdonck D, Erasmus M, Dark J, Love R, et al. International Society for Heart and Lung Transplantation donation after circulatory death registry report. J Heart Lung Transplant. 2015;34(10):1278–82.
8. Kootstra G, Daemen JH, Oomen AP. Categories of non-heart-beating donors. Transplant Proc. 1995;27(5):2893–4.
9. Levvey BJ, Westall GP, Kotsimbos T, Williams TJ, Snell GI. Definitions of warm ischemic time when using controlled donation after cardiac death lung donors. Transplantation. 2008;86(12):1702–6.
10. Australian and New Zealand Cardiothoracic Transplant Registry. 2016 report. http://www.anzcotr.org.au/. Accessed 29 Dec 2018.
11. Reeb J, Keshavjee S, Cypel M. Successful lung transplantation from a donation after cardiocirculatory death donor taking more than 120 minutes to cardiac arrest after withdrawal of life support therapies. J Heart Lung Transplant. 2016;35(2):258–9.
12. Levvey B, Harkness M, Chambers D, Lawrence S, Musk M, Hopkins P, et al. Warm ischemic time (WIT) measurements do not correlate with early lung allograft function: analysis from the Australian donation after circulatory death (DCD) lung transplant (LTx) collaborative. J Heart Lung Transplant. 2016;35(4):S88.
13. Levvey BJ, Whitford HM, Williams TJ, Westall GP, Paraskeva M, Manterfield C, et al. Donation after circulatory determination of death lung transplantation for pulmonary arterial hypertension: passing the toughest test. Am J Transplant. 2015;15(12):3208–14.
14. Snell G, Levvey BJ, Paraskeva M, Whitford H, Williams T, Hobson J, et al. Controlled DCD donors and pediatric lung transplant: enhanced opportunities and excellent outcomes. J Heart Lung Transplant. 2016;35(4):S34–5.
15. Opdam HI, Silvester W. Potential for organ donation in Victoria: an audit of hospital deaths. Med J Aust. 2006;185(5):250–4.
16. Opdam H. Intensive care solely to facilitate organ donation-new challenges. Transplantation. 2017;101(8):1746–7.
17. Cypel M, Keshavjee S. Extracorporeal lung perfusion (ex-vivo lung perfusion). Curr Opin Organ Transplant. 2016;21(3):329–35.
18. Coulson TG, Pilcher DV, Graham SM, Snell GI, Levvey BJ, Philpot S, et al. Single-centre experience of donation after cardiac death. Med J Aust. 2012;197(3):166–9.
19. Rakhra S, Gladkis L, Arcia B, Fink M, Kanellis J, MacDonald P, et al. Untapped potential for donation after circulatory death in Australian hospitals. Med J Aust. 2017;207:294–301.
20. Detry O, Le Dinh H, Noterdaeme T, De Roover A, Honore P, Squifflet JP, et al. Categories of donation after cardiocirculatory death. Transplant Proc. 2012;44(5):1189–95.
21. Valapour M, Lehr C, Skeans M, Smith J, Carrico J, Uccellini K, et al. OPTN/SRTR 2016 annual data report: lung. Am J Transplant. 2017;18(Suppl 1):363–433.
22. Cypel M, Levvey B, Van Raemdonck D, Erasmus M, Dark J, Mason D, et al. Lung transplantation using controlled donation after circulatory death donors: trials and tribulations. J Heart Lung Transplant. 2016;35(1):146–7.
23. http://www.anzdata.org.au/anzod/v1/report_2017.html. Accessed 29 Jan 18.
24. Eurotransplant International Foundation. Annual report 2016. https://www.eurotransplant.org/cms/index.php?page=annual_reports.
25. UK Transplant. 2016 annual report. https://www.odt.nhs.uk/statistics-and-reports/annual-activity-report.

Chapter 4
ECMO and EVLP

Andreas Fiene

4.1 Introduction

Extracorporeal membrane oxygenation (ECMO) was made possible due to the introduction of membrane oxygenation during open heart surgery in the 1950s by John Gibbon. Initially such support was restricted to intra-operative use during heart operations. Earlier treatment attempts for patients with severe respiratory disease in an intensive care unit (ICU) setting carried a very high mortality and were deemed unsuccessful [1]. Technical advances and increased experience from the use of cardiac bypass machines during surgery allowed the reintroduction of the concept of ECMO for critically ill patients with respiratory failure. More recently the H1N1 flu epidemic in 2009 saw an increased use of ECMO circuits in ICUs worldwide, with a global gain in expertise. The Extracorporeal Life Support Organization (ELSO) was founded thereafter and has created internationally accepted treatment guidelines [2]. The use of ECMO for lung transplant candidates and recipients has become a routine part of the therapeutic options.

4.2 Circulatory Set Up of ECMO Support

ECMO provides maintenance of oxygen and carbon dioxide gas exchange in the case of cardio-respiratory failure. A centrifugal pump transports blood via cannulae and tubing to an external membrane oxygenator and heat exchanger and then returns it to the body.

A. Fiene
Lung Transplant Queensland, The Prince Charles Hospital, Brisbane, QLD, Australia
e-mail: Andreas.Fiene@health.qld.gov.au

A. R. Glanville (ed.), *Essentials in Lung Transplantation*,
https://doi.org/10.1007/978-3-319-90933-2_4

Different types of ECMO circuits exist: A venous-venous (VV) or venous-arterial circuit (VA) will be chosen based on the patient's pathophysiological needs. Each of these set-ups has its own risks and benefits, which will need to be carefully considered.

The VV ECMO circuit membrane is in series with the patient's lungs. Both the organ and the artificial membrane contribute towards gas exchange. The blood is drawn from the superior vena cava or inferior vena cava to the artificial membrane and returned to the right atrium. The rate of the gas exchange is in large part dependent on the patient's cardiac output. Therefore this type of support is only suitable for patients with respiratory but not cardiovascular failure. VV ECMO is the most commonly used mode with patients who suffer from respiratory failure.

Central VA ECMO requires direct placement of a cannula into the right atrium and a second cannula into the aorta. Sterile surgical approach in theatre is required to set up VA ECMO. Central VA ECMO is most commonly used in lung transplant recipients to treat cardio-respiratory shock during the transplant operation. It may be used as a planned upgrade from other ineffective forms of ECMO. The circuit of peripheral VA ECMO delivers oxygenated blood to the aorta via the femoral artery in retrograde fashion. The potential haemodynamic complications as a result of this include: separate perfusion of the lower and upper part of the body (watershed phenomenon), and distention of the left ventricle, and resulting pulmonary oedema due to increased afterload produced by ECMO. The latter requires close monitoring and careful adjustment of the flows, peripheral vascular resistance, vasopressor support and oxygenation. More advanced configuration of peripheral VA-ECMO employing three cannulas can be used to optimize cardiorespiratory support and deal with the aforementioned problems.

4.3 Indications for VV ECMO

This chapter will focus on VV ECMO, as it is the most common type of ECMO therapy in lung transplant candidates and recipients.

General indications for the use of VV ECMO include: reversible hypoxic respiratory failure when the risk of mortality is 80% or greater and reversible CO_2 retention on mechanical ventilation despite maximal safe ventilation.

ELSO guidelines suggest to consider the use of ECMO when the ratio of PaO_2 to FiO_2 is <150. ECMO is indicated when the ratio is <80. A $PaCO_2$ >80 mmHg or end-inspiratory plateau pressure >30 cm H_2O are also considered to be indications for ECMO in patients with ARDS.

Patients listed for lung transplantation may undergo VV ECMO therapy as a bridge to lung transplantation [3]. In such cases the patient's overall clinical state and the problems of urgent organ allocation need to be considered: An older, frail patient with worsening pulmonary fibrosis would in most institutions not be treated

with ECMO therapy as a bridge to transplant. Individual centres differ in their approach and advanced age alone is not a universally accepted contraindication. Younger patients with catastrophic respiratory failure due to cystic fibrosis or ARDS are more likely to be placed on ECMO therapy as bridge to transplantation. It is not uncommon that a transplant centre is asked to consider a patient for lung transplantation who is already on ECMO therapy at time of the referral. This poses a significant challenge, as the usually thorough assessment process needs to be performed in a very short time and in most cases with a patient who is deeply sedated and unable to give a history. To prevent this, a proposed strategy could be that Lung Transplant Units are consulted about all patients being placed on VV ECMO for respiratory failure so that a decision can be made about their candidacy for potential bridge to lung transplantation early.

The specific indications for a lung transplant recipient in the postoperative period for VV ECMO therapy include: treatment of primary graft dysfunction, bronchopulmonary fistulas, Sepsis, anastomotic dehiscence and severe air leak. These conditions are regarded as potentially reversible. In many cases of primary graft dysfunction, VV ECMO therapy is started in theatre when the transplanted lungs fail to achieve sufficient oxygen and carbon dioxide exchange. Whilst the patient is treated with VV ECMO therapy, the treating physicians can address the causes of primary graft dysfunction, allow the lungs to recover and if required, further operative management can be safely planned.

4.4 Complications of VV ECMO Therapy

With its invasive nature, ECMO has a vast array of complications, affecting almost every organ system. Generally VV ECMO is better tolerated than VA ECMO. The complications of ECMO therapy can be divided into 2 groups: Those caused by the condition requiring ECMO therapy or as a result of the ECMO therapy.

Bleeding is the most common complication. The blood loss may occur because of surgical trauma due to cannula placement, surgery or as a complication of the essential anticoagulation, haemolysis, or thrombocytopenia. Pulmonary bleeding is a common complication and may require repeated bronchoscopy and washouts.

Thrombus formation in the extracorporeal circuit is rare and more significant in VA ECMO compared to VV ECMO, as thrombus may enter the systemic circulation.

Neurological complications due to intracranial haemorrhage, focal infarction and generalized brain oedema may occur. Renal failure and oliguria may require additional support with dialysis, which then further complicates systemic blood pressure and fluid management. Gastrointestinal complications include malnutrition, bleeding and ileus.

The risk of sepsis due to the presence of a large intravascular foreign body plays a particularly important role in the immunosuppressed lung transplant recipient. As the ECMO circuit temperature is actively regulated, the patient's body temperature is not an indicator of sepsis and regular blood culture samples are part of an ECMO management protocol. The ECMO circuit may influence the serum concentration of medications due to the altered volume of distribution. Drugs may be absorbed by the inner surface lining of cannula and tubing. Monitoring of therapeutic drug levels is often required and drugs with a narrow therapeutic range may need to be avoided [4]. Mechanical failure may occur in the key components of the ECMO circuit such as the pump or the oxygenator.

The significant pathophysiological consequences of deep sedation and inability to participate in physiotherapy often result in severe loss of muscle bulk and the emergence of non-respiratory organ involvement. The period during which an ECMO dependent patient can be safely transplanted is therefore limited and a daily review of the patient's likelihood to successfully undergo lung transplantation needs to be performed [5]. Patients on ECMO therapy as a bridge to lung transplantation are regarded as most urgent and this is reflected in the relevant national lung allocation system.

In selected centres there has been growing expertise in providing ECMO support to patients who are awake whilst receiving ECMO therapy. Such patients can participate in rehabilitation and have a longer period during which they may be successfully transplanted. Case reports of patients who were successfully transplanted after a very long period of ECMO support are published [6].

4.5 Outcome of VV ECMO Use for Respiratory Failure

The ELSO statistical data demonstrate that in 2017 more than 13,000 ECMO runs were performed in registered centres. Adults with respiratory failure receiving VV ECMO therapy have a survival rate of 66% (Tables 4.1, 4.2, and 4.3).

The mortality risk for patients who receive ECMO therapy as bridge to lung transplantation is reported to be as high as 50% [7]. This high mortality risk signifies the importance of appropriate patient selection prior to commencing ECMO therapy, in particular in lung transplant recipients (Fig. 4.1).

Table 4.1 General indication for VV ECMO therapy

Reversible respiratory failure with a mortality of higher than 80%
Reversible CO_2 retention on mechanical ventilator support
Pulmonary contusion
Pulmonary haemorrhage
Airway obstruction

Table 4.2 Indications for VV ECMO therapy for lung transplant recipients

Pre-transplant:
Bridge to lung transplantation
Post-transplant:
Hyperacute rejection
Anastomotic dehiscence
Bronchopulmonary fistula
Primary graft dysfunction (PGD)
Sepsis

Table 4.3 Contraindications for VV ECMO therapy

Unsupportable cardiac failure/cardiac arrest
Treatment resistant pulmonary hypertension, in a non-transplant candidate
Irreversible respiratory failure, in a non-transplant candidate
Chronic lung allograft dysfunction in a transplant recipient
Irreversible CNS comorbidities
Terminal malignancy

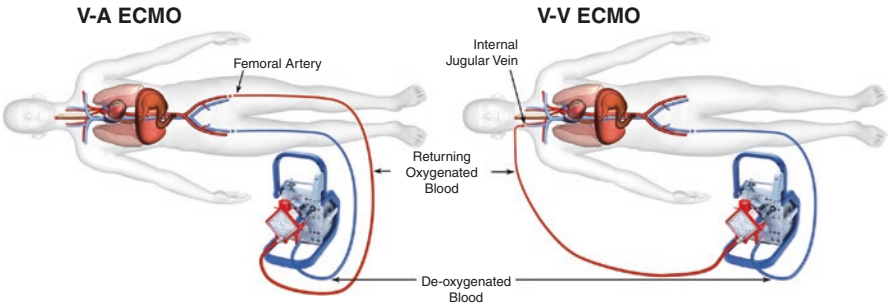


Fig. 4.1 Comparison of cannula placement of V-A versus V-V ECMO

4.6 Ex-Vivo Lung Perfusion

4.6.1 Introduction

The initial assessment of a potential donor lung is based on a combination of clinical donor information, blood gas measurements and imaging results. The final decision to accept donor organs is made during the retrieval operation and surgical inspection. Donor lungs are typically transported in a static hypothermic environment after the retrieval. In the past, a functional assessment of the organ could not be performed prior to implantation. Many potentially suitable organs have not been used due to the uncertainty about marginal results in the organ assessment. Such marginal results may have been due to reversible causes such as fluid overload or

tolerable levels of aspiration. Up to 40% of such lungs which have been rejected due to marginal criteria were in a research setting later found to be useable for transplantation [8]. The demand for donor organs greatly exceeds the availability of donor lungs and therefor the identification of suitable organs with reversible dysfunction will lead to an increase in donor numbers.

Ex-vivo lung perfusion allows functional assessment prior to implantation and potentially treatment of reversible complications.

This highly sophisticated method of assessing donor lungs is based on the pioneering work of Professor Stig Steen, Sweden, who in the 1990s published conceptual data. The same group published the first case of successful transplantation of a donor lung which was rejected during the initial donor assessment in 2006 [9]. EVLP systems have become commercially available and numerous institutions world-wide have now published short and long term outcome data.

The choice of perfusate is a current topic of research:

"Steen solution" contains human serum albumin to provide normal oncotic pressure as well as an electrolyte solution which resembles extracellular fluid. This solution has been found to be protective against pulmonary oedema. In addition, "Steen solution" contains dextran which is a mild oxygen scavenger which coats and protects endothelium from subsequent excessive leucocyte interaction and thrombogenesis. "Steen solution" itself is acellular. Adding donor blood to the "Steen solution" creates a cellular perfusate which contains red blood cells as oxygen carriers [10]. The cellular solution may more closely mimic physiological conditions, but it has not been shown that either approach is superior.

Different institutions use either an open left atrium or a closed left atrium during the EVLP: Closing the left atrium with a funnel shaped device when connecting the cannulas creates a positive left atrial pressure which consequently is thought to be protective to the donor lung. It has been shown that the closed left atrium approach may lead to a lower pulmonary vascular resistance and less pulmonary oedema compared to an open atrium approach [11]. Neither of the anatomical approaches has yet been accepted as international standard.

4.6.2 Assessment of Marginal Donor Lungs

The decision to perform further testing on an ex-vivo set-up may be based on:

- A donor blood gas oxygen level below the local accepted minimum. (In our institution a level below 300 mmHg on a FiO_2 of 100% and a PEEP of 5.)
- High ventilator pressure requirements, without clinical or radiological explanation and otherwise acceptable donor organs.
- Marginal changes on chest imaging, which require further inspection, exceeding what could be assessed in a routine transplant retrieval operation. Typical examples are minor structural lung changes or changes suggestive of infection.

- Lungs from older donors with an expected long ischemic time.
- To allow for prolonged explant operation.

Following donor lung retrieval and transportation back to the recipient hospital in the usual fashion the lungs are placed in the EVLP machine. The ex-vivo lung perfusion requires a sterile approach in the operating theatre, with a perfusionist, surgeon, transplant physician and anaesthetist being essential members of the team. The EVLP setup consists of a sterile chamber with connection to a mechanical ventilator and gas mixture. The perfusate is pumped through closed circuit cannulas, via an external heater into the pulmonary artery. A monitor displays temperature and pressure measurements from probes which are placed into the airway and pulmonary artery. Different types of ex-vivo lung perfusion set-ups exist, but the principle of the assessment process is identical. The local protocol determines the type of perfusate (cellular vs acellular), height of the target temperature, target ventilation, FiO2 used and if the left atrium remains closed during the assessment [12]. The lungs are slowly warmed to body temperature and then perfused and ventilated. Oxygenation, airway pressure and lung compliance get regularly monitored. Repeated CXR images allow monitoring the progress of radiological changes. Therapeutic intervention such as recruitment manoeuvres on the ventilator, bronchoscopic removal of secretions and administration of antibiotics can be performed during the evaluation process.

In our institution we aim for a perfusion period of no more than 4 h. In the experimental setting, it has been demonstrated that lungs which have been on the EVLP setup for as long as 12 h are physiologically functional. The repeated monitoring of PaO_2, pulmonary vascular resistance, pulmonary compliance and peak inspiratory pressure guide the final decision regarding whether the organs are suitable for transplantation. Once the decision to use the lungs has been made, the lungs are cooled, ventilation and perfusion are ceased and the lungs are stored in a hypothermic environment in an inflated state (Fig. 4.2).

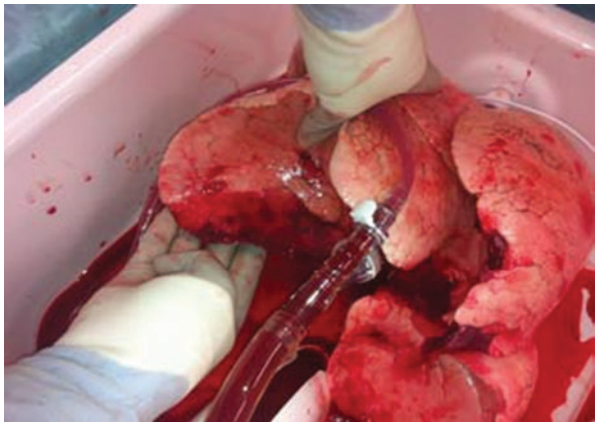


Fig. 4.2 Donor lungs on EVLP setup

4.6.3 Outcome

Several institutions have now published their EVLP outcome data. There is a demonstrated net increase in transplantation overall as a consequence of EVLP use. The world wide data demonstrate that short term complications such as primary graft dysfunction [13], functional parameters such as the FEV_1 and long term freedom from chronic lung allograft dysfunction do not significantly differ between lungs that underwent EVLP prior to transplantation and those which did not [14].

These are encouraging findings, justifying the use of these expensive resources for donor organ assessment.

References

1. Zapol WM, et al. Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study. JAMA. 1979;242(20):2193–6.
2. Extracorporeal Life Support Organization. ELSO guidelines for cardiopulmonary extracorporeal life support. 2017.
3. Tsiouris A, Budev MM, Yun JJ. Extracorporeal membrane oxygenation as a bridge to lung transplantation in the United States: a multicenter survey. ASAIO J. 2017.
4. Hahn J, Choi JH, Chang MJ. Pharmacokinetic changes of antibiotic, antiviral, antituberculosis and antifungal agents during extracorporeal membrane oxygenation in critically ill adult patients. J Clin Pharm Ther. 2017;42(6):661–71.
5. Abrams D, Brodie D, Arcasoy SM. Extracorporeal life support in lung transplantation. Clin Chest Med. 2017;38(4):655–66.
6. Langer T, et al. "Awake" extracorporeal membrane oxygenation (ECMO): pathophysiology, technical considerations, and clinical pioneering. Crit Care. 2016;20:150.
7. Chiumello D, et al. Extracorporeal life support as bridge to lung transplantation: a systematic review. Crit Care. 2015;19:19.
8. Van Raemdonck D, et al. Lung donor selection and management. Proc Am Thorac Soc. 2009;6(1):28–38.
9. Steen S, et al. First human transplantation of a nonacceptable donor lung after reconditioning ex vivo. Ann Thorac Surg. 2007;83(6):2191–4.
10. Loor G, et al. Prolonged EVLP using OCS lung: cellular and acellular perfusates. Transplantation. 2017;101(10):2303–11.
11. Linacre V, et al. Importance of left atrial pressure during ex vivo lung perfusion. J Heart Lung Transplant. 2016;35(6):808–14.
12. Courtwright A, Cantu E. Evaluation and management of the potential lung donor. Clin Chest Med. 2017;38(4):751–9.
13. Cypel M, et al. Normothermic ex vivo lung perfusion in clinical lung transplantation. N Engl J Med. 2011;364(15):1431–40.
14. Tikkanen JM, et al. Functional outcomes and quality of life after normothermic ex vivo lung perfusion lung transplantation. J Heart Lung Transplant. 2015;34(4):547–56.

Chapter 5
Immunosuppression: Have We Learnt Anything

Miranda Paraskeva

Abbreviations

ACR	Acute rejection/acute cellular rejection
ATG	Anti-thymocyte globulin
BOS	Bronchiolitis obliterans syndrome
C0	Trough drug level
C2	Drug level taken 2 h post dose
CLAD	Chronic allograft dysfunction
CNI	Calcineurin inhibitor
FEV_1	Forced expiratory volume in 1 s
IL-2	Interleukin 2
ISHLT	International Society for Heart and Lung Transplantation
MHC	Major histocompatibility complex
MMF	Mycophenolate mofetil
mTOR	Mammalian target of rapamycin
SD	Standard deviation
TDM	Therapeutic drug monitoring
UNOS	United Network for Organ Sharing

5.1 Introduction

Despite early surgical successes, it was the development of effective immunosuppressive drugs that heralded the advent of successful solid organ transplantation (SOT). The discovery of cyclosporine in 1976 revolutionised transplant outcomes [1],

M. Paraskeva
Department of Respiratory Medicine, Alfred Hospital, Melbourne, VIC, Australia
e-mail: M.Paraskeva@alfred.org.au

A. R. Glanville (ed.), *Essentials in Lung Transplantation*,
https://doi.org/10.1007/978-3-319-90933-2_5

progressing lung transplantation from a surgical possibility to a viable therapeutic option in end-stage lung disease.

5.2 The Immune System and the Lung Allograft

All cells of the body possess unique surface proteins which identify them as "self". These self-markers or antigens are coded for by the human leukocyte antigen (HLA) complex. HLA antigens are found on the cell surface and allow the host immune system to differentiate between self and non-self (foreign) peptides (Fig. 5.1).

The immune system is designed to defend the host against foreign invaders (e.g. bacteria, fungi, viruses), therefore the recognition of non-self peptides stimulates the activation of immune cells leading to the destruction of any foreign antigen. This is of benefit in fighting infection however, in transplantation the host immune system sees the allograft (lung transplant) as foreign leading to immune activation that if uncontrolled leads to destruction of the transplanted organ (rejection). The success of lung transplantation therefore depends on our ability to pharmacologically manipulate the immune system, preventing immune activation and thereby rejection.

Control of this immune response is dependent on the use of immunosuppressive drugs. There are a variety of drug classes and types, many of which are used in combination to maximise immunosuppressive action whilst minimising side effects (Tables 5.1 and 5.2).

In general, the pharmacological management of lung transplant recipients changes with time from transplantation. Therapy in the perioperative and early post-transplant period aims to prevent the risk of early immune responses whilst in the long-term regimens are influenced by the rejection and infection profile of the individual. Regimens are broadly divided into:

1. Induction phase.
2. Maintenance phase.

Fig. 5.1 Immune recognition of self and non-self antigens

Table 5.1 Induction agents

Drug	Description and mechanism of action	Toxicities and comments	Administration and monitoring
Basiliximab	Monoclonal antibody that binds to IL-2 receptor subunit CD25, selectively blocking activated T-cells	Well tolerated Rarely causes gastrointestinal disturbances or hypersensitivity reactions	No monitoring Given pre-implantation to up to a number of hours after transplant
Anti-thymocyte globulin (ATG)	Rabbit or equine derived polyclonal antibody. Acts by targeting T-cell surface antigens and leading indirectly to cytotoxic T-cell depletion through complement and cell mediated antibody related cell lysis	Commonly results in an acute reaction at time of initial administration due to cytokine release syndrome (fevers, rigors, myalgias and rash) Other toxicities: Leukopenia, thrombocytopenia, immune complex glomerulonephritis and serum sickness	Monitoring of CD3 levels can be used to minimise toxicities if multiple doses to be given. Aim for level of 50–100 cells/μL
Alemtuzumab	Monoclonal antibody against the CD52 receptor present on the surface of T-cells, B-cells, macrophages, monocytes and NK cells. Leads to T-cell depletion, depressing CD4 and CD8 cells for up to 3 years	Mild cytokine release syndrome, anaemia, neutropenia, autoimmune thrombocytopenia	No therapeutic drug monitoring required

Table 5.2 Maintenance immunosuppression

Drug	Description and mechanism of action	Toxicities and comments	Administration and monitoring
Calcineurin inhibitors			
Tacrolimus	Macrolide antibiotic which inhibits T-cell activation and IL-2 production by binding to the immunophillin FK506 binding protein leading to inactivation of calcineurin Is 10–100 times more potent in inhibiting T-cell activation than cyclosporine	Nephrotoxicity, hypertension, hyperlipidaemia, diabetes mellitus, haemolytic uraemic syndrome, neurotoxicity (tremor, posterior reversible encephalopathy syndrome) Similar to cyclosporine but with different distribution, more commonly causes new onset diabetes mellitus Metabolised by CYP3A4 system: Many drug-drug interactions	Multiple preparations including: Intravenous, sublingual and prolonged release Narrow therapeutic window, requires therapeutic drug monitoring with trough levels (C0)

(continued)

Table 5.2 (continued)

Drug	Description and mechanism of action	Toxicities and comments	Administration and monitoring
Cyclosporine	Fungal polypeptide which forms complexes with the intracytoplasmic protein, cytophillin, leading to inhibition of calcineurin and preventing T-cell activation	Nephrotoxicity, hypertension, hyperlipidaemia, diabetes mellitus, haemolytic uraemic syndrome, neurotoxicity (tremor, posterior reversible encephalopathy syndrome) Metabolised by CYP3A4 system: Many drug-drug interactions	Highly lipophilic, needs bile acids for absorption leading to high intra- and inter- patient variability Patients with cystic fibrosis and pancreatic insufficiency may require larger, more frequent dosing to achieve therapeutic levels Monitored with trough (C0) and/or 2-h post level (C2). C2 correlates better with systemic exposure
Anti-metabolites/cell-cell cycle inhibitors			
Azathioprine	Prodrug for 6-mercaptopurine which suppresses de novo purine synthesis inhibiting T and B cell proliferation	Bone marrow suppression (in particular leukopenia), macrocytosis, hepatotoxicity Allopurinol co-administration significantly increases toxicities and should be avoided	No therapeutic drug monitoring required, monitor for bone marrow and hepato- toxicities Part metabolised by thiopurine methyltransferase (TPMT). TPMT genetic polymorphism leading to decreased enzyme activity and increasing the likelihood of myelosuppression is present in 10% of people. TPMT genotyping can be used to predict risk
Mycophenolate mofetil (MMF)	MMF is a pro-drug which converts to its active compound mycophenolic acid Inhibits inosine monophosphate dehydrogenate, the rate limiting step of de novo purine synthesis inhibiting T- and B-cell proliferation	Myelosuppression (in particular leukopenia) Gastrointestinal symptoms (nausea, vomiting, diarrhoea)	No therapeutic drug monitoring required, monitor for bone marrow toxicities

5.3 Current Practices

There are few lung transplant specific randomised control trials. Regimens currently in use have been informed by evidence extrapolated from other SOT groups, retrospective series and expert consensus. This has led to variations in protocols between

centres, a diversity of practice reflected in the International Society for Heart and Lung Transplantation (ISHLT) Registry data [2].

5.4 The Induction Phase

Immune activation is highest in the first six-months following transplant with an initial robust predominantly T-cell response that targets the allograft making this period the time of highest risk for the development of acute cellular rejection (ACR). The aim of induction therapy is to interrupt this robust T-cell response by using additional immunosuppression in an attempt to reduce the incidence of ACR and thereby the longer-term consequences of the development of chronic lung allograft dysfunction (CLAD) and in particular bronchiolitis obliterans syndrome (BOS). Induction therapy is also used for those recipients at high risk of renal insufficiency at the time of transplant, allowing delay in the introduction of nephrotoxic calcineurin inhibitors (CNI) and time for renal recovery.

5.4.1 Types of Induction Agents and Their Use

The use of induction agents was initially encouraged by evidence in other SOT groups showing a reduction in ACR and improvement in longer term outcomes [3–5]. Lung transplant specific data from the ISHLT Registry has suggested the use of induction leads to improved outcomes with a reduced incidence of BOS [2]. This has been supported by a number of studies utilising United Network for Organ Sharing (UNOS) registry data which demonstrated improved survival and lower rejection rates [6, 7]. Despite this, other case series and randomised control trials [8–10] have not confirmed these results and it remains unclear whether induction has a definitive role in lung transplant management.

Of the lung transplants reported to the ISHLT registry between January 2005 and June 2016, 60% received an induction agent, with the majority (80%) receiving an IL-2 blocker. Over the last decade the use of IL-2 blockers has steadily increased with reduction in the use of lymphocyte depleting agents and relatively stable use of alemtuzumab [2].

The most commonly used IL-2 receptor antagonist is basiliximab (Table 5.1). ISHLT and UNOS Registry data have suggested its use leads to improved survival and reduced ACR [6, 11]. However, other studies have produced conflicting results with some showing benefits associated with its use [7, 12] and others showing none [13].

Lymphocyte depleting agents are antibodies that bind to T-cell surface antigens leading to profound and long-lasting depletion of cytotoxic T-cells. The polyclonal antithymocyte globulin (ATG) and the monoclonal antibody alemtuzumab are included in this class of induction agents. Whilst alemtuzumab is in use internationally, it is not routinely used in an Australian setting (Table 5.1).

ATG is produced by immunising horses or rabbits with human lymphoid cells. It has been studied in a number of randomised control trials comparing its use to no induction. These trials did not show a significant reduction in ACR, graft loss or death in the medium (1-year) [8] or long-term [14, 15].

The lack of definitive evidence of the benefits of induction or the superiority of one agent over another has led to the variability of practice from centre to centre and the fact that only 60% of lung transplant recipients receive induction treatment.

5.5 The Maintenance Phase

Compared to other SOTs, lung transplant recipients are at a higher risk of rejection and require greater amounts of immunosuppression. This is likely related to the unique features of the lung allograft including: its exposure to the outside environment and exogenous antigens, the large number of donor derived dendritic cells and the proinflammatory state that can occur secondary to brain death all of which can lead to immune activation.

Typically, maintenance immunosuppression involves a three-drug combination. The use of multiple drug classes which target different pathways of T-cell activation is thought to provide more effective immunosuppression whilst minimising side-effects by allowing lower target levels to be aimed for.

5.5.1 Calcineurin Inhibitors

CNIs (tacrolimus and cyclosporine) remain the lynchpin of lung transplant management with ISHLT Registry data showing that they are invariably used as part of a regimen that includes corticosteroids and an anti-metabolite (mycophenolate mofetil or azathioprine) (Table 5.2). Calcineurin is an essential part of the pathway required in T-cell activation and IL-2 production, these drugs work via different mechanisms to inhibit calcineurin and prevent this process occurring.

There are limited studies comparing tacrolimus to cyclosporine in lung transplantation and the superiority of one over another has not been confirmed. ISHLT registry data shows that the incidence of ACR in the first year following transplant is lowest in tacrolimus-based regimens and highest in cyclosporine-based regimens [11]. Whilst some studies have supported this suggesting fewer ACR episodes [16, 17] and lower rates of BOS [16, 18] others have not [18]. Of note there has been no evidence of a survival advantage with the use of tacrolimus [16, 18, 19]. Despite this more than 80% of lung transplant recipients internationally are now prescribed a tacrolimus-based regimen [2] with the use of cyclosporine decreasing over the last decade.

Both cyclosporine and tacrolimus have narrow therapeutic windows and require close therapeutic drug monitoring (TDM). Cyclosporine is monitored using trough (C0) and 2-h post levels (C2). Although C0 is more convenient to measure, studies

have shown that C2 better reflects the systemic exposure [20] associated with its use. Tacrolimus however, is monitored using trough levels (C0) with no evidence for post-dose measurement.

Both tacrolimus and cyclosporine are metabolised by the CYP3A4 pathway and levels are influenced by many drug-drug interactions, in particular azole antifungals, which have been reported to increase immunosuppressant levels by up to 4 times [21]. Their toxicity profile is similar, both have the potential to cause significant nephrotoxicity but tacrolimus more likely to lead to new onset diabetes mellitus and cyclosporine more likely to cause systemic hypertension.

5.5.2 The Cell Cycle Inhibitors

One of the cell cycle inhibitors (azathioprine or mycophenolate (MMF)) tends to be utilised in conjunction with a calcineurin inhibitor and corticosteroid in the majority of lung transplant recipients (Table 5.2). Whilst large prospective randomised control studies in other SOT groups suggests a superiority of MMF over azathioprine in terms of ACR rates and survival [22, 23], similar studies in lung transplantation have not confirmed this [24–28]. Non-randomised data from the ISHLT Registry has previously suggested that the highest rates of ACR occur in those recipients prescribed a combination of azathioprine and cyclosporine [11] suggesting that the advantage of MMF over azathioprine may be related to the CNI used. Despite a lack of evidence of its superiority, the use of MMF continues to increase with more than 80% of lung transplant recipients at 12-months being prescribed a regimen that includes MMF [2].

5.5.3 Mammalian Target of Rapamycin (mTOR) Inhibitors

The mammalian target of rapamycin (mTOR) is blocked by both everolimus and sirolimus leading to inhibition of T-cell proliferation (Table 5.2).

Everolimus is a derivative of sirolimus and has an improved toxicity profile and better bioavailability. It has been shown to be effective in other SOT [29–31] however its use in lung transplantation remains informed by few trials which have examined its use in conjunction with a CNI [14, 30, 32]. The results of these studies have suggested greater lung function preservation [30] and reduction in the incidence of BOS [32] with the use of everolimus, as well as a reduction ACR [14, 30, 32] and cytomegalovirus infection [14]. Of note, the use of an everolimus based regimen has been associated with early treatment withdrawl in the majority of trials due to side effects and no benefit in terms of survival [14, 30, 32].

mTOR inhibitors impair fibroblast proliferation and their use has been associated with impairment of wound healing and bronchial anastomotic dehiscence [33]. As a result, their use has tended to be avoided in the early post-transplant period, with increasing use as time after transplant progresses [11].

5.5.3.1 The Use of mTOR Inhibitors in Special Situations

Prolonged CNI exposure often leads to nephrotoxicity. There is evidence in other SOT that replacing the CNI with an mTOR inhibitor improves creatinine clearance [34, 35]. Small studies in lung transplantation have shown the introduction of mTORs has resulted in significant improvement in renal function without changes in acute rejection rates [36] or significant changes in FEV1 [37, 38]. However, there is limited evidence to support the long-term use of CNI-free regimens. In regimens that utilise both CNI and mTOR inhibitor, renal function has tended to decline [14, 30, 32].

Intracellular viruses such as CMV, rely on a cellular protein synthesis pathway to support genomic replication and viral synthesis and it is believed that mTOR inhibitors interrupt this pathway. An increasing body of evidence suggests that mTOR inhibitor use is associated with a decreased incidence of CMV disease [39–41]. Whilst this is not sufficient to generalise advice, in the presence of persistent or recurrent CMV infection the use of an mTOR inhibitor should at least be considered.

There is also a potential role for mTORs in the management of recurrent non-melanomatous skin cancers with a number of small studies in renal transplant showing that switch from a CNI to an mTOR reduces the risk of skin cancers possibly due to its antitumor effect [42–44].

5.5.4 The Use of Azithromycin

Azithromycin has been extensively assessed in the treatment and prevention of BOS. Its effect is likely due to a combination of its immunomodulatory effects in addition to its antibacterial and antiviral actions. Evidence from a number of studies suggests that azithromycin attenuates inflammatory responses and can lead to improvements in FEV_1 and BOS incidence [45–47]. Whilst it is uncertain as to the optimal time to institute therapy, it appears to be most successful when commenced early [46].

5.6 Therapeutic Drug Monitoring and Adherence

Whilst there have been no significant changes in the availability of immunosuppressive drugs and no new drug classes discovered in recent times, our understanding of therapeutic drug monitoring and the impact of adherence on transplant outcomes has evolved.

With the capacity to measure CNI levels in particular, evidence in a number of SOT groups has shown that variability in these immunosuppressive levels is associ-

ated with higher rates of ACR and graft loss [48–50]. Whilst variability in immunosuppressive levels can be attributed to non-adherence, it is also likely to be influenced by intercurrent illness, associated medications and poor absorption. But irrespective of the cause, emerging evidence suggests that variability in levels predicts poor outcomes.

The most common way to measure variability is through standard deviation of tacrolimus. The use of the tacrolimus standard deviation to assess for variability has been associated with late rejection in liver transplant recipients [50]. In lung transplant recipients similar findings were found with the risk for ACR increasing by 23% for each 1 unit increase in SD [51].

Variability of CNI levels has also been used to compare different drug formulations. Comparison of the standard twice daily and once-daily extended release formulations of tacrolimus have shown 50% less variance with the extended release formulation [52].

5.7 Conclusion

Immunosuppression remains the cornerstone of transplantation management. Whilst the holy grail of effective immunosuppression, with few or no side effects or the induction of tolerance has yet to be attained we have made inroads into the management of transplant recipients with effective control of the immune system. Hopefully the future will bring greater understanding of the immune system and thereby more effective ways to control it.

References

1. Borel JF, Feurer C, Gubler HU, Stahelin H. Biological effects of cyclosporin A: a new antilymphocytic agent. Agents Actions. 1976;6:468–75.
2. Chambers DC, Yusen RD, Cherikh WS, Goldfarb SB, Kucheryavaya AY, Khusch K, Levvey BJ, Lund LH, Meiser B, Rossano JW, Stehlik J, International Society for Heart and Lung Transplantation. The registry of the International Society for Heart and Lung Transplantation: thirty-fourth adult lung and heart-lung transplantation report-2017; focus theme: allograft ischemic time. J Heart Lung Transplant. 2017;36:1047–59.
3. Mehra MR, Zucker MJ, Wagoner L, Michler R, Boehmer J, Kovarik J, Vasquez A. A multicenter, prospective, randomized, double-blind trial of basiliximab in heart transplantation. J Heart Lung Transplant. 2005;24:1297–304.
4. Szczech LA, Berlin JA, Aradhye S, Grossman RA, Feldman HI. Effect of anti-lymphocyte induction therapy on renal allograft survival: a meta-analysis. J Am Soc Nephrol. 1997;8:1771–7.
5. Vincenti F, Kirkman R, Light S, Bumgardner G, Pescovitz M, Halloran P, Neylan J, Wilkinson A, Ekberg H, Gaston R, Backman L, Burdick J. Interleukin-2-receptor blockade with daclizumab to prevent acute rejection in renal transplantation. Daclizumab Triple Therapy Study Group. N Engl J Med. 1998;338:161–5.

6. Whitson BA, Lehman A, Wehr A, Hayes D Jr, Kirkby S, Pope-Harman A, Kilic A, Higgins RS. To induce or not to induce: a 21st century evaluation of lung transplant immunosuppression's effect on survival. Clin Transpl. 2014;28:450–61.
7. Furuya Y, Jayarajan SN, Taghavi S, Cordova FC, Patel N, Shiose A, Leotta E, Criner GJ, Guy TS, Wheatley GH, Kaiser LR, Toyoda Y. The impact of alemtuzumab and basiliximab induction on patient survival and time to bronchiolitis obliterans syndrome in double lung transplantation recipients. Am J Transplant. 2016;16:2334–41.
8. Snell GI, Westall GP, Levvey BJ, Jaksch P, Keshavjee S, Hoopes CW, Ahya V, Mehta A, Trulock EP 3rd. A randomized, double-blind, placebo-controlled, multicenter study of rabbit ATG in the prophylaxis of acute rejection in lung transplantation. Am J Transplant. 2014;14:1191–8.
9. Hartwig MG, Snyder LD, Appel JZ 3rd, Cantu E 3rd, Lin SS, Palmer SM, Davis RD. Rabbit anti-thymocyte globulin induction therapy does not prolong survival after lung transplantation. J Heart Lung Transplant. 2008;27:547–53.
10. Palmer SM, Miralles AP, Lawrence CM, Gaynor JW, Davis RD, Tapson VF. Rabbit antithymocyte globulin decreases acute rejection after lung transplantation: results of a randomized, prospective study. Chest. 1999;116:127–33.
11. Christie JD, Edwards LB, Kucheryavaya AY, Benden C, Dipchand AI, Dobbels F, Kirk R, Rahmel AO, Stehlik J, Hertz MI. The registry of the International Society for Heart and Lung Transplantation: 29th adult lung and heart-lung transplant report-2012. J Heart Lung Transplant. 2012;31:1073–86.
12. Swarup R, Allenspach LL, Nemeh HW, Stagner LD, Betensley AD. Timing of basiliximab induction and development of acute rejection in lung transplant patients. J Heart Lung Transplant. 2011;30:1228–35.
13. Hachem RR, Chakinala MM, Yusen RD, Lynch JP, Aloush AA, Patterson GA, Trulock EP. A comparison of basiliximab and anti-thymocyte globulin as induction agents after lung transplantation. J Heart Lung Transplant. 2005;24:1320–6.
14. Glanville AR, Aboyoun C, Klepetko W, Reichenspurner H, Treede H, Verschuuren EA, Boehler A, Benden C, Hopkins P, Corris PA, European and Australian Investigators in Lung Transplantation. Three-year results of an investigator-driven multicenter, international, randomized open-label de novo trial to prevent BOS after lung transplantation. J Heart Lung Transplant. 2015;34:16–25.
15. Appel JZ 3rd, Hartwig MG, Davis RD, Reinsmoen NL. Utility of peritransplant and rescue intravenous immunoglobulin and extracorporeal immunoadsorption in lung transplant recipients sensitized to HLA antigens. Hum Immunol. 2005;66:378–86.
16. Keenan RJ, Konishi H, Kawai A, Paradis IL, Nunley DR, Iacono AT, Hardesty RL, Weyant RJ, Griffith BP. Clinical trial of tacrolimus versus cyclosporine in lung transplantation. Ann Thorac Surg. 1995;60:580–84; discussion 584-585.
17. Treede H, Klepetko W, Reichenspurner H, Zuckermann A, Meiser B, Birsan T, Wisser W, Reichert B. Tacrolimus versus cyclosporine after lung transplantation: a prospective, open, randomized two-center trial comparing two different immunosuppressive protocols. J Heart Lung Transplant. 2001;20:511–7.
18. Treede H, Glanville AR, Klepetko W, Aboyoun C, Vettorazzi E, Lama R, Bravo C, Knoop C, Aubert JD, Reichenspurner H. Tacrolimus and cyclosporine have differential effects on the risk of development of bronchiolitis obliterans syndrome: results of a prospective, randomized international trial in lung transplantation. J Heart Lung Transplant. 2012;31:797–804.
19. Penninga L, Penninga EI, Moller CH, Iversen M, Steinbruchel DA, Gluud C. Tacrolimus versus cyclosporin as primary immunosuppression for lung transplant recipients. Cochrane Database Syst Rev. 2013;5:CD008817. https://doi.org/10.1002/14651858.CD008817.pub2.
20. Glanville AR, Aboyoun CL, Morton JM, Plit M, Malouf MA. Cyclosporine C2 target levels and acute cellular rejection after lung transplantation. J Heart Lung Transplant. 2006;25:928–34.
21. Capone D, Tarantino G, Gentile A, Sabbatini M, Polichetti G, Santangelo M, Nappi R, Ciotola A, D'Alessandro V, Renda A, Basile V, Federico S. Effects of voriconazole on tacrolimus metabolism in a kidney transplant recipient. J Clin Pharm Ther. 2010;35:121–4.
22. Halloran P, Mathew T, Tomlanovich S, Groth C, Hooftman L, Barker C. Mycophenolate mofetil in renal allograft recipients: a pooled efficacy analysis of three randomized, double-

blind, clinical studies in prevention of rejection. The International Mycophenolate Mofetil Renal Transplant Study Groups. Transplantation. 1997;63:39–47.
23. Kobashigawa J, Miller L, Renlund D, Mentzer R, Alderman E, Bourge R, Costanzo M, Eisen H, Dureau G, Ratkovec R, Hummel M, Ipe D, Johnson J, Keogh A, Mamelok R, Mancini D, Smart F, Valantine H. A randomized active-controlled trial of mycophenolate mofetil in heart transplant recipients. Mycophenolate Mofetil Investigators. Transplantation. 1998;66:507–15.
24. Glanville AR, Corris PA, McNeil KD, Wahlers T. Mycophenolate mofetil (MMF) vs azathioprine (AZA) in lung transplantation for the prevention of bronchiolitis obliterans syndrome (BOS): results of a 3 year international randomised trial. J Heart Lung Transplant. 2003;22:S207.
25. O'Hair DP, Cantu E, McGregor C, Jorgensen B, Gerow-Smith R, Galantowicz ME, Schulman LL. Preliminary experience with mycophenolate mofetil used after lung transplantation. J Heart Lung Transplant. 1998;17:864–8.
26. Palmer SM, Baz MA, Sanders L, Miralles AP, Lawrence CM, Rea JB, Zander DS, Edwards LJ, Staples ED, Tapson VF, Davis RD. Results of a randomized, prospective, multicenter trial of mycophenolate mofetil versus azathioprine in the prevention of acute lung allograft rejection. Transplantation. 2001;71:1772–6.
27. Ross DJ, Waters PF, Levine M, Kramer M, Ruzevich S, Kass RM. Mycophenolate mofetil versus azathioprine immunosuppressive regimens after lung transplantation: preliminary experience. J Heart Lung Transplant. 1998;17:768–74.
28. Zuckermann A, Birsan T, Thaghavi S, Artemiou O, Kupilik N, Dekan G, Wolner E, Klepetko W. Mycophenolate mofetil in lung transplantation. Transplant Proc. 1998;30:1514–6.
29. Dantal J, Berthoux F, Moal MC, Rostaing L, Legendre C, Genin R, Toupance O, Moulin B, Merville P, Rerolle JP, Bayle F, Westeel PF, Glotz D, Kossari N, Lefrancois N, Charpentier B, Quere S, Di Giambattista F, Cassuto E. Efficacy and safety of de novo or early everolimus with low cyclosporine in deceased-donor kidney transplant recipients at specified risk of delayed graft function: 12-month results of a randomized, multicenter trial. Transpl Int. 2010;23:1084–93.
30. Snell GI, Valentine VG, Vitulo P, Glanville AR, McGiffin DC, Loyd JE, Roman A, Aris R, Sole A, Hmissi A, Pirron U. Everolimus versus azathioprine in maintenance lung transplant recipients: an international, randomized, double-blind clinical trial. Am J Transplant. 2006;6:169–77.
31. Vigano M, Tuzcu M, Benza R, Boissonnat P, Haverich A, Hill J, Laufer G, Love R, Parameshwar J, Pulpon LA, Renlund D, Abeywickrama K, Cretin N, Starling RC, Eisen HJ. Prevention of acute rejection and allograft vasculopathy by everolimus in cardiac transplants recipients: a 24-month analysis. J Heart Lung Transplant. 2007;26:584–92.
32. Strueber M, Warnecke G, Fuge J, Simon AR, Zhang R, Welte T, Haverich A, Gottlieb J. Everolimus versus mycophenolate mofetil de novo after lung transplantation: a prospective, randomized, open-label trial. Am J Transplant. 2016;16:3171–80.
33. King-Biggs MB, Dunitz JM, Park SJ, Kay Savik S, Hertz MI. Airway anastomotic dehiscence associated with use of sirolimus immediately after lung transplantation. Transplantation. 2003;75:1437–43.
34. Hunt J, Lerman M, Magee MJ, Dewey TM, Herbert M, Mack MJ. Improvement of renal dysfunction by conversion from calcineurin inhibitors to sirolimus after heart transplantation. J Heart Lung Transplant. 2005;24:1863–7.
35. Mulay AV, Cockfield S, Stryker R, Fergusson D, Knoll GA. Conversion from calcineurin inhibitors to sirolimus for chronic renal allograft dysfunction: a systematic review of the evidence. Transplantation. 2006;82:1153–62.
36. Gullestad L, Iversen M, Mortensen SA, Eiskjaer H, Riise GC, Mared L, Bjortuft O, Ekmehag B, Jansson K, Simonsen S, Gude E, Rundqvist B, Fagertun HE, Solbu D, Bergh CH. Everolimus with reduced calcineurin inhibitor in thoracic transplant recipients with renal dysfunction: a multicenter, randomized trial. Transplantation. 2010;89:864–72.
37. Villanueva J, Boukhamseen A, Bhorade SM. Successful use in lung transplantation of an immunosuppressive regimen aimed at reducing target blood levels of sirolimus and tacrolimus. J Heart Lung Transplant. 2005;24:421–5.

38. Shitrit D, Rahamimov R, Gidon S, Bakal I, Bargil-Shitrit A, Milton S, Kramer MR. Use of sirolimus and low-dose calcineurin inhibitor in lung transplant recipients with renal impairment: results of a controlled pilot study. Kidney Int. 2005;67:1471–5.
39. Ghassemieh B, Ahya VN, Baz MA, Valentine VG, Arcasoy SM, Love RB, Seethamraju H, Alex CG, Bag R, Deoliveira NC, Vigneswaran WT, Charbeneau J, Garrity ER, Bhorade SM. Decreased incidence of cytomegalovirus infection with sirolimus in a post hoc randomized, multicenter study in lung transplantation. J Heart Lung Transplant. 2013;32:701–6.
40. Brennan DC, Legendre C, Patel D, Mange K, Wiland A, McCague K, Shihab FS. Cytomegalovirus incidence between everolimus versus mycophenolate in de novo renal transplants: pooled analysis of three clinical trials. Am J Transplant. 2011;11:2453–62.
41. Vigano M, Dengler T, Mattei MF, Poncelet A, Vanhaecke J, Vermes E, Kleinloog R, Li Y, Gezahegen Y, Delgado JF. Lower incidence of cytomegalovirus infection with everolimus versus mycophenolate mofetil in de novo cardiac transplant recipients: a randomized, multicenter study. Transpl Infect Dis. 2010;12:23–30.
42. Lim WH, Russ GR, Wong G, Pilmore H, Kanellis J, Chadban SJ. The risk of cancer in kidney transplant recipients may be reduced in those maintained on everolimus and reduced cyclosporine. Kidney Int. 2017;91:954–63.
43. Campistol JM, Eris J, Oberbauer R, Friend P, Hutchison B, Morales JM, Claesson K, Stallone G, Russ G, Rostaing L, Kreis H, Burke JT, Brault Y, Scarola JA, Neylan JF. Sirolimus therapy after early cyclosporine withdrawal reduces the risk for cancer in adult renal transplantation. J Am Soc Nephrol. 2006;17:581–9.
44. Caroti L, Zanazzi M, Paudice N, Tsalouchos A, Carta P, Larti A, Pimpinelli N, Moscarelli L, Salvadori M, Bertoni E. Conversion from calcineurin inhibitors to everolimus with low-dose cyclosporine in renal transplant recipients with squamous cell carcinoma of the skin. Transplant Proc. 2012;44:1926–7.
45. Vos R, Vanaudenaerde BM, Ottevaere A, Verleden SE, De Vleeschauwer SI, Willems-Widyastuti A, Wauters S, Van Raemdonck DE, Nawrot TS, Dupont LJ, Verleden GM. Long-term azithromycin therapy for bronchiolitis obliterans syndrome: divide and conquer? J Heart Lung Transplant. 2010;29:1358–68.
46. Vos R, Vanaudenaerde BM, Verleden SE, De Vleeschauwer SI, Willems-Widyastuti A, Van Raemdonck DE, Schoonis A, Nawrot TS, Dupont LJ, Verleden GM. A randomised controlled trial of azithromycin to prevent chronic rejection after lung transplantation. Eur Respir J. 2011;37:164–72.
47. Jain R, Hachem RR, Morrell MR, Trulock EP, Chakinala MM, Yusen RD, Huang HJ, Mohanakumar T, Patterson GA, Walter MJ. Azithromycin is associated with increased survival in lung transplant recipients with bronchiolitis obliterans syndrome. J Heart Lung Transplant. 2010;29:531–7.
48. Pollock-Barziv SM, Finkelstein Y, Manlhiot C, Dipchand AI, Hebert D, Ng VL, Solomon M, McCrindle BW, Grant D. Variability in tacrolimus blood levels increases the risk of late rejection and graft loss after solid organ transplantation in older children. Pediatr Transplant. 2010;14:968–75.
49. Shemesh E, Fine RN. Is calculating the standard deviation of tacrolimus blood levels the new gold standard for evaluating non-adherence to medications in transplant recipients? Pediatr Transplant. 2010;14:940–3.
50. Venkat VL, Nick TG, Wang Y, Bucuvalas JC. An objective measure to identify pediatric liver transplant recipients at risk for late allograft rejection related to non-adherence. Pediatr Transplant. 2008;12:67–72.
51. Chiang CY, Schneider HG, Levvey B, Mitchell L, Snell GI. Tacrolimus level variability is a novel measure associated with increased acute rejection in lung transplant (LTx) recipients. J Heart Lung Transplant. 2013;32:S170.
52. Kurnatowska I, Krawczyk J, Oleksik T, Nowicki M. Tacrolimus dose and blood concentration variability in kidney transplant recipients undergoing conversion from twice daily to once daily modified release tacrolimus. Transplant Proc. 2011;43:2954–6.

Chapter 6
Cellular Rejection: Is it Still Relevant?

Adrian Havryk

6.1 Introduction

In lung transplantation the maintenance of lung allograft function is essential. Lung allograft dysfunction can occur due to a variety of reasons, rejection, infection, mechanical obstruction and muscle dysfunction to name a few. Acute allograft rejection is a significant problem and up to one third of patients will have biopsy proven cellular rejection in the first year post transplantation. The clinical features of rejection can be subtle, particularly in the early post-transplant period and the pathology, clinical features, investigation findings, treatment and outcomes of cellular rejection will be discussed in this chapter.

6.2 Risk Factors

The highest rates of cellular rejection are seen early in the post-transplant period. Up to 1/3 of patients will have documented cellular rejection in the first year post transplant [1]. The majority of centres performing lung transplantation have a surveillance bronchoscopic biopsy protocol to identify early rejection in the first year post transplant. Our routine is to perform routine surveillance bronchoscopy and transbronchial biopsy at 3, 6, and 12 weeks post-transplant. Biopsy following that period is performed when there is a clinical suspicion of rejection.

Risk factors for rejection include HLA mismatch between patient and donor [2], age [3] and the immunosuppressive regime. Increasing HLA mismatch leads to higher rates of cellular rejection. Younger patients statistically have more rejection episodes than

A. Havryk
Heart and Lung Transplant Unit, St. Vincent's Hospital, Darlinghurst, NSW 2010, Australia
e-mail: Adrian.Havryk@svha.org.au

A. R. Glanville (ed.), *Essentials in Lung Transplantation*,
https://doi.org/10.1007/978-3-319-90933-2_6

older patients and this may be related to differences in immunological tolerance with immuosenescence occurring with age [3]. Variable immunosuppressive levels correlate with graft loss and the choice of calcineurin inhibitor appears to affect the rate of rejection, with patients on Tacrolimus having lower rates of rejection than those maintained on Cyclosporin as part of their immunosuppressive regime [4].

6.3 Clinical Features

Many of the clinical features of rejection are centred around allograft dysfunction. Initially the patient may be asymptomatic, but as severity increases the degree of organ dysfunction increases. The individual patient requires thorough clinical assessment and laboratory testing, especially in the early post-transplant period when the full function of the graft may not yet have been achieved. Rejection may be asymptomatic or manifest as dyspnoea with or without a cough [5]. Occasionally there is a low grade fever. On physical examination the chest may be clear, or there may be creptitations and signs of a pleural effusion. Pulmonary function testing can reveal a fall in FEV1 (sensitivity of 60%) [5, 6]. Radiographic infiltrates may become apparent. On radiographic examination the CXR may show ground glass opacities, consolidation, changes of interstitial oedema or pleural effusions. CT scanning of the chest may demonstrate ground glass changes, septal thickening and effusions. It does not however differentiate between rejection and infection [6].

Given that the presentation of rejection is often mimicked by infection and other clinical syndromes it is often necessary to obtain tissue confirmation of rejection in patients with suspected rejection. This is best achieved by transbronchial biopsy, or in instances of unstable patients video assisted thoracoscopic lung biopsy or even open lung biopsy. In planning a tissue biopsy CT scanning can be useful in directing the bronchoscopist or surgeon to the area of greatest radiological change to maximise the utility of diagnostic procedures.

Bronchoscopy is useful in determining infection or colonisation by microbiological agents of a patient. In episodes of rejection the bronchoalveolar lavage may show a lymphocyte predominant alveolitis. With infection there is a neutrophil predominant lavage.

6.4 Monitoring for Rejection

Most centres performing lung transplants have a schedule of routine surveillance bronchoscopy and biopsy to monitor patients for rejection. In the early post-transplant period patients suffer from varying degrees of debility. Often, during the pre-transplant period physical activity is severely limited by respiratory failure leading to sarcopaenia and loss of cardiovascular fitness [7]. Post-transplant deconditioning can occur if there has been an extended hospital stay. Under such

circumstances the ability of the patient to exercise adequately to perceive dyspnoea, with well-functioning lungs but relatively debilitated general condition, is limited, increasing the difficulty of obtaining clinical clues to the possibility of rejection. The highest rate of rejection post lung transplantation is in the first year, with early rejection being the most common [8, 9].

6.4.1 Determining Rejection

When a lung transplant patient presents with symptoms of graft dysfunction the identification of cause can be complicated and requires a combination of history and physical examination, as well as testing to determine whether the cause may be rejection, airway infection or possible mechanical graft dysfunction such as obstruction from slough and mucus or anastomotic stricture. If allograft rejection is suspected additional testing will generally comprise lung function testing, pathology and bronchoscopy. From a symptom perspective determining whether a patient has rejection or infection is difficult and only further testing can definitively delineate between the two processes [5]. In general it is desirable to obtain a pathological diagnosis for certainty and this is most commonly achieved with bronchoscopy and transbronchial biopsy, but on occasion formal surgical lung biopsy is required.

6.4.2 Lung Function Testing

Spirometry is generally performed at every patient attendance in our unit. Patients are also supplied with a home spirometer for self-measurement, ideally performing spirometry twice daily and recording their results [10]. This allows patients to identify an asymptomatic loss of lung function and present for early clinical review. Typically in rejection there is a loss of forced expiratory volume in 1 s (FEV1) with acute rejection, although forms of rejection such as restrictive allograft dysfunction syndrome manifest a combined reduction in both FEV1 and forced vital capacity (FVC) [11]. Reduction in FEV1 can be caused by infection, chest wall pain and rejection, amongst other entities and is not specific for rejection. The sensitivity of FEV1 for rejection is 60% [6]. In our institution we consider an unexplained FEV1 drop of 10% to be an indication for bronchoscopy with biopsy to exclude rejection.

6.4.3 Pathological Testing

Clues to the possibility of rejection can also be found in biochemical and haematological testing. The presence of recent or current low levels of immunosuppressants suggests a higher likelihood of rejection. It has recently been reported that rejection

occurs more frequently in patients with high tacrolimus level variability [12, 13]. For every 1 mcg/L increase in standard deviation of Tacrolimus levels the risk of rejection increased by 23%, despite higher mean levels of tacrolimus. On occasion an eosinophilia may be present, but this is not a sensitive measure and may correlate better with difficult to treat rejection. Ideally a blood biomarker would give information regarding the likelihood of rejection. Many trials have looked at potential markers but none have been either sensitive or specific in the determination of rejection.

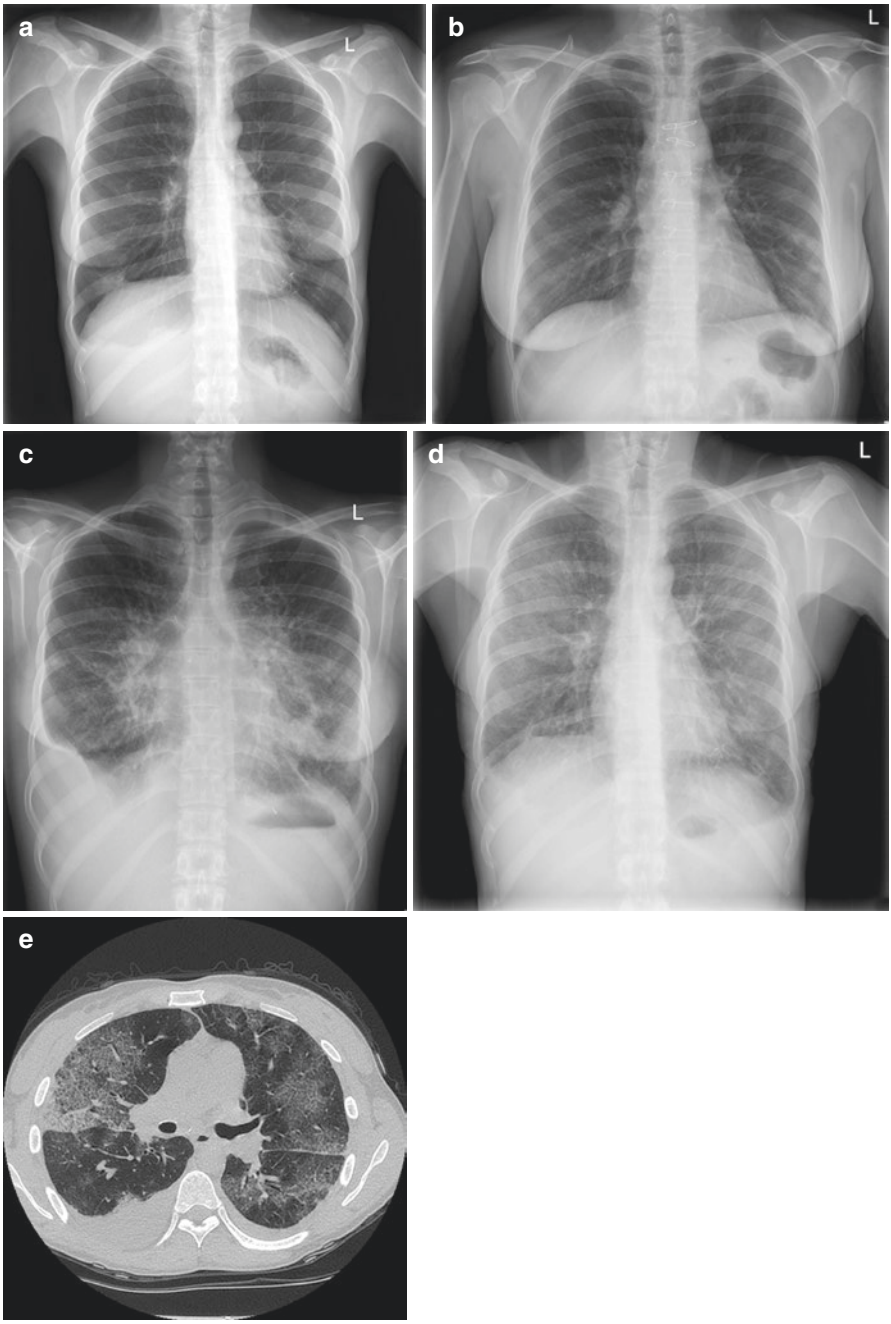
6.4.4 Radiology

For every routine and emergency visit by a patient a chest X-ray is performed. Changes that may signal rejection include ground glass changes, perihilar opacities as well as interstitial changes consistent with pulmonary oedema. Pleural effusions and frank consolidative changes may also occur. The chest x-ray can also be clear in episodes of rejection [27]. If a computed tomography (CT) scan is performed further changes may be identified, typically including ground glass changes and septal thickening [14, 15]. See Fig. 6.1a–e for representative examples of radiology ranging from normal post-transplant to Grade A3/4 rejection.

6.4.5 Bronchoscopy

Confirmation of rejection relies on the demonstration of the characteristic pathological changes with tissue usually being obtained via transbronchial biopsy at the time of bronchoscopy. On occasion, due to clinical circumstance, thoracoscopic or open lung biopsy may be performed. Many centres perform routine surveillance

Fig. 6.1 Standard chest X rays with presentation of rejection. (**a**) No evidence of rejection—biopsy grade A0. Essentially normal CXR with the expected post operative clips and minor stable changes at the right base. (**b**) Grade A2. Patchy airspace changes noted at the left base peripherally. The remainder of the lungs are clear. (**c**) Grade A3. Perihilar peribronchial increased air space and reticular markings. There is slightly greater air space change at the left base. Complex right effusion slightly increased in size. (**d**) Grade A3/A4 rejection. There is interval increase in probably mixed ground-glass and airspace infiltrates in both lungs, worse in the mid to lower zones and more prominent in the right lung. Small bibasal pleural effusions are also seen. (**e**) Corresponding CT Scan, Grade A3/4 rejection. There is very extensive ground-glass septal thickening and becoming confluent opacity in the particularly right upper lobe but involving all lobes bilaterally


a
L
b
L
c
L
d
L
e

bronchoscopies in the initial post-transplant period. In our centre we routinely perform bronchoscopies with additional transbronchial biopsies at 3, 6, and 12 weeks. Additional biopsies are performed if there is a clinical suspicion of rejection during this period, as well as in the ongoing care of the patient. Biopsy is also typically performed following the identification of an acute episode of rejection and its subsequent treatment to ensure clearance of the episode following therapy [21].

The role of bronchoscopy is dealt with in a further chapter of this book. In general it is a safe procedure [9, 20]. In brief, inspection of the bronchial anatomy is performed to screen for anastomotic strictures and mucosal abnormalities, as well as excessive mucus or slough which may account for reduction in lung function. Samples, usually bronchoalveolar lavage for microbiological analysis, are also taken at the time of bronchoscopy to screen for alternative causes of loss of lung function. When progressing to transbronchial biopsy only one lung is sampled, to avoid the possibility of bilateral pneumothorax, and 6–10 adequate biopsies are obtained, generally six from the lower lobe and four from the middle lobe or lingula. This yields a sensitivity for rejection between 60 and 94%, with a specificity of 90% [16, 17]. In patients who have radiographic abnormalities, that area is targeted in an effort to maximise yield from the procedure.

6.5 Pathology

The immune system is a highly complex mechanism designed to discriminate self from non-self. Acute allograft rejection is a result of immunological defence. It results from inadequate immunosuppression of the recipient's immune system which then responds to non-self antigens, the lung allograft in the setting of lung transplantation. Confirmation of rejection relies on the demonstration of the characteristic pathological changes.

Cellular rejection is characterised by a lymphocyte predominant inflammatory response. It is the result of T lymphocyte recognition of foreign antigens. In the case of allograft rejection, lymphocytes recognise foreign HLA antigens as non-self and mount an immune response [18]. In the lung allograft this is characterised by lymphcocyte invasion into two primary centres, the blood vessels and the airways. The ISHLT working party on rejection released the latest guidelines on the pathological staging of cellular rejection in 2007 [19]. Essentially this comprises an A grade, the depth of lymphocytes surrounding blood vessels. This is often termed vascular rejection with initial infiltration of mononuclear cells around endothelium which then spreads around alveoli in higher grades. Please see Figs. 6.2, 6.3, 6.4, and 6.5 for representative examples of transbronchial biopsies. The B grade comprises the degree of infiltration centred on the airways. In low grades there is a lymphocytic infiltrate in the bronchiolar submucosa which extends through the basement membrane and can lead to ulceration of the airway epithelium in high grade cases.

Grading is as follows:

A: Acute rejection
Grade 0—None
Grade 1—Minimal
Grade 2—Mild
Grade 3—Moderate
Grade 4—Severe
B: Airway inflammation
Grade 0—None
Grade 1R—Low grade
Grade 2R—High grade
Grade X—Ungradeable

6.5.1 Prevalence of Rejection

In the first 3 months following transplantation the rate of acute rejection grade A2 or greater has been reported as up to 24.8% of routine surveillance biopsies on patients and a further 16% of biopsies in the ensuing 9 months [20].

A biopsy driven study looking at rejection in the first year in 230 patients demonstrated a 40% prevalence of rejection in specimens. Of these biopsies 57% had no

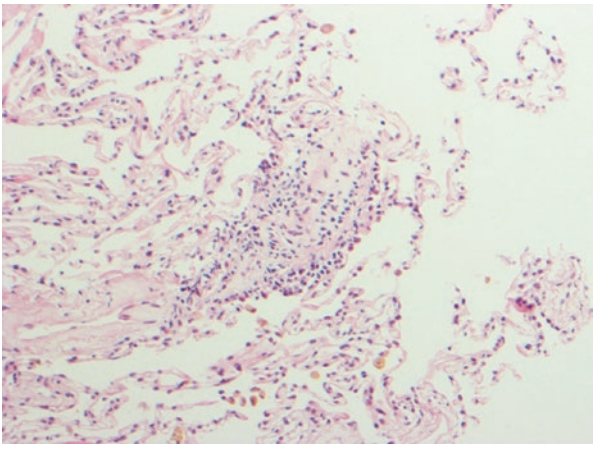


Fig. 6.2 Grade A0 B0 (no acute rejection). Transbronchial lung biopsy. In grade A0 acute rejection, normal pulmonary parenchyma is present without evidence of mononuclear cell infiltration, hemorrhage or necrosis. There is no perivascular lymphocytosis and the portions of airway wall and epithelium do not appear inflamed. Only isolated occasional lymphocytes are noted within the basal layers of the airway epithelium. Histopathology courtesy of Dr. Min Ru Qiu, Department of Pathology, St. Vincent's Hospital, Darlinghurst, Sydney Australia

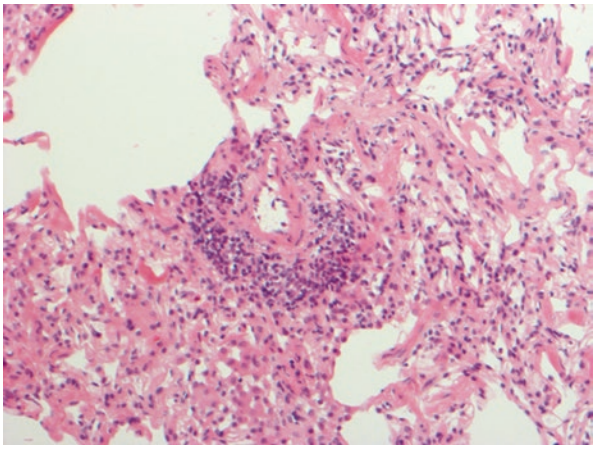


Fig. 6.3 Grade A1 B1 (minimal acute rejection). Transbronchial lung biopsy. In grade A1 acute rejection, there are scattered, infrequent perivascular mononuclear infiltrates in alveolated lung parenchyma. There is focal perivascular lymphocytosis. There is no bronchiolar inflammation. The bronchial epithelium or alveolar wall does not appear markedly inflamed. A1 B1. Histopathology courtesy of Dr. Min Ru Qiu, Department of Pathology, St. Vincent's Hospital, Darlinghurst, Sydney Australia

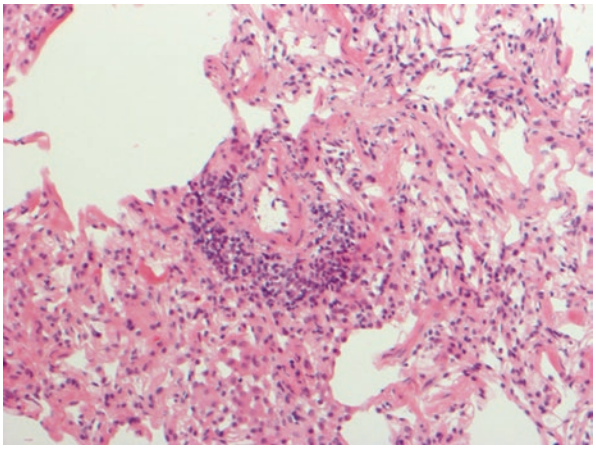


Fig. 6.4 Grade A2 (mild acute rejection). Transbronchial lung biopsy. In Grade A2 mild rejection, more frequent perivascular mononuclear infiltrates are seen surrounding venules and arterioles and are readily recognizable at low magnification. Concurrent lymphocytic bronchiolitis may be seen in association with mild acute rejection. In this sample there is a focus of compact circumferential perivascular lymphocytosis with rare eosinophils. A number of small vessels are surrounded by four to five layers of lymphocytes together with small numbers of eosinophils. The alveolar spaces are clear. Histopathology courtesy of Dr. Min Ru Qiu, Department of Pathology, St. Vincent's Hospital, Darlinghurst, Sydney Australia

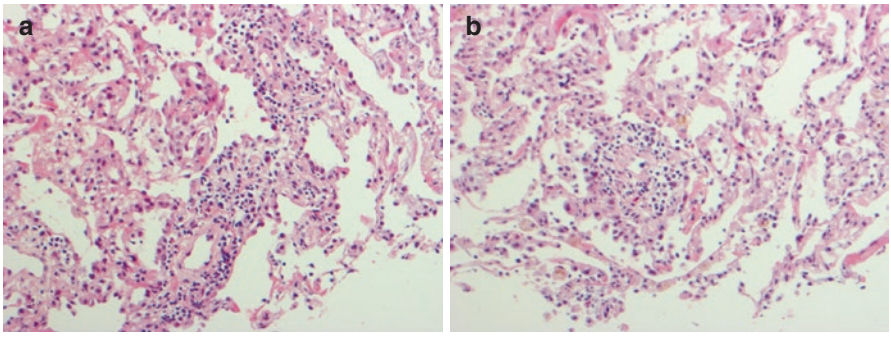


Fig. 6.5 (**a**, **b**). Grade A3/A4 (moderate and severe acute rejection). Transbronchial lung biopsy. Grade A3 acute rejection shows easily recognizable cuffing of venules and arterioles by dense perivascular mononuclear cell infiltrates, which are commonly associated with endothelialitis. Eosinophils and even occasional neutrophils are common. In this sample there are multiple foci of marked and tight perivascular lymphocytosis with mixed eosinophils. In many places, the infiltrate extends into the adjacent alveolar septae with marked interstitial edema. In addition there is associated alveolar damage in which fibrin exudates and macrophages are seen in the attenuated alveolar spaces. Associated myxoid fibrosis is also seen. Very occasionally lymphocytes are found within the intima of a small artery. The limited airway mucosa (bronchial mucosa) shows mild intraepithelial lymphocytes with subepithelial monocyte infiltration. Scattered eosinophils are also seen. The overall features are those of high grade acute cellular rejection between Grade A3 and A4 due to the presence of alveolar damage (**a**). Histopathology courtesy of Dr. Min Ru Qiu, Department of Pathology, St. Vincent's Hospital, Darlinghurst, Sydney Australia. (**b**) Grade A3/A4. Histopathology courtesy of Dr. Min Ru Qiu, Department of Pathology, St. Vincent's Hospital, Darlinghurst, Sydney Australia

rejection, 22% minimal A1 grade, 14.8% mild (A2), 4.4% moderate (A3) and 0.2% severe (A4) [21].

Within the first year 1/3 of lung transplant recipients will have had a documented episode of rejection.

6.5.2 Treatment

Treatment largely depends on the severity of rejection. Biopsy proof of rejection gives a minimum grade, but due to spatial heterogeneity of rejection and consequent possible sampling error the grade of rejection may be higher than that determined by tissue biopsy. In general treatment will be predicated on a combination of the clinical severity of allograft dysfunction and the pathological grading of rejection. Variable routines are utilised depending on centre, but therapy is centred around the use of pulse oral or intravenous glucocorticoids. For grade A1 and in some cases A2 rejection a typical regime would be 1 mg/kg of oral prednisolone in a divided dose daily, tapering by a total of 5 mg every second day to the patients baseline dosage. In higher grades of rejection this is preceded by up to 15 mg/kg (500–1000 mg) of parenteral methylprednisolone daily for 3 days followed by oral tapering [22].

In conjunction with this the immunosuppressive regime should be optimised. Follow-up tissue biopsy to determine the effectiveness of treatment is usually performed 3–4 weeks later. The value of repeat biopsy was demonstrated by Glanville et al. in 2001 who identified that 26% of patients will have persistent features of rejection at follow up biopsy and 19% developed new CMV pneumonitis [21]. Changes in immunosuppressive therapy since that time and a broader use of prophylactic antivirals have lowered the risk of ongoing rejection and CMV pneumonitis.

6.5.3 Outcomes

Symptomatic improvement generally commences within 24–48 h following the institution of corticosteroid therapy, with pulmonary function and radiologic improvement occurring over a period of days to some weeks. The majority of patients respond to initial corticosteroid therapy with an earlier onset of rejection after transplantation increasing the likelihood of response [23].

Acute rejection is the cause of mortality in approximately 4% of patients in the first 30 days post-transplant [24]. Even following treatment acute cellular rejection remains a risk factor for the development of bronchiolitis obliterans syndrome [25]. Multiple positive low grade A1 lesions have also been determined to be a risk factor for the development of bronchiolitis obliterans syndrome. The cumulative sum total of B grade rejection correlates with long term outcomes with regards to loss of graft function and death [26]. The severity of lymphocytic airway inflammation, or B grade rejection, is associated with the severity of A grade rejection [27] and the longer term development of bronchiolitis obliterans syndrome and death [26].

References

1. Martinu T, Chen DF, Palmer SM. Acute rejection and humoral sensitization in lung transplant recipients. Proc Am Thorac Soc. 2009;6(1):54–65.
2. Martinu T, et al. Acute allograft rejection: cellular and humoral processes. Clin Chest Med. 2011;32(2):295–310.
3. Christie JD, et al. The Registry of the International Society for Heart and Lung Transplantation: twenty-eighth adult lung and heart-lung transplant report—2011. J Heart Lung Transplant. 2011;30(10):1104–22.
4. Christie JD, et al. The Registry of the International Society for Heart and Lung Transplantation: 29th adult lung and heart-lung transplant report—2012. J Heart Lung Transplant. 2012;31(10):1073–86.
5. De Vito Dabbs A, et al. Are symptom reports useful for differentiating between acute rejection and pulmonary infection after lung transplantation? Heart Lung. 2004;33(6):372–80.
6. Van Muylem A, et al. Role of pulmonary function in the detection of allograft dysfunction after heart-lung transplantation. Thorax. 1997;52(7):643–7.
7. Walsh JR, et al. Impaired exercise capacity after lung transplantation is related to delayed recovery of muscle strength. Clin Transpl. 2013;27(4):E504–11.

8. Burton CM, et al. Minimal acute cellular rejection remains prevalent up to 2 years after lung transplantation: a retrospective analysis of 2697 transbronchial biopsies. Transplantation. 2008;85(4):547–53.
9. Hopkins PM, et al. Prospective analysis of 1,235 transbronchial lung biopsies in lung transplant recipients. J Heart Lung Transplant. 2002;21(10):1062–7.
10. Kugler C, et al. Effect of adherence to home spirometry on bronchiolitis obliterans and graft survival after lung transplantation. Transplantation. 2009;88(1):129–34.
11. Sato M, et al. Restrictive allograft syndrome (RAS): a novel form of chronic lung allograft dysfunction. J Heart Lung Transplant. 2011;30(7):735–42.
12. Gallagher HM, et al. Erratic tacrolimus exposure, assessed using the standard deviation of trough blood levels, predicts chronic lung allograft dysfunction and survival. J Heart Lung Transplant. 2015;34(11):1442–8.
13. Chiang CY, et al. Tacrolimus level variability is a novel measure associated with increased acute rejection in lung transplant (LTx) recipients. J Heart Lung Transplant. 2013;32(4):S170.
14. Gotway MB, et al. Acute rejection following lung transplantation: limitations in accuracy of thin-section CT for diagnosis. Radiology. 2001;221(1):207–12.
15. Millet B, et al. The radiographic appearances of infection and acute rejection of the lung after heart-lung transplantation. Am Rev Respir Dis. 1989;140(1):62–7.
16. Tazelaar HD, et al. The sensitivity of transbronchial biopsy for the diagnosis of acute lung rejection. J Thorac Cardiovasc Surg. 1993;105(4):674–8.
17. Faro A, Visner G. The use of multiple transbronchial biopsies as the standard approach to evaluate lung allograft rejection. Pediatr Transplant. 2004;8(4):322–8.
18. Angaswamy N, et al. Interplay between immune responses to HLA and non-HLA self-antigens in allograft rejection. Hum Immunol. 2013;74(11):1478. https://doi.org/10.1016/j.humimm.2013.07.002.
19. Stewart S, et al. Revision of the 1996 working formulation for the standardization of nomenclature in the diagnosis of lung rejection. J Heart Lung Transplant. 2007;26(12):1229–42.
20. McWilliams TJ, et al. Surveillance bronchoscopy in lung transplant recipients: risk versus benefit. J Heart Lung Transplant. 2008;27(11):1203–9.
21. Aboyoun CL, et al. Diagnostic value of follow-up transbronchial lung biopsy after lung rejection. Am J Respir Crit Care Med. 2001;164(3):460–3.
22. Levine SM. A survey of clinical practice of lung transplantation in North America. Chest. 2004;125(4):1224–38.
23. Fuehner T, et al. Indicators for steroid response in biopsy proven acute graft rejection after lung transplantation. Respir Med. 2009;103(8):1114–21.
24. Yusen RD, et al. The Registry of the International Society for Heart and Lung Transplantation: thirty-second official adult lung and heart-lung transplantation report—2015; focus theme: early graft failure. J Heart Lung Transplant. 2015;34(10):1264–77.
25. Burton CM, et al. Acute cellular rejection is a risk factor for bronchiolitis obliterans syndrome independent of post-transplant baseline FEV1. J Heart Lung Transplant. 2009;28(9):888–93.
26. Glanville AR, et al. Severity of lymphocytic bronchiolitis predicts long-term outcome after lung transplantation. Am J Respir Crit Care Med. 2008;177(9):1033–40.
27. Burton CM, et al. Is lymphocytic bronchiolitis a marker of acute rejection? An analysis of 2,697 transbronchial biopsies after lung transplantation. J Heart Lung Transplant. 2008;27(10):1128–34.

Chapter 7
Antibody Mediated Rejection: Are We There Yet?

Glen P. Westall and Lucy C. Sullivan

Patients with end-stage lung disease, unlike those with terminal heart or renal disease do not have access to artificial long-term organ support devices and instead face a race-against-time to obtain a life-saving lung transplant. Today, the challenge is extending the longevity of this transformative gift that saves lives, restores health and improves quality of life. The Achilles heel of lung transplantation is chronic lung allograft dysfunction (CLAD). While short-term results are excellent (>90%) and match those of other solid organ transplants, the long-term survival of the transplanted lung falls a long way short with 10-year survival of only 30–40%. This disappointing result is linked to the development of CLAD, which results from allo-immune and infectious injuries, leading to graft destruction, falling lung function and death.

The underlying immune mechanisms of allograft rejection and how they contribute to CLAD continue to be poorly understood. The early days of transplant surgery demonstrated that it was surgically feasible to keep a patient alive to allow replacement of a damaged organ with a donated organ. However, these early transplant patients did not survive beyond a few days and weeks, because little was known of the immunological (and infectious) sequeale of solid organ transplantation. As history has shown, the success of transplant surgery is intrinsically linked to our evolving knowledge of transplant immunology. Sir Peter Medewar was awarded the Noble Prize in 1960 for his pioneering work on graft rejection and demonstrating the central importance of the T-cell in alloreactivity. The discovery of the calcineurin inhibitor, cyclosporine, an immunosuppressive drug that achieved selective

G. P. Westall (✉)
Lung Transplant Service, Alfred Hospital and Monash University, Melbourne, VIC, Australia
e-mail: G.Westall@alfred.org.au

L. C. Sullivan
Lung Transplant Service, Alfred Hospital and Monash University, Melbourne, VIC, Australia

Department of Microbiology and Immunology, The University of Melbourne at The Peter Doherty Institute for Infection and Immunity, Melbourne, VIC, Australia

A. R. Glanville (ed.), *Essentials in Lung Transplantation*,
https://doi.org/10.1007/978-3-319-90933-2_7

inhibition of recently-activated T-cells, without exposure to life-threatening side effects, heralded the modern era of lung transplantation.

Increasingly, there is recognition that antibody-mediated rejection (AMR), wherein B-cells produce donor-specific antibodies (DSA) against the donor lung allograft may also contribute to CLAD. An immunological understanding of the pathophysiological pathways whereby the humoral immune response predominates and leads to lung allograft damage informs the transplant physician how we clinically identify AMR and what investigations need to be ordered to secure the diagnosis.

The major, although not only, transplant antigen is the human leukocyte antigen (HLA) molecule. For logistic reasons, HLA matching is not performed in lung transplantation, but the impact of HLA matching on long-term outcomes in renal and lung transplantation is well described. Anti-HLA antibodies directed against non-self HLA within the lung allograft, termed donor-specific antibodies (DSA), are potentially injurious through several mechanisms. Firstly, the linking of an anti-HLA antibody with a HLA molecule can result in complement activation through the classical pathway. The complement cascade when activated results in amplification of the immune response against the transplanted organ leading to graft damage. Histological evidence of complement activation by assessing staining of C4d (a split product of complement component C4) within the transplanted lung suggests a diagnosis of AMR. DSA can also contribute to graft damage by antibody-dependent cellular mechanisms, most notably by activating NK cells; an immune cell that is increasingly has been recognised as being involved in the rejection process [1], particularly AMR [2].

7.1 Pre-transplant Sensitization

The presence of anti-HLA antibodies in a patient prior to lung transplantation may limit access to this life-saving therapy. Predictors for sensitization include previous pregnancies, blood transfusions or other solid-organ transplants. Sensitized patients wait longer for transplant, require augmented immunosuppression following transplant and experience a higher incidence of both acute and chronic rejection [3]. Strategies to reduce pre-transplant sensitization include intravenous immunoglobulin (IVIg), antithymocyte globulin (ATG) and cyclophosphamide [4].

7.2 Clinical Diagnosis of AMR

Making a clinical diagnosis of AMR remains challenging. The International Society of Heart and Lung Transplantation (ISHLT) recently convened a working group to produce a consensus report on pulmonary AMR [5]. In doing so, the working group recognised that AMR represents a continuum whereby firstly anti-HLA donor-specific antibodies can be detected in the circulation. DSA then have the potential to drive complement activation and disrupt the lung architecture; both of which may be detected on transbronchial biopsy, but may not be associated with symptoms and

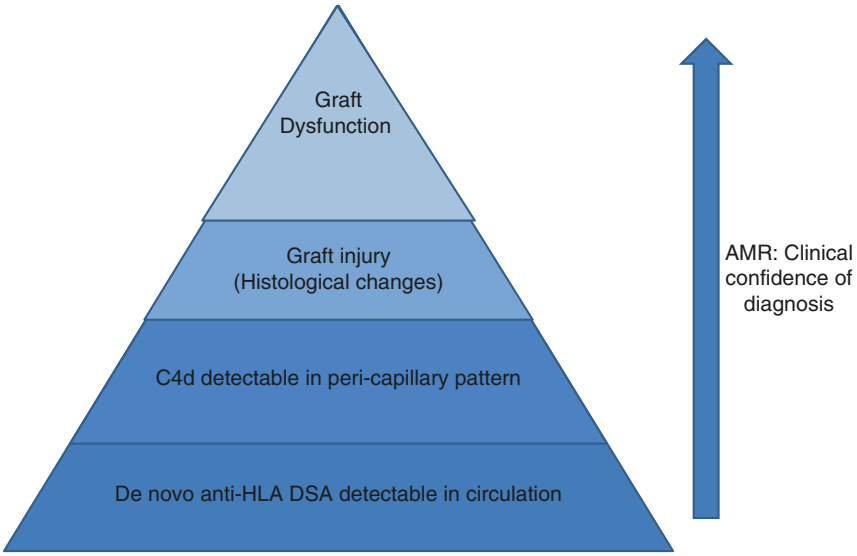


Fig. 7.1 AMR diagnosis: confidence of diagnosis increases if all 4 diagnostic tenets are present; (1) circulating anti-HLA DSA; (2) C4d positive staining; (3) characteristic histological changes and (4) allograft dysfunction

signs in the patient, in a condition that is termed sub-clinical AMR. If left to progress the patient will eventually present with clinical AMR with dyspnoea and evidence of deteriorating pulmonary function tests (Fig. 7.1). Clinically, there are no characteristic symptoms and/or signs of AMR that distinguish it from other forms of acute allograft dysfunction. Likewise the phenotype of chronic AMR is not fully defined, but an emerging literature suggests that the restrictive allograft syndrome (RAS) form of CLAD may represent chronic AMR [6, 7].

Reflecting the pathophysiology of AMR, the diagnostic work-up involves looking for evidence of circulating DSA, positive C4d staining plus characteristic histological changes on transbronchial biopsy, and evidence of allograft dysfunction. The presence or absence of allograft dysfunction differentiates clinical from sub-clinical AMR, respectively. The confidence for the diagnosis increases from possible, through probable, to definite depending on how many of the diagnostic features are present (Table 7.1).

7.3 Diagnostic Challenges: #1 Donor-Specific Antibodies

Local tissue typing laboratories use solid phase assays such as the Luminex platform to assess the presence and magnitude of circulating anti-HLA antibodies. DSA may be present prior to transplant in sensitized individuals or develop de novo following lung transplantation. The mean fluorescence intensity (MFI) does not reflect the true titre of the antibody response but can be used as a surrogate for the magnitude of the

Table 7.1 Definition and grade of pulmonary AMR (modified from [5])

	DSA	C4d staining	Histology	Allograft Dysfunction	
Definite	+	+	+	+	Clinical AMR
Probable	+	+	-	+	
Probable	+	-	+	+	
Probable	-	+	+	+	
Possible	+	-	-	+	
Possible	-	+	-	+	
Possible	-	-	+	+	
Definite	+	+	+	_	Subclinical AMR
Probable	+	+	-	-	
Probable	+	-	+	-	
Probable	-	+	+	-	
Possible	+	-	-	-	
Possible	-	+	-	-	
Possible	-	-	+	-	

circulating antibody. A number of factors need to be considered when interpreting a positive Luminex result. The presence of DSA does not automatically imply immune activation via complement fixation. To address this, some centres have access to the C1q assay that is a modification of the standard Luminex assay but differentiates complement-fixing from non-complement-fixing DSA; the former being more likely to damaging to the allograft than the latter [8]. Additionally, just because DSA are present in the circulation does not necessarily imply that the antibody is being bound to the lung tissue antigen. Detecting anti-HLA antibodies within the transplanted allograft is feasible but the assay remains a research tool in most centers [9]. Non-HLA antibodies such as antibodies to angiotensin type 1 receptor (AT1R) and endothelin type A receptor (ETAR) may also develop and contribute to allograft damage [10, 11]. Finally, the financial costs associated with the Luminex assay are considerable and limits the widespread and/or frequent use of the assay.

7.4 Diagnostic Challenges: #2 C4d Staining

C4d is a breakdown product of the complement system and its detection in the lung allograft by either immunohistochemistry (IHC) (Fig. 7.2) or immunofluorescence (IF) suggests complement activation and, by implication, a humoral alloresponse.

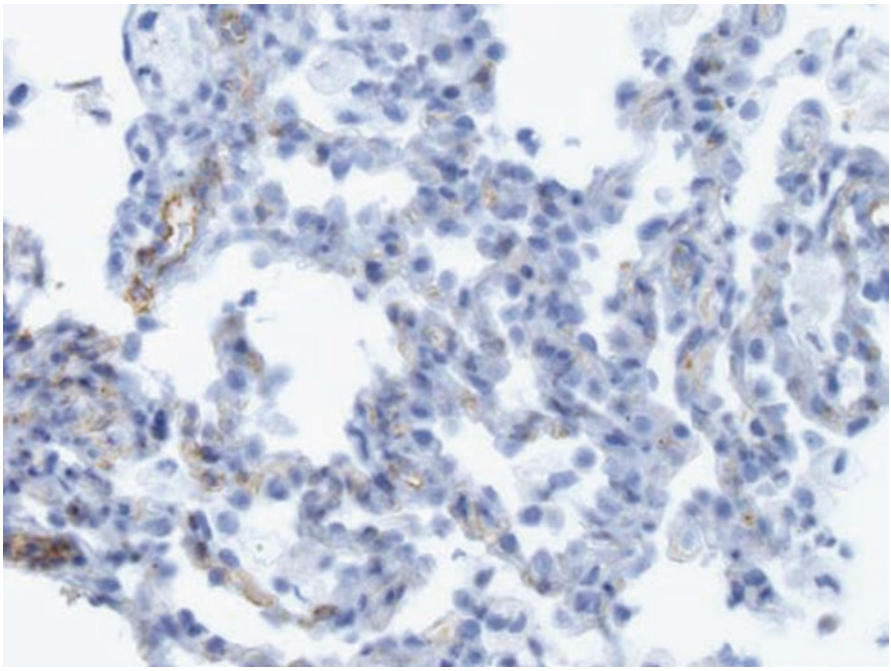


Fig. 7.2 Positive peri-capillary C4d staining (immunoperoxidase) suggestive of complement activation as a result of pulmonary AMR

The literature for detecting C4d deposition in renal transplantation secured its role in diagnosing AMR however the assay is more problematic in lung transplantation [12]. Reproducibility between IHC and IF, and between different centres is poor [13]. Background staining is common and hinders the interpretation of true peri-capillary staining. C4d staining can also be observed with primary graft dysfunction (PGD) and infection [14]. Finally, reflecting that DSA are not always complement-fixing, and may also promote activation of NK cells, the entity of C4d-negative AMR is recognised in renal transplantation [15], and is also likely in lung transplantation [16].

7.5 Diagnostic Challenges: #3 Histological Features of AMR

Unlike the situation in other solid-organ transplant settings, there are no pathognomonic AMR features on histology for diagnosis following lung transplantation. Rather, any injury pattern seen on transbronchial biopsy may reflect AMR (Table 7.2). Suggestive histological features of AMR include the presence of neutrophils within the peri-capillary septae [17]. Histology remains an adjunct to the clinical diagnosis of AMR.

Table 7.2 Histological patterns associated with pulmonary AMR (modified from [17])

Histological pattern
Neutrophilic capillaritis
Neutrophil septal margination
Acute cellular rejection
Acute lung injury
Lymphocytic bronchiolitis
Obliterative bronchiolitis
Arteritis

Table 7.3 Management of AMR

AMR stage	Management
Circulating de novo anti-HLA DSA	Mycophenolate mofetil added to maintenance immunosuppression Track DSA every 3 months
de novo DSA with C4d deposition	As above, early follow-up biopsy
de novo DSA, C4d staining and histological changes	IV methyprednisolone (10 mg/kg/day for 3 days) IVIg (1 g/kg over 2 days)
Definite AMR	Day 1, 2, 3 IV methyprednisolone (10 mg/kg/day) Day 5—IVIg (1 g/kg over 2 days) Day 7–21 Plasmaphoresis alternate days for 5–6 treatments Day 21+ monthly rituximab (375 mg/M^2) × 4 doses

Bortezomib may be considered for refractory AMR

7.6 Treatment of AMR

Reflecting the difficulties in diagnosing AMR, there is little consensus on how and when to treat AMR. The principles of therapy follow that for other medical conditions caused by pathogenic antibodies, namely firstly target the cells producing the antibody and secondly, remove the antibody from the circulation. Unfortunately, in lung transplantation, it is unknown whether the clinician should target B cells with Rituximab or whether it would be more efficacious to target mature plasma cells with Bortezomib. This represents a fundamental gap in our AMR knowledge given that these are costly therapies with potential for adverse side effects. Alternative agents include the monoclonal antibody, Eculizumab that targets C5 blocking complement activation [18].

Strategies to remove DSA from the circulation include plasmaphoreis and Intravenous Immunoglobulin (IVIg). Typically, a course of plasmaphoresis involves giving 5–6 cycles over a two-week period, while IVIg is given at high-dose (2 g/kg) over two divided doses over two consecutive days. The mechanism whereby IVIg is efficacious is not fully understood but does appear to provide both immunomodulatory and immunosuppressive actions [19]. Combinational treatment strategies are typically implemented for AMR although there is no universal consensus on what this should comprise or the timing of therapy. An approach used in our centre is

shown in Table 7.3. The efficacy of therapy is partially related to whether a decrease in the MFI of the DSA can be achieved [20, 21], with some evidence suggesting that this is more achievable early post-lung transplant compared to later time-points [22]. Unfortunately, many patients with AMR continue to clinically worsen despite therapy and go on to develop CLAD [23].

7.7 Conclusion

While there is near universal agreement that AMR contributes to both acute and chronic allograft damage following lung transplantation, there remains considerable difficulties in diagnosing the condition. Reflecting large knowledge gaps in the pathophysiology of how AMR contributes to allograft dysfunction, there is very little agreement and thus a limited evidence base on how best to treat pulmonary AMR. Future studies need to fully dissect how HLA (and non-HLA) antibodies amplify the alloimmune response and describe the resulting clinical phenotypes arising from acute and chronic AMR.

Acknowledgments The Alfred's Lung Transplant Service gratefully acknowledges the Lungitude Foundation for their research and education support.

References

1. Meehan AC, Sullivan LC, Mifsud NA, Brooks AG, Snell GI, Kotsimbos TC, Westall GP. Natural killer cell activation in the lung allograft early posttransplantation. Transplantation. 2010;89:756–63.
2. Legris T, Picard C, Todorova D, Lyonnet L, Laporte C, Dumoulin C, Nicolino-Brunet C, Daniel L, Loundou A, Morange S, Bataille S, Vacher-Coponat H, Moal V, Berland Y, Dignat-George F, Burtey S, Paul P. Antibody-dependent NK cell activation is associated with late kidney allograft dysfunction and the complement-independent alloreactive potential of donor-specific antibodies. Front Immunol. 2016;7:288.
3. Kim M, Townsend KR, Wood IG, Boukedes S, Guleria I, Gabardi S, El-Chemaly S, Camp PC, Chandraker AK, Milford EL, Goldberg HJ. Impact of pretransplant anti-HLA antibodies on outcomes in lung transplant candidates. Am J Respir Crit Care Med. 2014;189:1234–9.
4. Tinckam KJ, Keshavjee S, Chaparro C, Barth D, Azad S, Binnie M, Chow CW, de Perrot M, Pierre AF, Waddell TK, Yasufuku K, Cypel M, Singer LG. Survival in sensitized lung transplant recipients with perioperative desensitization. Am J Transplant. 2015;15:417–26.
5. Levine DJ, Glanville AR, Aboyoun C, Belperio J, Benden C, Berry GJ, Hachem R, Hayes D Jr, Neil D, Reinsmoen NL, Snyder LD, Sweet S, Tyan D, Verleden G, Westall G, Yusen RD, Zamora M, Zeevi A. Antibody-mediated rejection of the lung: a consensus report of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2016;35:397–406.
6. Vandermeulen E, Verleden SE, Bellon H, Ruttens D, Lammertyn E, Claes S, Vandooren J, Ugarte-Berzal E, Schols D, Emonds MP, Van Raemdonck DE, Opdenakker G, Verleden GM, Vos R, Vanaudenaerde BM. Humoral immunity in phenotypes of chronic lung allograft dysfunction: a broncho-alveolar lavage fluid analysis. Transpl Immunol. 2016;38:27–32.

7. Walton DC, Hiho SJ, Cantwell LS, Diviney MB, Wright ST, Snell GI, Paraskeva MA, Westall GP. HLA matching at the eplet level protects against chronic lung allograft dysfunction. Am J Transplant. 2016;16:2695–703.
8. Loupy A, Lefaucheur C, Vernerey D, Prugger C, Duong van Huyen JP, Mooney N, Suberbielle C, Fremeaux-Bacchi V, Mejean A, Desgrandchamps F, Anglicheau D, Nochy D, Charron D, Empana JP, Delahousse M, Legendre C, Glotz D, Hill GS, Zeevi A, Jouven X. Complement-binding anti-HLA antibodies and kidney-allograft survival. N Engl J Med. 2013;369:1215–26.
9. Huibers MM, Gareau AJ, Beerthuijzen JM, Siera-de Koning E, van Kuik J, Kamburova EG, Vink A, de Jonge N, Lee TD, Otten HG, de Weger RA. Donor-specific antibodies are produced locally in ectopic lymphoid structures in cardiac allografts. Am J Transplant. 2017;17:246–54.
10. Cozzi E, Calabrese F, Schiavon M, Feltracco P, Seveso M, Carollo C, Loy M, Cardillo M, Rea F. Immediate and catastrophic antibody-mediated rejection in a lung transplant recipient with anti-angiotensin II receptor type 1 and anti-endothelin-1 receptor type a antibodies. Am J Transplant. 2017;17:557–64.
11. Reinsmoen NL, Mirocha J, Ensor CR, Marrari M, Chaux G, Levine DJ, Zhang X, Zeevi A. A 3-center study reveals new insights into the impact of non-HLA antibodies on lung transplantation outcome. Transplantation. 2017;101:1215–21.
12. Aguilar PR, Carpenter D, Ritter J, Yusen RD, Witt CA, Byers DE, Mohanakumar T, Kreisel D, Trulock EP, Hachem RR. The role of C4d deposition in the diagnosis of antibody-mediated rejection after lung transplantation. Am J Transplant. 2017;18:936.
13. Roden AC, Maleszewski JJ, Yi ES, Jenkins SM, Gandhi MJ, Scott JP, Aubry MC. Reproducibility of complement 4d deposition by immunofluorescence and immunohistochemistry in lung allograft biopsies. J Heart Lung Transplant. 2014;33:1223–32.
14. Westall GP, Snell GI, McLean C, Kotsimbos T, Williams T, Magro C. C3d and C4d deposition early after lung transplantation. J Heart Lung Transplant. 2008;27:722–8.
15. Orandi BJ, Lonze BE, Jackson A, Terezakis S, Kraus ES, Alachkar N, Bagnasco SM, Segev DL, Orens JB, Montgomery RA. Splenic irradiation for the treatment of severe antibody-mediated rejection. Am J Transplant. 2016;16:3041–5.
16. Wallace WD, Li N, Andersen CB, Arrossi AV, Askar M, Berry GJ, Denicola MM, Neil DA, Pavlisko EN, Reed EF, Remmelink M, Weigt SS, Weynand B, Zhang JQ, Budev MM, Farver CF. Banff study of pathologic changes in lung allograft biopsy specimens with donor-specific antibodies. J Heart Lung Transplant. 2016;35:40–8.
17. Berry G, Burke M, Andersen C, Angelini A, Bruneval P, Calabrese F, Fishbein MC, Goddard M, Leone O, Maleszewski J, Marboe C, Miller D, Neil D, Padera R, Rassl D, Revello M, Rice A, Stewart S, Yousem SA. Pathology of pulmonary antibody-mediated rejection: 2012 update from the Pathology Council of the ISHLT. J Heart Lung Transplant. 2013;32:14–21.
18. Dawson KL, Parulekar A, Seethamraju H. Treatment of hyperacute antibody-mediated lung allograft rejection with eculizumab. J Heart Lung Transplant. 2012;31:1325–6.
19. Schwab I, Nimmerjahn F. Intravenous immunoglobulin therapy: how does IgG modulate the immune system? Nat Rev Immunol. 2013;13:176–89.
20. Otani S, Davis AK, Cantwell L, Ivulich S, Pham A, Paraskeva MA, Snell GI, Westall GP. Evolving experience of treating antibody-mediated rejection following lung transplantation. Transpl Immunol. 2014;31:75–80.
21. Vacha M, Chery G, Hulbert A, Byrns J, Benedetti C, Finlen Copeland CA, Gray A, Onwuemene O, Palmer SM, Snyder LD. Antibody depletion strategy for the treatment of suspected antibody-mediated rejection in lung transplant recipients: does it work? Clin Transpl. 2017;31:e12886.
22. Witt CA, Gaut JP, Yusen RD, Byers DE, Iuppa JA, Bennett Bain K, Alexander Patterson G, Mohanakumar T, Trulock EP, Hachem RR. Acute antibody-mediated rejection after lung transplantation. J Heart Lung Transplant. 2013;32:1034–40.
23. Roux A, Bendib Le Lan I, Holifanjaniaina S, Thomas KA, Hamid AM, Picard C, Grenet D, De Miranda S, Douvry B, Beaumont-Azuar L, Sage E, Devaquet J, Cuquemelle E, Le Guen M, Spreafico R, Suberbielle-Boissel C, Stern M, Parquin F, Foch Lung Transplantation Group. Antibody-mediated rejection in lung transplantation: clinical outcomes and donor-specific antibody characteristics. Am J Transplant. 2016;16:1216–28.

Chapter 8
The Human Respiratory Microbiome: The End of the Beginning?

Alicia B. Mitchell and Allan R. Glanville

8.1 Introduction

We live in exciting times. Our concept of the world around us and particularly the world within, is rapidly changing, driven by the development of tools that allow a precise definition of the richness and diversity of the microbial species that inhabit the respiratory tract. Yet we have only just begun to understand this silent world that was till recently, was unknown and unexplored. Indeed, the lung was once considered sterile below the vocal cords, protected by vigorous host immune defences which included efficient mucociliary clearance, the cough reflex and both innate and adaptive immune responses. The historical development of our current understanding is worth reflection. The earliest essays into our complex microbial milieu began with the examination of mouth flora in the late 1950s and progressed episodically thereafter. This was based on the translation of novel scientific techniques such as polymerase chain reactions which augmented, if not supplanted, traditional culture techniques. Two seismic phase shifts in our ability to probe this silent world, namely Seldinger technology and ultimately next generation sequencing (NGS), have opened the door into the realisation that the lung contains a vast array of

A. B. Mitchell
The Lung Transplant Unit, Department of Thoracic Medicine, St Vincent's Hospital, Sydney, NSW, Australia

The Woolcock Institute of Medical Research, Sydney, NSW, Australia

School of Medical and Molecular Biosciences, University of Technology Sydney, Ultimo, NSW, Australia

A. R. Glanville (✉)
The Lung Transplant Unit, Department of Thoracic Medicine, St Vincent's Hospital, Sydney, NSW, Australia
e-mail: allan.glanville@svha.org.au

A. R. Glanville (ed.), *Essentials in Lung Transplantation*,
https://doi.org/10.1007/978-3-319-90933-2_8

resident viral species, many of which are as yet uncharacterised and unnamed. In truth, we are very much at the beginning of our exploration of this domain but we do have the tools to permit a robust assessment. Where this assessment will take us remains to be discovered but the threshold of a new dawn in our relationship with our inner world is upon us.

8.2 The Lung Microbiome

The human body is host to a large range of microbial cells, including bacteria, viruses, bacteriophages, fungi, and archaea. These microscopic organisms substantially outnumber the quantity of human cells in the body, with the presence of up to a trillion microbial cells and a 1:100 ratio of human-coded genes to microbial-associated genes [1]. Complex interactions between the human microbiome and the immune system have developed over a long history of co-evolution, leading to an ongoing symbiotic relationship [2]. The human microbiome project (HMP) was a turning point in our understanding of the rich and diverse communities of microbes that call many of our body surfaces home [3]. After the initial stages of the HMP where the lung was omitted as a priority site, a further project was funded, which focused specifically on the microbiome of the respiratory tract. The advent of next-generation sequencing techniques revolutionized our understanding of microbial presence within the lung. For many years, there was a commonly held belief that the respiratory tract was sterile, and the presence of any micro-organism was assumed to be pathogenic and associated with symptomatic illness. The use of culture-based techniques, which required a significant initial microbial load in samples, was important in maintaining the sterility theory. After the initial efforts of the HMP, studies started to emerge showing that the lower respiratory tract was home to a diverse range of microbes, with clear distinctions between healthy and chronic disease states [4, 5].

Establishment of resident microbiomes within different body compartments are crucial in immune development. Early exposure to allergens, such as house dust mite, have been shown to be associated with increased inflammation and allergic responses in mouse models. However, development of the lung microbiome and shifts towards certain species of bacteria appeared to be protective and led to a decrease in allergic responses [6]. This study supports the notion that the microbiota of the lungs is critical in later development of asthma in children. Further studies have shown that diet, genetics and environmental exposures all play a role in determining the composition of the microbiome and their effects on immune development [7, 8]. Interactions between the lung microbiome and the gut microbiome have been established [9], and the cross-talk between these two vital organs appears to be important in development of disease [10, 11]. The absence of a normal gut microbiome predisposes individuals to an increased risk of lung infections [12], indicating that the intestinal microbiome may have important effects on dysbiotic states in the lung microbiome.

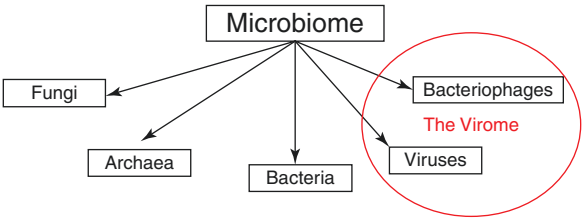


Fig. 8.1 Constituents of the human respiratory microbiome. The human respiratory microbiome comprises all organisms that live in or on the human lung and respiratory tract including bacteria, fungi, archaea, viruses and bacteriophages. The virome includes viruses and bacteriophages

The respiratory microbiome includes all airway and lung-tissue associated microbes, and is more specifically defined as the lower respiratory tract beneath the larynx (Fig. 8.1). Above this, the oropharyngeal and nasal-associated microbiota are distinct and defined as the upper respiratory tract. The microbiome of the nasal and oral regions have been researched more thoroughly and are currently, better defined than the microbial communities of the lower respiratory tract. This is largely due to the difficulties in obtaining samples from the distal airways, while attempting to minimise upper-airway contamination. Studies have shown that the biological signals obtained from both sputum and bronchoalveolar lavage (BAL) obtained by bronchoscopy are clinically meaningful [13–15] and not significantly confounded by signals from the oral microbiome [16, 17].

A further challenge presented when investigating the microbiota of the lower respiratory tract, is the greatly reduced biomass of microbes compared with the upper respiratory tract and gut microbiota [16, 18]. The lower biomass may be due to low availability of nutrient sources in the lungs, and a number of selective pressures based on variations in physiology within this organ such as variable pH, relative blood perfusion, relative alveolar ventilation, temperature, oxygen concentration, epithelial cell structure, deposition of inhaled particles, and number of inflammatory cells present [19, 20]. The greatest impact of these physiological changes is seen in severe chronic respiratory diseases where the lung microenvironment becomes maladaptive due to extra-cellular matrix remodelling and inflammation [21, 22].

The microbial composition contained within the lungs appears to be a balance between immigration of species, likely due to microaspiration and direct movement of species into the lungs from the upper respiratory tract; elimination as a result of mucociliary mechanisms, cough and innate and adaptive immune responses; and selective pressures present within the lungs themselves. Early studies established that microbiota from the oral cavity are constantly being introduced into the lower respiratory tract, most commonly as microaspiration events during sleep [23, 24] and also due to the direct mucosal extension between the oral cavity and the lungs [4]. Elimination is achieved through trapping of microbes by the secreted mucus within the lower respiratory tract, and is either removed through the beating of cilia to move microbes up and out of the tract, or coughing mechanisms. Inflammatory

cells and cytokines produced by the host are also involved in the clearance of potential pathogens [17]. Through these mechanisms, a steady state of immigration and elimination processes is reached which is involved in determining the resultant composition of the lung microbiome [16].

8.3 Lung Transplantation and the Respiratory Microbiome

Lung transplantation provides us with a unique opportunity to investigate a range of factors involved in shaping the microbiome, including host-specific, immune-related and extrinsic factors, after donor lungs have been transplanted into a recipient. In effect, this is transplantation of the respiratory microbiome into a new host within the transplanted set of lungs. Lung transplantation offers hope to many individuals with end-stage lung disease for whom other therapies have failed. However, compared with other solid organ transplantation, lung transplants are still associated with the lowest long-term survival rates [25].

In the early post-transplant period, patients who have undergone lung transplantation have regular surveillance bronchoscopies to monitor the allograft for signs of infection and rejection. In some cases, extra bronchoscopies are also organized for clinical indications. This allows ample opportunity to sample the microbiome longitudinally in these subjects (Fig. 8.2). Many early longitudinal microbiome studies were conducted in lung transplant cohorts due to the ability to easily and regularly collect lower respiratory tract samples [26]. One of the first studies to monitor the microbiome within transplanted lungs, showed that less than 10% of microbial species were retained during the early post-transplant period [26]. A further study monitored the lung microbiome for up to 12 months post lung transplantation, and showed that over the first 9 months, bacterial diversity continued to increase, likely reflecting the decrease in immunosuppressive regimes in these patients. After this time point, bacterial diversity measures plateaued and decreased, which may be associated with the development of a stable state [27]. Antibiotic use post-transplant has demonstrated

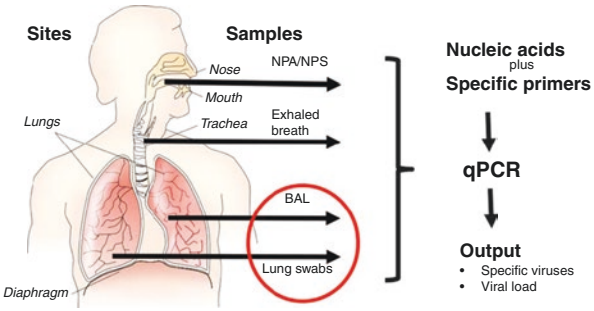


Fig. 8.2 Sampling and analysing the human respiratory microbiome. Both upper and lower respiratory tract samples can be collected using a variety of invasive and non-invasive methods and processed to determine microbial load and diversity using conventional techniques as well as next generation sequencing technology

association with dynamic fluctuations in the lung microbiome [28]. These studies suggest that there are early changes in microbiome burden and diversity post-transplant, however the clinical implications of these fluctuations are yet to be elucidated.

Many of the studies focusing on donor transmission of microbes have looked specifically at reducing the transmission of blood-borne viruses such as human immunodeficiency virus (HIV), and Hepatitis B (HBV) and C (HCV) viruses. It was previously thought that donor microbe transmission was a rare and dangerous event [29], however new evidence suggests that the lung microbiome is transplanted into the recipient at the time of lung transplantation and the composition of the donor microbiome may be significant in influencing recipient outcomes. There are a number of factors which will influence the microbiome post-transplant including nosocomial acquisition of microbes while in hospital, interaction between lower respiratory tract microbiota in the transplanted lungs and upper respiratory tract microbes, impact of aspiration of gastric organisms due to gastro-oesophageal reflux [30], and denervation of the allograft causing decreased lung clearance mechanisms. At the time of transplantation, the vagus nerve is necessarily transected, as part of the surgical process, leading to a decreased cough reflex, impaired ciliary beat frequency leading to impaired mucociliary clearance and possibly decreased gastro-oesophageal motility [31]. These factors all contribute to impaired elimination, and persistence of inhaled micro-organisms. Furthermore, the high-dose immunosuppression in the early post-transplant period will further impact microbial elimination [32] (Figs. 8.3, 8.4, and 8.5).

There has been little evidence exploring the role of the microbiome in acute allograft dysfunction including primary graft failure. However, up to 55% of lung transplant recipients have to be treated for acute rejection events within the first year of transplant [33], indicating the importance of elucidating contributing factors. A limited number of studies have shown that both bacterial and viral infections cause perturbations to the underlying microbiota, which may play a role in early allograft dysfunction. *Chlamydia pneumoniae* infection has been shown to be associated with acute rejection events [34], comparably with parainfluenza virus, which has

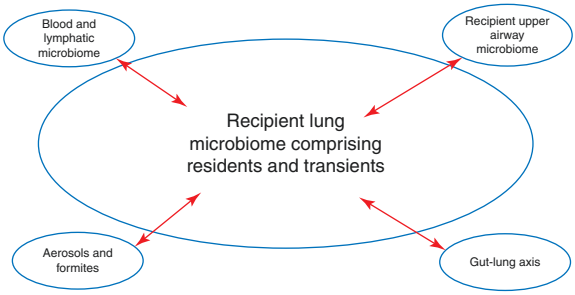


Fig. 8.3 The healthy lung microbiome. In the healthy lung, there is an equilibrium between resident and transient species with inputs from the upper airway, blood borne agents, the gut-lung axis and aerosols and fomites. Numerous forces combine to create a dynamic situation such that the net result represents the balance between acquisition, elimination and local defence measures designed to maintain an equilibrium between resident and transient species

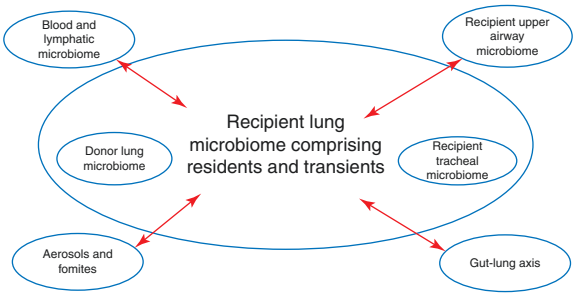


Fig. 8.4 The healthy lung microbiome after lung transplantation. After lung transplantation, the healthy lung maintains an equilibrium between resident and transient species also with inputs from the upper airway, blood borne agents, the gut-lung axis and aerosols and fomites. However, the new lungs now contain the donor microbiome which may be qualitatively and quantitatively different from the microbiome of the explanted native lungs. Part of the original microbiome is retained in the non-transplanted large airways

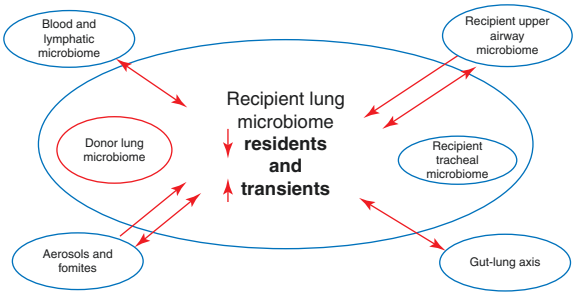


Fig. 8.5 Dysbiosis of the lung microbiome after lung transplantation. After lung transplantation, the healthy lung equilibrium between resident and transient species may be challenged by the donor microbiome transplanted within the new lungs which may be qualitatively and quantitatively different from the microbiome of the explanted native lungs. Other external events can also lead to dysbiosis including community acquired respiratory virus infection, the ex-vivo stage of lung procurement and the impact of immune suppression. Figure reproduced with permission from Seminars in Respiratory and Critical Care Medicine, 2018 (39): the human respiratory microbiome: implications and impact; Mitchell et al.

also demonstrated a role in later development of bronchiolitis obliterans syndrome (BOS) [35]. Conversely, Epstein Barr Virus (EBV) has not been shown to have any effects on the development of acute rejection, instead it appears to be a surrogate marker of effective immunosuppression [36].

BOS is one of the major factors which limits long term survival in lung transplantation. The primary pathological feature is intraluminal airway fibrosis located predominantly within the terminal bronchioles limiting lung function [37]. Recent studies show that there are variations in the lung microbiome in the early post-transplant period when compared with healthy controls. A single study showed an increase in the bacterial burden [26], while multiple other studies have shown decreased bacterial burden post lung transplantation [28, 38, 39]. Specific bacterial species appear to play an important role in mediating BOS development. Of note is

Pseudomonas, where multiple studies using culture-based methodologies have shown that airway colonization with *P. aeruginosa* is predictive of later development of chronic rejection [40–42]. However, one study has shown a protective effect of *Pseudomonas* in the development of BOS [28]. Therefore, more research in this area, especially in the era of next generation sequencing techniques, is required to better understand these effects.

8.4 The Human Respiratory Mycobiome

The fungal component of the microbiome, termed the 'mycobiome', remains largely uncharacterized. There are a very limited number of studies published investigating the effect of fungal species on the greater microbiota of the lungs. Studies have shown that there is a resident mycobiome in healthy individuals dominated by *Cladosporium*, *Eurotium*, *Penicillium*, *Aspergillus*, *Candida*, and *Pneumocystis* [39, 43]. This knowledge has been greatly enhanced by the use of sequencing methods, as up to 82% of the fungal species in sputum are unable to be cultured and thus had previously been missed [44]. In lung transplantation, there is limited evidence regarding how the mycobiome is impacted post-transplant, however a small study has shown there to be decreased fungal abundance and diversity in the lungs of transplant patients compared with healthy controls [39]. In this group of patients, the mycobiome was largely dominated by *Candida* species which were found in both upper and lower respiratory tract samples. *Aspergillus* sp. was detected in the BAL samples of two individuals at high levels, and *Cryptococcus* was also found at low levels in 6 individuals [39]. Furthermore, presence of certain fungal species such as *Aspergillus* have been associated with the development of BOS, and increased BOS-related mortality [45]. This was further demonstrated by Willner et al., where the absence of *Aspergillus* in transplant patients was associated with a lower frequency of BOS development [28]. Research on the impact of fungal species on both the mycobiome and on transplant outcomes is still in its early stages, but this remains an important area to focus on in characterizing the different aspects of microbiome in lung transplantation.

8.5 The Human Respiratory Virome

There are inherent challenges in investigating the viral component of the respiratory microbiome due to the extremely low biomass of viruses present. However, some evidence is emerging that supports an important role for viruses within the lung microbiome and that highlights variations in the virome in different disease states. In lung transplantation, the viral burden has been shown to be significantly greater when compared with healthy controls with a range of viral species detected. Furthermore, the most dominant viral family detected were *Anelloviruses*, including torque teno virus (TTV), accounting for 68% of all viral reads detected [46]. This same

research group went on to investigate the role of TTV in the peri-operative period, and demonstrated that the magnitude by which the viral load during this period was associated with the development of primary graft dysfunction (PGD) [47]. It was hypothesized that those with smaller increases in TTV load had more potent immune activation which may be responsible for the tissue injury associated with PGD [47].

Many studies have investigated the relationship between viral infections and the development of BOS. It has been shown that infection with influenza virus is associated with a decline in lung function which may be associated with graft dysfunction [48]. The one-year incidence of progression to BOS is significantly increased in patients with a PCR-detected respiratory virus [49], with multiple other studies confirming the positive correlation between viral detection and both acute [50] and chronic rejection events [51]. Furthermore, donor transmission of EBV to an EBV-naïve recipient demonstrates the greatest risk for development of post-transplant lymphoproliferative disease (PTLD) which is associated with significant mortality [52, 53]. Cytomegalovirus (CMV) is also a virus of particular interest in transplant populations due to the associated CMV pneumonia and death. The risks associated with CMV have largely been ameliorated in recent times due to the widespread use of CMV prophylaxis in lung transplant patients [54, 55].

There has been a limited amount of studies focusing on the role of the virome in lung transplant subjects, however these studies have shown a significant role for respiratory viruses. Further research is needed in this area, specifically prospective, longitudinal studies to determine the direct impact of the presence of viruses on both early and late transplant outcomes. Early evidence suggests that certain viruses and their respective viral loads, may be able to be used as biomarkers of effective immunosuppression and early treatment. Advances in sequencing technologies have allowed a whole new world of viruses to be identified from within the lung, but much work is needed in naming and characterizing the plethora of new viruses which have been uncovered.

8.6 Conclusions

Our knowledge regarding the breadth of constituents of the lung microbiome is still in its infancy. The bacterial component of the microbiome has received the most attention as part of the human microbiome project, and evidence is beginning to emerge that describes significant differences in both bacterial burden and diversity in lung transplantation. However, the challenge now remains of determining the impact of these differences on transplant outcomes.

The advent of next-generation sequencing techniques allows ample opportunity for new discoveries to be made, and to further elucidate the details of these different aspects of the lung microbiome and how they may vary in different disease states. Our knowledge regarding the role and influence of both fungal and viral species as part of the greater microbiome is limited. Additional research in these areas may prove important for monitoring changes as precursors to rejection events and chronic lung allograft dysfunction.

Furthermore, understanding the interactions between the different microbial members which constitute the microbiome may be critical in future attempts to modify the microbiome for therapeutic gain. There have been both technological and financial limitations previously, which may have hindered our ability to gain a full understanding of the respiratory microbiome. However, as sequencing technologies become more commonly available and affordable, it is expected that we will develop a deeper understanding regarding all members of this complex and often silent world which will drive insights into possible therapeutic endeavours.

References

1. Gill SR, Pop M, Deboy RT, et al. Metagenomic analysis of the human distal gut microbiome. Science. 2006;312:1355–9.
2. Backhed F, Ley RE, Sonnenburg JL, Peterson DA, Gordon JI. Host-bacterial mutualism in the human intestine. Science. 2005;307:1915–20.
3. Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett CM, Knight R, Gordon JI. The human microbiome project. Nature. 2007;449:804–10.
4. Dickson RP, Erb-Downward JR, Huffnagle GB. The role of the bacterial microbiome in lung disease. Expert Rev Respir Med. 2013;7:245–57.
5. The Lung HIV Microbiome Project (LHMP). National Heart, Lung and Blood Institute. 2015. https://biolincc.nhlbi.nih.gov/studies/lhmp/. Accessed 30 June 2017.
6. Gollwitzer ES, Saglani S, Trompette A, et al. Lung microbiota promotes tolerance to allergens in neonates via PD-L1. Nat Med. 2014;20:642–7.
7. Teo SM, Mok D, Pham K, et al. The infant nasopharyngeal microbiome impacts severity of lower respiratory infection and risk of asthma development. Cell Host Microbe. 2015;17:704–15.
8. Biesbroek G, Tsivtsivadze E, Sanders EA, et al. Early respiratory microbiota composition determines bacterial succession patterns and respiratory health in children. Am J Respir Crit Care Med. 2014;190:1283–92.
9. Trompette A, Gollwitzer ES, Yadava K, et al. Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis. Nat Med. 2014;20:159–66.
10. Bruzzese E, Callegari ML, Raia V, et al. Disrupted intestinal microbiota and intestinal inflammation in children with cystic fibrosis and its restoration with Lactobacillus GG: a randomised clinical trial. PLoS One. 2014;9:e87796.
11. Bisgaard H, Li N, Bonnelykke K, et al. Reduced diversity of the intestinal microbiota during infancy is associated with increased risk of allergic disease at school age. J Allergy Clin Immunol. 2011;128:646–52.e1-5.
12. Inagaki H, Suzuki T, Nomoto K, Yoshikai Y. Increased susceptibility to primary infection with Listeria monocytogenes in germfree mice may be due to lack of accumulation of L-selectin+ CD44+ T cells in sites of inflammation. Infect Immun. 1996;64:3280–7.
13. Rogers GB, van der Gast CJ, Cuthbertson L, et al. Clinical measures of disease in adult non-CF bronchiectasis correlate with airway microbiota composition. Thorax. 2013;68:731–7.
14. Rogers GB, Zain NM, Bruce KD, et al. A novel microbiota stratification system predicts future exacerbations in bronchiectasis. Ann Am Thorac Soc. 2014;11:496–503.
15. Molyneaux PL, Mallia P, Cox MJ, et al. Outgrowth of the bacterial airway microbiome after rhinovirus exacerbation of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2013;188:1224–31.
16. Bassis CM, Erb-Downward JR, Dickson RP, et al. Analysis of the upper respiratory tract microbiotas as the source of the lung and gastric microbiotas in healthy individuals. MBio. 2015;6:e00037.

17. Segal LN, Alekseyenko AV, Clemente JC, et al. Enrichment of lung microbiome with supraglottic taxa is associated with increased pulmonary inflammation. Microbiome. 2013;1:19.
18. Sze MA, Dimitriu PA, Hayashi S, et al. The lung tissue microbiome in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2012;185:1073–80.
19. West JB. Regional differences in the lung. Chest. 1978;74:426–37.
20. O'Dwyer DN, Dickson RP, Moore BB. The lung microbiome, immunity, and the pathogenesis of chronic lung disease. J Immunol. 2016;196:4839–47.
21. Dickson RP, Erb-Downward JR, Martinez FJ, Huffnagle GB. The microbiome and the respiratory tract. Annu Rev Physiol. 2016;78:481–504.
22. Bidan CM, Veldsink AC, Meurs H, Gosens R. Airway and extracellular matrix mechanics in COPD. Front Physiol. 2015;6:346.
23. Gleeson K, Eggli DF, Maxwell SL. Quantitative aspiration during sleep in normal subjects. Chest. 1997;111:1266–72.
24. Huxley EJ, Viroslav J, Gray WR, Pierce AK. Pharyngeal aspiration in normal adults and patients with depressed consciousness. Am J Med. 1978;64:564–8.
25. Rana A, Gruessner A, Agopian VG, et al. Survival benefit of solid-organ transplant in the United States. JAMA Surg. 2015;150:252–9.
26. Borewicz K, Pragman AA, Kim HB, Hertz M, Wendt C, Isaacson RE. Longitudinal analysis of the lung microbiome in lung transplantation. FEMS Microbiol Lett. 2013;339:57–65.
27. Luna R, Sagar M, Crabtree S, et al. Characterization of the lung microbiome in pediatric lung transplant recipients. J Heart Lung Transplant. 2013;32:S291.
28. Willner DL, Hugenholtz P, Yerkovich ST, et al. Reestablishment of recipient-associated microbiota in the lung allograft is linked to reduced risk of bronchiolitis obliterans syndrome. Am J Respir Crit Care Med. 2013;187:640–7.
29. Ison MG, Hager J, Blumberg E, et al. Donor-derived disease transmission events in the United States: data reviewed by the OPTN/UNOS Disease Transmission Advisory Committee. Am J Transplant. 2009;9:1929–35.
30. Davis CS, Shankaran V, Kovacs EJ, et al. Gastroesophageal reflux disease after lung transplantation: pathophysiology and implications for treatment. Surgery. 2010;148:737–44; discussion 44-5.
31. Ferdinande P, Bruyninckx F, Van Raemdonck D, Daenen W, Verleden G, Leuven Lung Transplant G. Phrenic nerve dysfunction after heart-lung and lung transplantation. J Heart Lung Transplant. 2004;23:105–9.
32. Bhorade SM, Villanueva J, Jordan A, Garrity ER. Immunosuppressive regimens in lung transplant recipients. Drugs Today (Barc). 2004;40:1003–12.
33. Martinu T, Chen DF, Palmer SM. Acute rejection and humoral sensitization in lung transplant recipients. Proc Am Thorac Soc. 2009;6:54–65.
34. Glanville AR, Gencay M, Tamm M, et al. Chlamydia pneumoniae infection after lung transplantation. J Heart Lung Transplant. 2005;24:131–6.
35. Vilchez RA, McCurry K, Dauber J, et al. The epidemiology of parainfluenza virus infection in lung transplant recipients. Clin Infect Dis. 2001;33:2004–8.
36. Ahya VN, Douglas LP, Andreadis C, et al. Association between elevated whole blood Epstein-Barr virus (EBV)-encoded RNA EBV polymerase chain reaction and reduced incidence of acute lung allograft rejection. J Heart Lung Transplant. 2007;26:839–44.
37. Thompson BR, Hodgson YM, Kotsimbos T, et al. Bronchiolitis obliterans syndrome leads to a functional deterioration of the acinus post lung transplant. Thorax. 2014;69:487–8.
38. Dickson RP, Erb-Downward JR, Freeman CM, et al. Changes in the lung microbiome following lung transplantation include the emergence of two distinct Pseudomonas species with distinct clinical associations. PLoS One. 2014;9:e97214.
39. Charlson ES, Diamond JM, Bittinger K, et al. Lung-enriched organisms and aberrant bacterial and fungal respiratory microbiota after lung transplant. Am J Respir Crit Care Med. 2012;186:536–45.
40. Gottlieb J, Mattner F, Weissbrodt H, et al. Impact of graft colonization with gram-negative bacteria after lung transplantation on the development of bronchiolitis obliterans syndrome in recipients with cystic fibrosis. Respir Med. 2009;103:743–9.

41. Vos R, Vanaudenaerde BM, Geudens N, Dupont LJ, Van Raemdonck DE, Verleden GM. Pseudomonal airway colonisation: risk factor for bronchiolitis obliterans syndrome after lung transplantation? Eur Respir J. 2008;31:1037–45.
42. Botha P, Archer L, Anderson RL, et al. Pseudomonas aeruginosa colonization of the allograft after lung transplantation and the risk of bronchiolitis obliterans syndrome. Transplantation. 2008;85:771–4.
43. Delhaes L, Monchy S, Frealle E, et al. The airway microbiota in cystic fibrosis: a complex fungal and bacterial community—implications for therapeutic management. PLoS One. 2012;7:e36313.
44. Harrison M, Twomey K, Mccarthy Y, et al. The role of second-generation sequencing to characterize the fungal microbiota in the adult cystic fibrosis airway, and its correlation with standard culture-based methods and clinical phenotype. Pediatr Pulmonol. 2012;47:322.
45. Weigt SS, Elashoff RM, Huang C, et al. Aspergillus colonization of the lung allograft is a risk factor for bronchiolitis obliterans syndrome. Am J Transplant. 2009;9:1903–11.
46. Young JC, Chehoud C, Bittinger K, et al. Viral metagenomics reveal blooms of anelloviruses in the respiratory tract of lung transplant recipients. Am J Transplant. 2015;15:200–9.
47. Abbas AA, Diamond JM, Chehoud C, et al. The perioperative lung transplant virome: torque teno viruses are elevated in donor lungs and show divergent dynamics in primary graft dysfunction. Am J Transplant. 2017;17:1313.
48. Garantziotis S, Howell DN, McAdams HP, Davis RD, Henshaw NG, Palmer SM. Influenza pneumonia in lung transplant recipients: clinical features and association with bronchiolitis obliterans syndrome. Chest. 2001;119:1277–80.
49. Gottlieb J, Schulz TF, Welte T, et al. Community-acquired respiratory viral infections in lung transplant recipients: a single season cohort study. Transplantation. 2009;87:1530–7.
50. Kumar D, Erdman D, Keshavjee S, et al. Clinical impact of community-acquired respiratory viruses on bronchiolitis obliterans after lung transplant. Am J Transplant. 2005;5:2031–6.
51. Khalifah AP, Hachem RR, Chakinala MM, et al. Respiratory viral infections are a distinct risk for bronchiolitis obliterans syndrome and death. Am J Respir Crit Care Med. 2004;170:181–7.
52. Bakker NA, Verschuuren EA, Erasmus ME, et al. Epstein-Barr virus-DNA load monitoring late after lung transplantation: a surrogate marker of the degree of immunosuppression and a safe guide to reduce immunosuppression. Transplantation. 2007;83:433–8.
53. Engelmann I, Welte T, Fuhner T, et al. Detection of Epstein-Barr virus DNA in peripheral blood is associated with the development of bronchiolitis obliterans syndrome after lung transplantation. J Clin Virol. 2009;45:47–53.
54. Finlen Copeland CA, Davis WA, Snyder LD, et al. Long-term efficacy and safety of 12 months of valganciclovir prophylaxis compared with 3 months after lung transplantation: a single-center, long-term follow-up analysis from a randomized, controlled cytomegalovirus prevention trial. J Heart Lung Transplant. 2011;30:990–6.
55. Hammond SP, Martin ST, Roberts K, et al. Cytomegalovirus disease in lung transplantation: impact of recipient seropositivity and duration of antiviral prophylaxis. Transpl Infect Dis. 2013;15:163–70.

Chapter 9
Community Acquired Respiratory Viruses

Marshall Plit

9.1 Introduction

Community acquired respiratory virus (CARV) infections have been associated with significant acute morbidity and occasional mortality in lung transplant (LTx) recipients. The exposure of the lung allograft to environmental pathogens in concert with an impaired immune response and local factors such as defective mucosal barrier function places makes it especially vulnerable as compared to other solid organ transplants. The lung allograft also has a unique microbiome that accompanies it when transplanted from the donor to the recipient. This includes bacteria and viruses, some of which may have pathogenic potential. There is also accumulating evidence that CARV infection triggers both innate and adaptive immune responses that have a particular propensity to amplify lung allograft injury. This may result in a permanent and progressive loss of lung function manifest as chronic lung allograft dysfunction (CLAD) of which bronchiolitis obliterans syndrome (BOS) is the most common phenotype). This complication remains the most important factor limiting the long-term success of lung transplantation and occurs in 50% of recipients within 5 years [1]. This phenomenon bears striking similarity to the development of alloimmune lung disease after hematopoietic stem cell transplantation (HSCT) where respiratory virus infections early after HSCT are an important predictor for the development of persistent airflow limitation due to obliterative bronchiolitis [2]. This review focuses on the spectrum of CARV in lung transplant patients and briefly explores available evidence that supports the association between CARV and the development of permanent and possibly progressive lung injury.

M. Plit
Thoracic Medicine and Medical Lung Transplant Unit, St Vincent's Hospital, Sydney, NSW, Australia
e-mail: Marshall.Plit@svha.org.au

A. R. Glanville (ed.), *Essentials in Lung Transplantation*,
https://doi.org/10.1007/978-3-319-90933-2_9

9.2 Paramyxoviruses

The paramyxoviridae family are enveloped RNA viruses which include the important pathogens respiratory syncytial virus (RSV), parainfluenzae (PI) 1–4 and human metapneumovirus (HMPV). This group of viruses have a similar pathogenesis with an incubation period of 2–8 days. They initially replicate in the nasopharyngeal epithelium, and then spread to the lower respiratory tract 1–3 days later [3, 4]. The frequency of RSV and PI virus infections throughout life indicates that there is a large susceptible population which is prone to recurrent mild reinfections and are the primary source of serious infections in infants and those with underlying medical conditions. Furthermore, reinfections in previously healthy adults persons results in a considerable burden of disease in the community. These viruses have a propensity to cause bronchiolitis with necrosis and sloughing of the epithelium of the small airways. The clinical presentation include chest hyperinflation, atelectasis, coughing and wheezing. Pneumonia with lung infiltrates and consolidation may complicate serious infections in adults. RSV respiratory tract infections tend to last longer than those caused by other common viruses. Parainfluenza causes a spectrum of respiratory illnesses to RSV but result in fewer hospitalizations. Human metapneumovirus (HMPV) was only discovered in 2001 and has been identified as a common cause of respiratory tract infections [5]. Its epidemiology and clinical presentation is very similar to RSV and PI virus. HMPV has a worldwide distribution and more than 90% of people have been infected by the age of 5 years typically during late autumn and winter. This virus has been implicated in 15–25% of all cases of bronchiolitis in and pneumonia in children <2 years of age. HMPV has however been associated with symptomatic infection in older children and adults. HMPV can cause also cause severe infections such as bronchiolitis and pneumonia and is responsible for 5–10% of hospitalizations of children suffering from acute respiratory tract infections [6].

9.3 Therapy for Paramyxovirus Infections

Paramyxoviruses appear to have a propensity to cause severe symptoms, possibly acute allograft rejection and initiate progressive airway injury in lung transplant recipients [7–20], Live attenuated vaccines produced by reverse genetics have shown good efficacy in animals but are not a viable clinical option at this stage. Ribavirin has shown activity both in vitro and in animal models against paramyxoviruses although there are no randomized clinical trials. Hopkins et al. published a large prospective study in 2008 and reported that HMPV treated with intravenous ribavirin and corticosteroids did not develop BOS [17]. However, 38% of patients with RSV treated with the same treatment regimen developed BOS. In contrast to this finding, we reported that only 1 in 18 (0.5%) of lung transplant recipients infected with RSV developed BOS within 3 months after receiving a similar treatment regimen [21]. In concert with Hopkins' study none of our patients with HMPV treated with ribavirin and corticosteroids developed BOS [21].PI virus infection was not associated with the development of BOS even without ribavirin treatment. This

raises the interesting question as to whether this anti-paramyxovirus treatment regimen is protective for the subsequent development of BOS in patients with HMPV and RSV. Similarly, McCurdy reported in 2003 that no decline in lung function occurred after 1 year in recipients with RSV or PIV treated with aerosolized ribavirin [22]. Liu et al. [23] and Pelaez et al. [24] published similar outcomes in recipients treated with aerosolized and oral ribavirin respectively. These findings have been duplicated in our large study of intravenous ribavirin followed by oral ribavirin [25]. RNA interference therapy is a small RNA targeting RSV replication which was shown in a large prospective randomized study to reduce the risk of BOS after RSV in LTx recipients. However, this therapy is as yet not commercially available [26].

9.4 Human Rhinovirus

Human rhinovirus (HRV) is a member of the family Picornaviridae and the genus Enterovirus. HRV is responsible for more than 50% of 'cold-like' illnesses and has been linked to exacerbations of chronic obstructive airway disease, asthma and bronchiolitis in infants as well as fatal pneumonia in the elderly and immunosuppressed [27]. However, a few pathological reports have also implicated HRV in causing interstitial lung disease, bronchiolitis obliterans and organizing pneumonia by mechanisms that suggest the virus induces a pro-inflammatory response [27]. With the advent of PCR-based diagnostic assays for CARV, HRV are increasingly recognized to cause acute respiratory illness in immunosuppressed hosts [28, 29].

9.5 Human Rhinovirus in Lung Transplant Recipients

Rhinovirus infection can persist in lung transplant recipients with graft dysfunction and may have a significant clinical impact in this high risk group of recipients [30]. In a study of 36 symptomatic lung transplant recipients in Italy in 2011, HRV was detected in bronchoalveolar lavage specimens in 41.7% of lung transplant recipients vs 14.5% from other patients [31]. The spectrum of disease in the HRV positive lung transplant patients included pneumonia, acute respiratory insufficiency and acute rejection. However, acute rejection in association with HRV does not appear to be a consistent finding [32].

9.6 Adenovirus

Adenoviruses are non-enveloped DNA viruses that belong to the Adenoviridae family. They are ubiquitous and primary infection usually occurs in the first few years of life. It is usually associated with mild self-limiting disease. Although the virus can remain latent in lymphoproliferative tissue, it is speculated that clinical illness

due to adenovirus infection in the immunocompromised host is due to primary infection from the environment or the result of transmission from the donor rather than due to reactivation of latent virus [33]. Adenovirus viraemia is reported to be relatively common in adult lung transplant recipients which is self-limiting and has not been associated with acute rejection or a loss of lung function [34]. However, severe infection has been reported in transplant patients.

9.7 Influenza

Influenza outbreaks mainly occur during winter. The factors that determine the extent and severity of outbreaks are not clearly understood but the susceptibility of the population as determined by the presence of antibodies to the prevailing virus plays a major role. However, the virulence and pathogenicity of the virus result in variations in disease severity. Influenza A (H1, H2, H3) in particular, has a high propensity to undergo antigenic change of their envelope glycoproteins, the hemagglutinin and the neuraminidases. Antigenic changes are less likely in influenza B and only antigenic drifts in the hemagglutinin have been described. Although the highest death rates from influenza during epidemics have a bimodal distribution involving the elderly and infants, pandemics have been associated with high morbidity and mortality in young adults. People with health problems or immunocompromised states are at increased risk of complications and death.

9.8 Influenza Vaccines

Current influenza vaccines are trivalent or quadrivalent. The trivalent vaccine contains two influenza A virus antigens and one influenza B virus antigen, whereas the quadrivalent vaccine contains two influenza A antigens and two influenza B antigens. The protective efficacy of the vaccine is largely determined by the relationship ("match") between the strains in the vaccine and viruses that circulate in the outbreak. Vaccination results in fewer infections and fewer missed days from work. In a 2014 meta-analysis of randomized trials and observational studies of healthy adults, the overall efficacy of inactivated vaccines in preventing laboratory-confirmed influenza was 60% [35].The overall effectiveness of inactivated vaccine against *influenza-like illness* was 16%. The discrepancy between protection against laboratory-confirmed influenza and influenza-like illness is likely related to the inability to always distinguish symptoms of influenza from illness due to non-influenza respiratory viruses. Vaccine efficacy in lung transplant patients is not

known but because of presumed lower efficacy, some units provide two consecutive vaccines 6 weeks apart to boost the immune response.

9.9 Pharmacological Agents for Influenza

The benefit of oseltamivir and zanamivir has been challenged in various meta-analysis studies [36–40]. In particular, the benefit of this treatment in lung transplant patients with influenza is not known. Treatment with a neuraminidase inhibitor is nevertheless recommended provided that oseltamivir-resistant influenza is not suspected [41]. This is consistent with the recommendations of the Infectious Diseases Society of America (IDSA) and the CDC [42, 43]. When initiated promptly, antiviral therapy with a neuraminidase inhibitor can shorten the duration of influenza symptoms by up to 3 days in immunocompetent patients. In most studies, the benefit has been greatest when given within the first 24–30 h and in patients with fever at presentation. The adamantanes, amantadine and rimantadine, are active only against influenza A viruses, but these drugs are infrequently indicated due to high rates of resistance and significant adverse effects.

9.10 Diagnostic Tests

Current diagnostic methods include viral culture, immunofluorescence, and enzyme-linked immunosorbent assays that detect antigens and multiplex reverse-transcriptase polymerase chain reaction (RT-PCR). Molecular methods such as reverse transcriptase polymerase chain reaction (RT-PCR) are the preferred diagnostic modality due to fastidious growth in cell culture [28, 29]. (RT-PCR) kits that test for multiple viruses simultaneously have become routinely available for rapid testing. These tests have a high diagnostic accuracy but this depends on the quality of specimen acquisition from the nasopharynx and each unit should have a protocoled technique. Figures 9.1 and 9.2 demonstrate the technique employed in our unit.

9.11 Immunological Response to CARV in Lung Transplant Patients

The mechanism whereby virus mediated epithelial injury may trigger progressive pro-inflammatory pathways with or without alloimmune or autoimmune responses resulting in CLAD represents a fertile and relatively unexplored area of research.

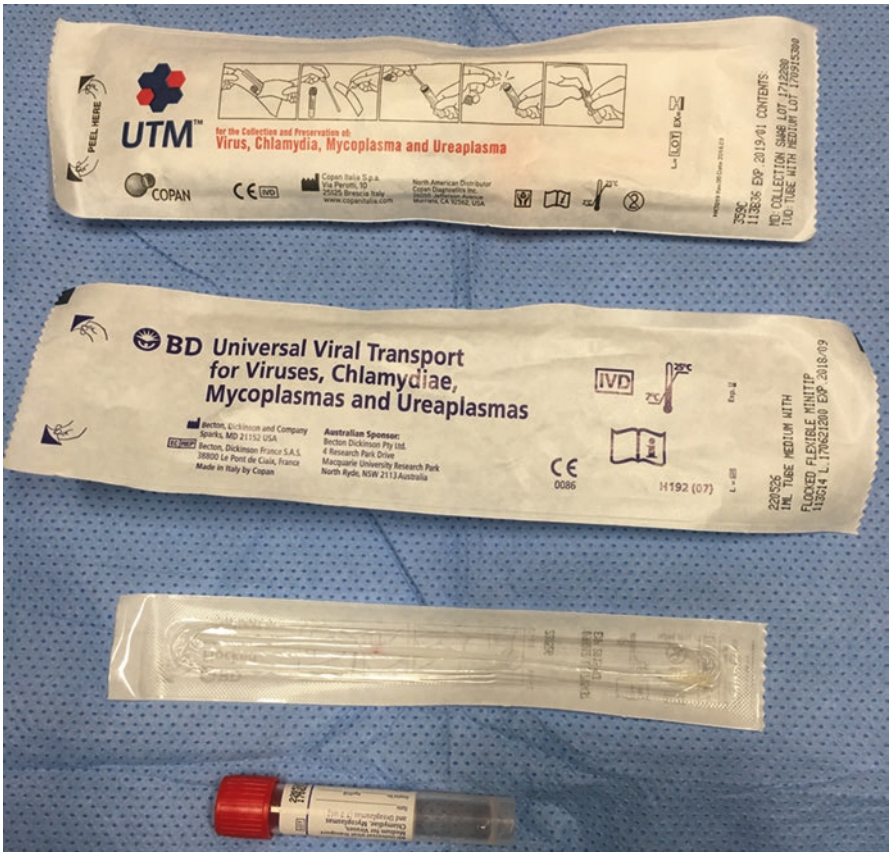


Fig. 9.1 The basic equipment used to undertake nasopharyngeal viral swabs including viral transport medium, swab and transport container

A detailed discussion of the putative immunological responses to CARV is however beyond the discussion of this chapter. The immunological responses to viral infections of the lung include pattern recognition receptors on airway epithelial cells triggering pro-inflammatory pathways [44, 45], upregulation of the major histocompatibility complex molecules [46, 47], cellular immunity and the production of non-HLA antibodies [48, 49], non-alloimmune insults in promoting airway epithelial damage [50] and autoimmune mechanisms [51–53].

Community acquired viral infections in lung transplant patients are common and can not only cause severe acute illness but have the potential to potentiate permanent and progressive allograft injury. Transplant units need to therefore educate their patients that "common cold" symptoms are not necessarily benign and self-limiting. Management strategies should include surveillance, anti-influenza vaccinations, and early diagnosis by means of nasopharyngeal swabs for viral PCR. Protocols should also include ribavirin and steroids for paramyxoviruses, neuraminidase inhibitors for influenza and the appropriate use of antibiotics for complicating bacterial infections.

Fig. 9.2 Nasopharyngeal swab protocol. The steps in undertaking this procedure are: (1) Confirm patient identification. (2) Explain the procedure to the patient and obtain verbal consent. Explain to the patient that the sensation they will experience may be briefly uncomfortable. This may include a stinging sensation in the nose, watery eyes or a gag reflex. (3) Ask the patient to close one nostril at a time with their finger and instruct them to breathe through this single nostril to determine which nostril is more open to allow the swab to be inserted on that side. (4) Ask the patient to sit in an upright position looking straight ahead. The head should not be flexed or extended. (5) The proceduralist should don a mask, goggles and non-sterile gloves. Place a hand on the patient's forehead and holding the swab as you would a pencil, gently insert the swab into the designated nostril ensuring that it extends all the way back to the nasopharynx. Rotate slowly to pick up epithelial cells and then withdraw. Place swab in viral transport medium and ensure proper labelling

References

1. Burton CM, Carlsen J, Mortensen J, Andersen CB, Milman N, Iversen M. Long-term survival after lung transplantation depends on development and severity of bronchiolitis obliterans syndrome. J Heart Lung Transplant. 2007;26:681–6.
2. Versluys AB, Rossen JW, van Ewijk B, Schuurman R, Bierings MB, Boelens JJ. Strong association between respiratory viral infection early after hematopoietic stem cell transplantation and the development of life-threatening acute and chronic alloimmune lung syndromes. Biol Blood Marrow Transplant. 2010;16:782–91.
3. Breese Hall C. Respiratory syncytial virus and parainfluenza virus. N Engl J Med. 2001;344:1917–28.
4. Henrickson KJ. Parainfluenza viruses. Clin Microbiol Rev. 2003;16:242–64.
5. van den Hoogen BG, de Jong JC, Groen J. A newly discovered human metapneumovirus isolated from young children with respiratory tract disease. Nat Med. 2001;7:719–24.

6. Greensill J, McNamara PS, Dove W, Flanagan B, Smyth RL, Hart CA. Human metapneumovirus in severe respiratory syncytial virus bronchiolitis. Emerg Infect Dis. 2003;9(3):372–5.
7. Verleden GM, Raghu G, Meyer KC, Glanville AR, Corris P. A new classification system for chronic lung allograft dysfunction. J Heart Lung Transplant. 2014;33:127–33.
8. Vu DL, Bridevaux PO, Aubert JD, Soccal PM, Kaiser L. Respiratory viruses in lung transplant recipients: a critical review and pooled analysis of clinical studies. Am J Transplant. 2011;11:1071–8.
9. Gotlieb J. Community-acquired respiratory viruses. Semin Respir Crit Care Med. 2018;2:213–8.
10. Kumar D, Erdman D, Keshavjee S, Peret T, Tellier R, Hadjiliadis D, Johnson G, Ayers M, Siegal D, Humar A. Clinical impact of community-acquired respiratory viruses on bronchiolitis obliterans after lung transplant. Am J Transplant. 2005;5:2031–6.
11. Kumar D, Husain S, Chen MH, Moussa G, Himsworth D, Manuel O, Studer S, Pakstis D, McCurry K, Doucette K, Pilewski J, Janeczko R, Humar A. A prospective molecular surveillance study evaluating the clinical impact of community-acquired respiratory viruses in lung transplant recipients. Transplantation. 2010;89:1028–33.
12. Winter JB, Gouw AS, Groen M, Wildevuur C, Prop J. Respiratory viral infections aggravate airway damage caused by chronic rejection in rat lung allografts. Transplantation. 1994;57:418–22.
13. Wendt CH, Fox JM, Hertz MI. Paramyxovirus infection in lung transplant recipients. J Heart Lung Transplant. 1995;14:479–85.
14. Vilchez RA, McCurry K, Dauber J, Iacono A, Keenan R, Zeevi A, Griffith B, Kusne S. The epidemiology of parainfluenza virus infection in lung transplant recipients. Clin Infect Dis. 2001;33:2004–8.
15. Vilchez RA, Dauber J, Kusne S. Infectious etiology of bronchiolitis obliterans: the respiratory viruses connection - myth or reality? Am J Transplant. 2003;3:245–9.
16. Billings JL, Hertz MI, Savik K, Wendt CH. Respiratory viruses and chronic rejection in lung transplant recipients. J Heart Lung Transplant. 2002;21:559–66.
17. Hopkins P, McNeil K, Kermeen F, Musk M, McQueen E, Mackay I, Sloots T, Nissen M. Human metapneumovirus in lung transplant recipients and comparison to respiratory syncytial virus. Am J Respir Crit Care Med. 2008;178:876–81.
18. Gottlieb J, Schulz TF, Welte T, Fuehner T, Dierich M, Simon AR, Engelmann I. Community-acquired respiratory viral infections in lung transplant recipients: a single season cohort study. Transplantation. 2009;87:1530–7.
19. Khalifah AP, Hachem RR, Chakinala MM, Schechtman KB, Patterson GA, Schuster DP, Mohanakumar T, Trulock EP, Walter MJ. Respiratory viral infections are a distinct risk for bronchiolitis obliterans syndrome and death. Am J Respir Crit Care Med. 2004;170:181–7.
20. Uckay I, Gasche-Soccal PM, Kaiser L, Stern R, Mazza-Stalder J, Aubert JD, van Delden C. Low incidence of severe respiratory syncytial virus infections in lung transplant recipients despite the absence of specific therapy. J Heart Lung Transplant. 2010;29:299–305.
21. Glanville AR, Scott AI, Morton JM, Aboyoun CL, Plit ML, Carter IW, Malouf MA. Intravenous ribavirin is a safe and cost-effective treatment for respiratory syncytial virus infection after lung transplantation. J Heart Lung Transplant. 2005;24:2114–9.
22. McCurdy LH, Milstone A, Dummer S. Clinical features and outcomes of paramyxoviral infection in lung transplant recipients treated with ribavirin. J Heart Lung Transplant. 2003;22:745–53.
23. Liu V, Dhillon GS, Weill D. A multi-drug regimen for respiratory syncytial virus and parainfluenza virus infections in adult lung and heart-lung transplant recipients. Transpl Infect Dis. 2010;12:38–44.
24. Pelaez A, Lyon GM, Force SD, Ramirez AM, Neujahr DC, Foster M, Naik PM, Gal AA, Mitchell PO, Lawrence EC. Efficacy of oral ribavirin in lung transplant patients with respiratory syncytial virus lower respiratory tract infection. J Heart Lung Transplant. 2009;28:67–71.
25. Burrows FS, Carlos LM, Benzimra M, Marriott DJ, Havryk AP, Plit ML, Malouf MA, Glanville AR. Oral ribavirin for respiratory syncytial virus infection after lung transplantation: efficacy and cost-efficiency. J Heart Lung Transplant. 2015;34(7):958–62.

26. Gottlieb J, Zamora MR, Hodges T, Musk AW, Sommerwerk U, Dilling D, Arcasoy S, DeVincenzo J, Karsten V, Shah S, Bettencourt BR, Cehelsky J, Nochur S, Gollob J, Vaishnaw A, Simon AR, Glanville AR. ALN-RSV01 for prevention of bronchiolitis obliterans syndrome after respiratory syncytial virus infection in lung transplant recipients. J Heart Lung Transplant. 2016;35:213–21.
27. Jacobs SE, Lamson DM, George KS, Walsh TJ. Human rhinoviruses. Clin Microbiol Rev. 2013;26:135–62.
28. Murali S, Langston AA, Nolte FS, Banks G, Martin R, Caliendo AM. Detection of respiratory viruses with a multiplex polymerase chain reaction assay (multicode-plx respiratory virus panel) in patients with hematologic malignancies. Leuk Lymphoma. 2009;50:619–24.
29. Kraft CS, Jacob JT, Sears MH, Burd EM, Caliendo AM, Lyon GM. Severity of human rhinovirus infection in immunocompromised adults is similar to that of 2009 H1N1 influenza. J Clin Microbiol. 2012;50:1061–3.
30. Kaiser L, Aubert JD, Pache JC, Deffernez C, Rochat T, Garbino J, Wunderli W, Meylan P, Yerly S, Perrin L, et al. Chronic rhinoviral infection in lung transplant recipients. Am J Respir Crit Care Med. 2006;174:1392–9.
31. Costa C, Bergallo M, Astegiano S, Sidoti F, Terlizzi ME, Gambarino S, Curtoni A, Simeone S, Solidoro P, Cavallo R. Detection of human rhinoviruses in the lower respiratory tract of lung transplant recipients. Arch Virol. 2011;156:1439–43.
32. Sayah DM, Koff JL, Leard LE, Hays SR, Golden JA, Singer JP. Rhinovirus and other respiratory viruses exert different effects on lung allograft function that are not mediated through acute rejection. Clin Transpl. 2013;27:E64–71.
33. Billings JL, Hertz MI, Wendt CH. Community respiratory virus infections following lung transplantation. Transpl Infect Dis. 2001;3:138–48.
34. Humar A, Doucette K, Kumar D, Pang XL, Lien D, Jackson K, Preiksaitis J. Assessment of adenovirus infection in adult lung transplant recipients using molecular surveillance. J Heart Lung Transplant. 2006;25:1441–6.
35. Demicheli V, Jefferson T, Al-Ansary LA, et al. Vaccines for preventing influenza in healthy adults. Cochrane Database Syst Rev. 2014:CD001269. doi:10.1002/14651858.CD001269.pub5.
36. Nicholson KG, Aoki FY, Hayden FG, Osterhaus AD, Treanor JJ, et al. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenza virus infections. GG167 Influenza Study Group. N Engl J Med. 1997;337:874.
37. Randomised trial of efficacy and safety of inhaled zanamivir in treatment of influenza A and B virus infections. The MIST (Management of Influenza in the Southern Hemisphere Trialists) Study Group. Lancet. 1998;352:1877.
38. Jefferson T, Jones M, Doshi P, et al. Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. BMJ. 2014;348:g2545.
39. Heneghan CJ, Onakpoya I, Thompson M, et al. Zanamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. BMJ. 2014;348:g2547.
40. Dobson J, Whitley RJ, Pocock S, Monto AS. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. Lancet. 2015;385:1729.
41. Fiore AE, Fry A, Shay D, et al. Antiviral agents for the treatment and prophylaxis of influenza – recommendations of the Advisory Committee on Immunization Practice (ACIP). MMWR Recomm Rep. 2011;60:1.
42. Statement by the Infectious Disease Society of America (IDSA) on the recent publication on "Neuraminidase inhibitors for preventing and treating influenza in health adults and children". 3 Jan 2015.
43. "Have you heard" CDC recommendations for influenza antiviral medications remain. 3 Jan 2015.
44. Schwarze J, Mackenzie KJ. Novel insights into immune and inflammatory responses to respiratory viruses. Thorax. 2013;68:108–10.

45. Kuo E, Bharat A, Shih J, Street T, Norris J, Liu W, Parks W, Walter M, Patterson GA, Mohanakumar T. Role of airway epithelial injury in murine orthotopic tracheal allograft rejection. Ann Thorac Surg. 2006;82:1226–33.
46. Rinaldo CR Jr. Modulation of major histocompatibility complex antigen expression by viral infection. Am J Pathol. 1994;144:637–50.
47. Papi A, Stanciu LA, Papadopoulos NG, Teran LM, Holgate ST, Johnston SL. Rhinovirus infection induces major histocompatibility complex class 1 and costimulatory molecule upregulation on respiratory epithelial cells. J Infect Dis. 2000;181:1780–4.
48. Burlingham WJ, Love RB, Jankowska-Gan E, Haynes LD, Xu Q, Bobadilla JL, Meyer KC, Hayney MS, Braun RK, Greenspan DS, et al. IL-17-dependent cellular immunity to collagen type v predisposes to obliterative bronchiolitis in human lung transplants. J Clin Invest. 2007;117:3498–506.
49. Goers TA, Ramachandran S, Aloush A, Trulock E, Patterson GA, Mohanakumar T. De novo production of k-alpha1 tubulin-specific antibodies: role in chronic lung allograft rejection. J Immunol. 2008;180:4487–94.
50. Halloran PF, Homik J, Goes N, Lui SL, Urmson J, Ramassar V, Cockfield SM. The “injury response”: a concept linking nonspecific injury, acute rejection, and long-term transplant outcomes. Transplant Proc. 1997;29:79–81.
51. Bharat A, Kuo E, Saini D, Steward N, Hachem R, Trulock EP, Patterson GA, Meyers BF, Mohanakumar T. Respiratory virus-induced dysregulation of T-regulatory cells leads to chronic rejection. Ann Thorac Surg. 2010;90:1637–44; discussion 1644.
52. Sakaguchi S. Naturally arising foxp3-expressing cd25+cd4+ regulatory t cells in immunological tolerance to self and non-self. Nat Immunol. 2005;6:345–52.
53. Zdrenghea MT, Telcian AG, Laza-Stanca V, Bellettato CM, Edwards MR, Nikonova A, Khaitov MR, Azimi N, Groh V, Mallia P, et al. RSV infection modulates IL-15 production and mica levels in respiratory epithelial cells. Eur Respir J. 2012;39:712–20.

Chapter 10
Bronchoscopy Post Lung Transplantation

Mark Benzimra

The ability to perform bronchoscopy is a desirable if not vital skill for clinicians caring for lung transplant patients. The lung is particularly susceptible to infection and recurrent injury through its ongoing direct exposure to the environment, which makes it different to other solid organ transplants. This ongoing inflammation may trigger an immune response which increases the risk of rejection [1]. Therefore, acute cellular rejection (ACR) and infection with subsequent development of chronic lung allograft dysfunction (CLAD) remains a significant cause of morbidity and mortality after LTX and a major limitation to long-term survival [2]. Bronchoscopy is also useful to monitor for airway complications such as anastomotic ischaemia, necrosis, dehiscence, infections, and long term stricture formation and tracheobronchomalacia (Fig. 10.1a–c). In this chapter we will explore the various ways by which bronchoscopy can aid clinicians manage their lung transplant recipients post operatively (Fig. 10.2).

10.1 Surveillance Bronchoscopy versus Clinically Mandated

When discussing bronchoscopy post transplantation we refer to either surveillance or clinically mandated bronchoscopies. Surveillance bronchoscopy is performed as part of a routine predefined protocol regardless of whether the patient is symptomatic, whether there is allograft dysfunction, or radiological change. Clinically mandated bronchoscopy is performed when a patient presents with new symptoms of cough, dyspnoea and reduction in lung function by greater than 10% from baseline forced expiratory volume in 1 s (FEV1), or if there is any radiological change.

M. Benzimra
Heart and Lung Transplant Unit, St. Vincent's Hospital, Sydney, Darlinghurst, NSW, Australia
e-mail: Mark.Benzimra@svha.org.au

A. R. Glanville (ed.), *Essentials in Lung Transplantation*,
https://doi.org/10.1007/978-3-319-90933-2_10

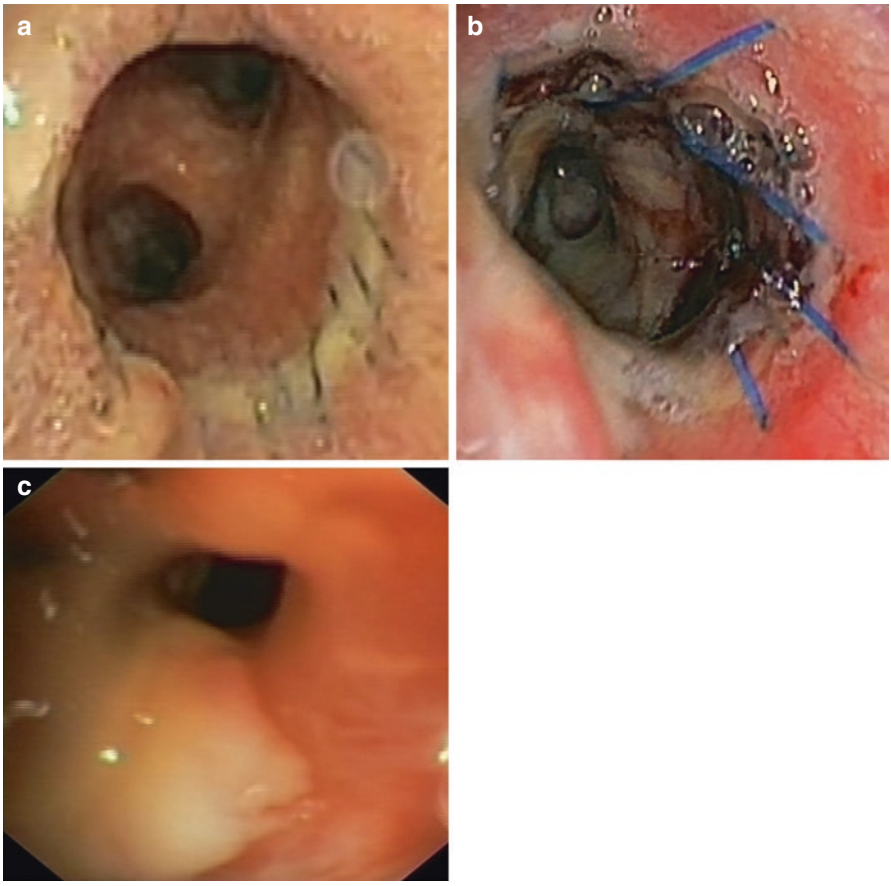


Fig. 10.1 (**a**) Normal bronchial anastomosis. (**b**) Shows bronchial anastomosis with ischaemic change distal to the anastomosis. (**c**) Showing airway stricture with some mucus plugging

Bronchoscopies performed as part of surveillance or clinically mandated procedures may involve bronchoalveolar lavage to diagnose infection as well as detect any airway complications, or may involve more invasive procedures such as transbronchial biopsies (TBBX) to diagnose rejection.

The role of surveillance bronchoscopy after lung transplantation, and the value of surveillance bronchoscopy versus clinically mandated bronchoscopy remains controversial, with some clinicians questioning the risk versus benefit ratio of performing the procedure and arguing that it exposes patients to unnecessary procedural risk, which would include bleeding, pneumothorax, cardiac arrhythmias, sedation related complications and even post procedural pneumonia [3, 4–11]. Therefore individual centres vary widely in their practices particularly since there is no consensus on the frequency in which we should be performing surveillance TBBX or whether we should be performing them at all [12].

Fig. 10.2 Typical bronchoscopy set up with bronchoscopy tower and bronchoscope

In support of surveillance bronchoscopy is the association between episodes of acute rejection and the development of CLAD [13–17]. One aim of routine surveillance bronchoscopy is early detection of clinically 'silent' episodes of acute cellular rejection that would otherwise have been missed by routine clinical monitoring using non-invasive methods such as spirometry and radiology that if left untreated could result in an increased risk of developing CLAD [18–20].

Clinicians who do not support surveillance bronchoscopy consider spirometry to be a non-invasive, cheap and easily reproducible method by which to monitor graft function in patients post LTX. A drop in FEV1 of greater than 10% from baseline, has traditionally been used by physicians to trigger investigations, including TBBX, in an attempt to find and treat any reversible causes [21, 22].

At our unit we perform the first bronchoscopy within the first 24 h post lung transplantation just prior to the patient being extubated in order to assess the anastomosis, clear secretions or clot that may have accumulated during the procedure, and provide early microbiological and virological samples to guide early therapy. We then follow up with a surveillance bronchoscopy at 1 week post-transplant to once again evaluate the anastomosis, airways, and ensure that our targeted microbiological therapies have been successful prior to cessation of antimicrobial treatment. Subsequent surveillance bronchoscopies with bronchoalveolar lavage and TBBX are performed at 3 weeks, 6 weeks, 9 weeks and 12 weeks. The 9-week surveillance bronchoscopy may be omitted if all other bronchoscopies have been normal and there has not been any rejection. Beyond the 3 months surveillance bronchoscopy +/− TBBX only clinically mandated bronchoscopies are performed.

As already mentioned, large variations in monitoring practice exist amongst centres with some centres following a similar protocol to ours, others performing annual surveillance bronchoscopy and TBBX, whilst others only do clinically mandated procedures.

10.2 Diagnosis of Infections

The risk of infection is much higher after lung transplantation than in any other solid organ transplant, and early detection of occult infection may lead to better outcomes [23–25]. Anastomotic infections can be secondary to necrosis, colonization, or aspiration. Due to their state of immune suppression patients are susceptible to both common airway pathogens as well as numerous rarer bacterial, viral, and fungal infections that often arise from the normal flora of the donor or recipient airway [26], with bacterial infections most likely in the first few weeks after lung transplantation [27]. With increasing population movement we may see the increased incidence of donor-derived infections such as tuberculosis which may be detected during surveillance bronchoscopies prior to clinical sequelae [28]. Although most patients undergoing bronchoscopy for diagnosis of infection will be doing so in order to obtain microbiological samples and would be clinically symptomatic at the time of bronchoscopy, up to one third of patients may be asymptomatic and harbouring infection [29]. This is most common in the 3–12 month period post lung transplantation [3].

10.3 Diagnosis of Acute Cellular Rejection

The clinical presentation of acute cellular rejection is variable with up to 40% patients being asymptomatic with no change in lung function—'silent rejection', to a more sinister presentation with shortness of breath, marked loss of lung function, radiological infiltrates and acute respiratory failure. The diagnosis can only confidently be made histologically by obtaining samples of lung parenchyma by TBBX which is considered the gold standard for the diagnosis of acute cellular rejection (Fig. 10.3).

An international grading system for pulmonary allograft rejection was first adopted by the ISHLT in 1990 [30], modified in 1996 [31] and then again in 2007 [32], and is based on the presence of perivascular and interstitial mononuclear infiltrates, Grade A0 (no rejection), Grade A1 (minimal rejection), Grade A2 (mild rejection), Grade A3 (moderate rejection) and Grade A4 (severe rejection). Lymphocytic bronchiolitis is classified according to the presence and severity of mononuclear inflammation in the airways and graded as Grade B0 (none), Grade B1R (low grade, which in the 1996 guidelines were described as grade B1 and B2), Grade B2R (high grade, which in the 1996 guidelines were described as grade B3

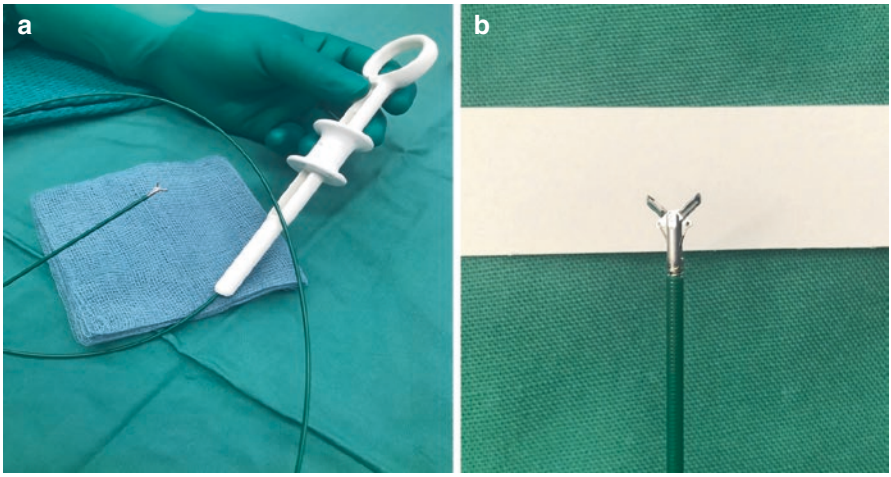


Fig. 10.3 (**a**) Transbronchial biopsy forceps. (**b**) Close up view of serrated forceps

and B4) and BX (ungradeable). Obliterative bronchiolitis (Grade C), is described as present (C1) or absent (C0), without reference to presence of inflammatory activity. Chronic vascular rejection is unchanged as Grade D diagnosis of acute rejection [32].

It is important to consider the fact that acute cellular rejection is a heterogeneous process with some parts of the lung being affected and others being entirely normal which means that one can miss an episode of rejection simply because there has been inadequate sampling of lung parenchyma [23]. As a result of this potential for sampling error The Lung Rejection Study Group (LRGS) has provided guidelines which recommend a minimum of 5 pieces of evaluable (2–3 mm; containing a minimum of 100 alveoli per high power field), well-expanded alveolar parenchyma from two separate lobes to provide adequate sensitivity for diagnosing ACR [31, 32].

The interpretation of the samples by individual pathologists has also been shown to be variable with studies showing only moderate agreement between two pathologists reading the same samples in determining the same grade of rejection (i.e. A0, A1, A2, A3, A4) although there is consistency with intra-reader agreement [33].

10.4 Diagnosis of Antibody Mediated Rejection

Antibody mediated rejection (AMR) is increasingly being recognised as a cause of acute lung allograft dysfunction as well as CLAD [32, 34–37], with a recent consensus document on pulmonary AMR being published by the ISHLT [37]. Histopathological samples obtained via bronchoscopy and TBBX provides essential information which enables the clinician to upgrade their diagnostic accuracy according to the current diagnostic classification.

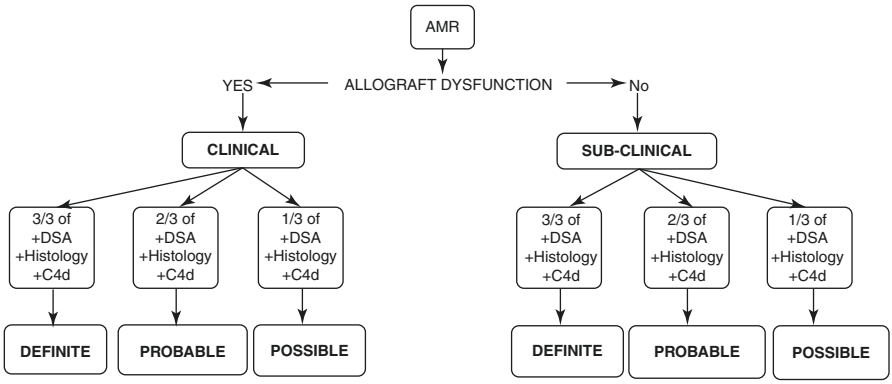


Fig. 10.4 Classification of antibody-mediated rejection (AMR) according to the presence or absence of diagnostic certainty and presence (clinical) or absence (sub-clinical) of allograft dysfunction. Adapted from the 2016 pulmonary AMR consensus document of the ISHLT

Pulmonary AMR as described by the ISHLT pulmonary AMR working group classifies patients into "Clinical" or "Sub-clinical" AMR depending on the presence or not of lung allograft dysfunction. Patients are then further classified as having possible, probable, or definite AMR depending on the presence of additional diagnostic criteria (histological changes consistent with AMR, positive C4d staining, and the presence of donor specific antibodies (DSA)) which adds further diagnostic certainty (Fig. 10.4) [37]. Neutrophil margination, neutrophil capillaritis, and arteritis, are typical pathological features of AMR.

10.5 Diagnosis and Management of Airway Complications

Direct visualisation of the airways via bronchoscopy allows us to not only assess for airway complications but also provides a therapeutic option e.g. balloon dilatation of anastomotic strictures [38]. With approximately 1/3 of airway complications post lung transplantation being asymptomatic [39] one must always consider that failure to achieve normal lung function post transplantation may be due to an undiagnosed stricture. Hence direct visualisation of the airways via bronchoscopy is critical to obtain optimal results for the patient. The direct mortality related to airway complications in the first year is approximately 2.3% [40], and overall 1 and 5 year survival rate of 88% and 73% as compared with 91% and 79% in the control group respectively [41].

In the early postoperative days we can assess anastomotic integrity and grade anastomotic ischaemia which arises due to the disruption of the usual blood supply to the bronchus which loses the antegrade bronchial artery component postoperatively and therefore relies on retrograde flow from the pulmonary arteries to the bronchial arteries via the capillary network and collaterals. Sputum plugs and

blood clots which may obstruct the anastomosis or other parts of the bronchial tree can also therapeutically be removed.

Anastomotic stricture is the most commonly reported long term airway complication post-transplant [42]. Therapeutic options for airway strictures include balloon dilatation and the insertion of stents. When performing balloon dilatation the patient often requires to return for multiple dilatations to obtain a long lasting result but the management of the strictures not only improves airflow, it enhances airway secretion clearance and reduces the risk of post stricture infections in patients who are already at an increased risk due to their immune suppressed status [41]. Potential complications are mucosal bleeding, airway tear, partial or complete rupture of the airway, and prolonged hypoxia. Other methods described include cryotherapy, electrocautery, laser, brachytherapy, bougie dilatation with rigid bronchoscopy, and stent placement.

When considering the insertion of stents to manage anastomotic strictures care must be exercised in choosing patients appropriate for stent insertion as there is significant morbidity associated with stents particularly stent migration and recurrent infections as a result of reduced sputum clearance. Ongoing inflammation at the site of stent insertion may also lead to the formation of granulation tissue resulting in within-stent stenosis [42].

10.6 Conclusion

The importance of bronchoscopy in the post-operative care of the lung transplant patient cannot be underestimated. As discussed in this chapter it provides clinicians with vital information required to make an accurate diagnosis in what are complex patients in whom the cause of allograft dysfunction may be multifactorial. Although often considered a diagnostic tool, advancements in interventional bronchoscopy have resulted in an increasing use of bronchoscopy as a therapeutic tool in complications such as those within the airway.

References

1. Gardiner BJ, Snydman DR. Editorial Commentary: Chronic lung allograft dysfunction in lung transplant recipients: another piece of the puzzle. Clin Infect Dis. 2016;62:320–2.
2. Weigt SS, DerHovanessian A, Wallace WD, Lynch JP 3rd, Belperio JA. Bronchiolitis obliterans syndrome: the Achilles' heel of lung transplantation. Semin Respir Crit Care Med. 2013;34:336–51.
3. McWilliams TJ, Williams TJ, Whitford HM, Snell GI. Surveillance bronchoscopy in lung transplant recipients: risk versus benefit. J Heart Lung Transplant. 2008;27:1203–9.
4. Valentine VG, Gupta MR, Weill D, et al. Single-institution study evaluating the utility of surveillance bronchoscopy after lung transplantation. J Heart Lung Transplant. 2009;28:14–20.
5. Kukafka DS, O'Brien GM, Furukawa S, Criner GJ. Surveillance bronchoscopy in lung transplant recipients. Chest. 1997;111:377–81.

6. Lehto JT, Koskinen PK, Anttila VJ, et al. Bronchoscopy in the diagnosis and surveillance of respiratory infections in lung and heart-lung transplant recipients. Transpl Int. 2005;18:562–71.
7. Sandrini A, Glanville AR. The controversial role of surveillance bronchoscopy after lung transplantation. Curr Opin Organ Transplant. 2009;14:494–8.
8. Trulock EP, Ettinger NA, Brunt EM, Pasque MK, Kaiser LR, Cooper JD. The role of transbronchial lung biopsy in the treatment of lung transplant recipients. An analysis of 200 consecutive procedures. Chest. 1992;102:1049–54.
9. Scott JP, Fradet G, Smyth RL, et al. Prospective study of transbronchial biopsies in the management of heart-lung and single lung transplant patients. J Heart Lung Transplant. 1991;10:626–36; discussion 36-7.
10. Sibley RK, Berry GJ, Tazelaar HD, et al. The role of transbronchial biopsies in the management of lung transplant recipients. J Heart Lung Transplant. 1993;12:308–24.
11. Valentine VG, Taylor DE, Dhillon GS, et al. Success of lung transplantation without surveillance bronchoscopy. J Heart Lung Transplant. 2002;21:319–26.
12. Glanville AR. The role of bronchoscopic surveillance monitoring in the care of lung transplant recipients. Semin Respir Crit Care Med. 2006;27:480–91.
13. Bando K, Paradis IL, Similo S, et al. Obliterative bronchiolitis after lung and heart-lung transplantation. An analysis of risk factors and management. J Thorac Cardiovasc Surg. 1995;110:4–13; discussion-4.
14. Boehler A, Estenne M. Post-transplant bronchiolitis obliterans. Eur Respir J. 2003;22:1007–18.
15. Girgis RE, Tu I, Berry GJ, et al. Risk factors for the development of obliterative bronchiolitis after lung transplantation. J Heart Lung Transplant. 1996;15:1200–8.
16. Heng D, Sharples LD, McNeil K, Stewart S, Wreghitt T, Wallwork J. Bronchiolitis obliterans syndrome: incidence, natural history, prognosis, and risk factors. J Heart Lung Transplant. 1998;17:1255–63.
17. Husain AN, Siddiqui MT, Holmes EW, et al. Analysis of risk factors for the development of bronchiolitis obliterans syndrome. Am J Respir Crit Care Med. 1999;159:829–33.
18. Hopkins PM, Aboyoun CL, Chhajed PN, et al. Association of minimal rejection in lung transplant recipients with obliterative bronchiolitis. Am J Respir Crit Care Med. 2004;170:1022–6.
19. Hachem RR, Khalifah AP, Chakinala MM, et al. The significance of a single episode of minimal acute rejection after lung transplantation. Transplantation. 2005;80:1406–13.
20. Khalifah AP, Hachem RR, Chakinala MM, et al. Minimal acute rejection after lung transplantation: a risk for bronchiolitis obliterans syndrome. Am J Transplant. 2005;5:2022–30.
21. Bjortuft O, Johansen B, Boe J, Foerster A, Holter E, Geiran O. Daily home spirometry facilitates early detection of rejection in single lung transplant recipients with emphysema. Eur Respir J. 1993;6:705–8.
22. Otulana BA, Higenbottam T, Ferrari L, Scott J, Igboaka G, Wallwork J. The use of home spirometry in detecting acute lung rejection and infection following heart-lung transplantation. Chest. 1990;97:353–7.
23. Glanville AR. The role of surveillance bronchoscopy post-lung transplantation. Semin Respir Crit Care Med. 2013;34:414–20.
24. Cagle PT, Truong LD, Holland VA, Lawrence EC, Noon GP, Greenberg SD. Lung biopsy evaluation of acute rejection versus opportunistic infection in lung transplant patients. Transplantation. 1989;47:713–5.
25. Wreghitt TG, Smyth RL, Scott JP, et al. Value of culture of biopsy material in diagnosis of viral infections in heart-lung transplant recipients. Transplant Proc. 1990;22:1809–10.
26. Paradis IL, Williams P. Infection after lung transplantation. Semin Respir Infect. 1993;8:207–15.
27. Nusair S, Kramer MR. The role of fibre-optic bronchoscopy in solid organ, transplant patients with pulmonary infections. Respir Med. 1999;93:621–9.
28. Jensen TO, Darley DR, Goeman EE, Shaw K, Marriott DJ, Glanville AR. Donor-derived tuberculosis (TB): isoniazid-resistant TB transmitted from a lung transplant donor with inadequately treated latent infection. Transpl Infect Dis. 2016;18:782–4.

29. Benden C, Harpur-Sinclair O, Ranasinghe AS, Hartley JC, Elliott MJ, Aurora P. Surveillance bronchoscopy in children during the first year after lung transplantation: is it worth it? Thorax. 2007;62:57–61.
30. Berry GJ, Brunt EM, Chamberlain D, et al. A working formulation for the standardization of nomenclature in the diagnosis of heart and lung rejection: Lung Rejection Study Group. The International Society for Heart Transplantation. J Heart Transplant. 1990;9:593–601.
31. Yousem SA, Berry GJ, Cagle PT, et al. Revision of the 1990 working formulation for the classification of pulmonary allograft rejection: Lung Rejection Study Group. J Heart Lung Transplant. 1996;15:1–15.
32. Stewart S, Fishbein MC, Snell GI, et al. Revision of the 1996 working formulation for the standardization of nomenclature in the diagnosis of lung rejection. J Heart Lung Transplant. 2007;26:1229–42.
33. Stephenson A, Flint J, English J, et al. Interpretation of transbronchial lung biopsies from lung transplant recipients: inter- and intraobserver agreement. Can Respir J. 2005;12:75–7.
34. Hachem R. Antibody-mediated lung transplant rejection. Curr Respir Care Rep. 2012;1:157–61.
35. Westall GP, Snell GI. Antibody-mediated rejection in lung transplantation: fable, spin, or fact? Transplantation. 2014;98:927–30.
36. Glanville AR. Antibody-mediated rejection in lung transplantation: myth or reality? J Heart Lung Transplant. 2010;29:395–400.
37. Levine DJ, Glanville AR, Aboyoun C, et al. Antibody-mediated rejection of the lung: a consensus report of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2016;35:397–406.
38. Chhajed PN, Malouf MA, Tamm M, Spratt P, Glanville AR. Interventional bronchoscopy for the management of airway complications following lung transplantation. J Heart Lung Transplant. 2001;20:177.
39. Murthy SC, Blackstone EH, Gildea TR, et al. Impact of anastomotic airway complications after lung transplantation. Ann Thorac Surg. 2007;84:401–9, 409.e1-4.
40. Van De Wauwer CVRD, Verleden GM, Dupont L, De Leyn P, Coosemans W, Nafteux P, Lerut T. Risk factors for airway complications within the first year after lung transplantation. Eur J Cardiothorac Surg. 2007;31:703–10.
41. Yserbyt J, Dooms C, Vos R, Dupont LJ, Van Raemdonck DE, Verleden GM. Anastomotic airway complications after lung transplantation: risk factors, treatment modalities and outcome-a single-centre experience. Eur J Cardiothorac Surg. 2016;49:e1–8.
42. Santacruz JF, Mehta AC. Airway complications and management after lung transplantation: ischemia, dehiscence, and stenosis. Proc Am Thorac Soc. 2009;6:79–93.

Chapter 11
Chronic Lung Allograft Dysfunction: Phenotypes and the Future

Daniel C. Chambers

11.1 What is Chronic Lung Allograft Dysfunction (CLAD)?

CLAD is a collective, clinically defined, diagnostic term which encompasses all forms of irreversible lung allograft dysfunction where no alternate cause can be identified. Terminology in this area has been, and remains, somewhat confusing. Other terms which are also used to refer to 'chronic rejection' of the lung allograft are BOS, OB, RAS and rCLAD (see Table 11.1 for definitions of these entities). Whilst the term CLAD has now been generally accepted by the transplant community and is in day-to-day use, this nomenclature has not yet been officially endorsed by the International Society for Heart and Lung Transplantation.

CLAD remains the most significant hurdle to achieving excellent post-transplant outcomes. CLAD is the main cause of death after transplantation, with median survival after diagnosis only 2–3 years. CLAD affects approximately 10% of patients each year after transplantation, so that 50% are affected by 5 years and nearly all patients by 10 years. Although there have been marked improvements in survival after lung transplantation over the past three decades, all of this improvement has occurred in the first six post-transplant months, with no improvement in longer-term mortality [1]. Unfortunately this reflects our lack of progress in addressing CLAD.

D. C. Chambers
Qld Lung Transplant Service, The Prince Charles Hospital, Brisbane, QLD, Australia

Faculty of Medicine, The University of Queensland, Brisbane, QLD, Australia
e-mail: daniel.chambers@health.qld.gov.au

A. R. Glanville (ed.), *Essentials in Lung Transplantation*,
https://doi.org/10.1007/978-3-319-90933-2_11

Table 11.1 Acronyms in common use in lung transplantation

	Full name	What is it
CLAD	Chronic lung allograft dysfunction	All encompassing clinical term describing irreversible graft loss (defined as a 20% fall in FEV1 from best post-transplant)
BOS	Bronchiolitis obliterans syndrome	Previously used term for CLAD. Now describes the major subtype of CLAD characterised by airflow obstruction. BOS accounts for over 85% of CLAD
OB	Obliterative bronchiolitis	The pathologic equivalent of BOS. Bronchioles are replaced by fibrous granulation tissue and eventually destroyed
RAS	Restrictive allograft syndrome	The less common subtype of CLAD, characterised by parenchymal fibrosis and a restrictive ventilatory defect. This subtype accounts for up to 15% of CLAD
rCLAD	Restrictive CLAD	Alternative name for RAS
COP	Cryptogenic organizing pneumonia	A common pathologic finding in transbronchial biopsies, with polypoid plugs of loose organizing connective tissue within alveoli and bronchioles. COP is usually exquisitely steroid responsive
BOOP	Bronchiolitis obliterans organising pneumonia	Outdated term for COP. Not to be confused with BOS or OB, which are fundamentally fibrotic

11.2 How is CLAD Diagnosed?

CLAD is a clinical diagnosis which can be made when an irreversible fall in forced expiratory volume in 1 s (FEV1), measured using spirometry, occurs after lung transplantation, when other causes have been excluded. Spirometry is a simple and reproducible test which is central to monitoring allograft function after transplantation. Spirometry should be performed at every post-transplant clinic visit, and many programs advocate home monitoring as well. Spirometry involves asking the subject to complete a forced exhalation manoeuvre from full inhalation to full exhalation. The total volume of gas exhaled during this manoeuvre is the forced vital capacity (FVC). The volume of gas exhaled in the first second is the FEV1 (Fig. 11.1). A fall in FEV1 of greater than 10% compared to previous measures is considered significant, although a 5% fall, if sustained, should also prompt further investigation.

In most instances new respiratory symptoms and a reduction in FEV1 after lung transplantation will have a relatively straightforward and readily treatable explanation (Fig. 11.2). Some of the more common causes of a fall in FEV1 are acute infection (commonly respiratory viral infection, or *P. aeruginosa* tracheobronchitis), acute rejection, or anastomotic stenosis or malacia. If alternate causes for the reduction in spirometric measures are excluded and the fall is sustained, a diagnosis of CLAD needs to be considered. Figure 11.3 provides a practical approach to the further investigation and management of a patient presenting to post-transplant clinic with a fall in FEV1.

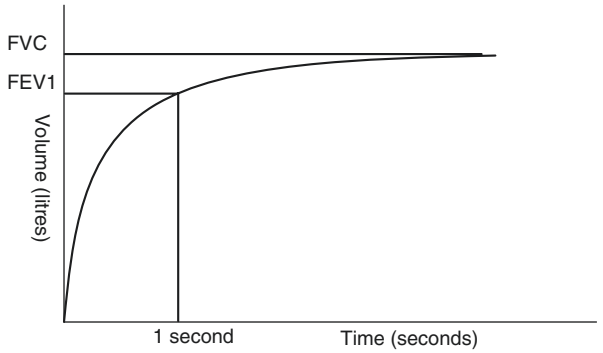


Fig. 11.1 Normal spirogram. The subject is asked to exhale forcefully from full inspiration to full exhalation. The total volume of gas exhaled during this manoeuvre is the forced vital capacity (FVC). The volume of gas exhaled in the first second is the forced expiratory volume in 1 s (FEV1) (Fig. 11.1). In normal individuals the FEV1 is 80% of the FVC. If the subject has airflow obstruction (e.g. bronchiolitis obliterans syndrome) the FEV1 will be low, whereas the FVC will be normal or near-normal. In subjects with restriction (e.g. restrictive allograft syndrome (RAS) or restrictive chronic lung allograft syndrome (rCLAD)) the FVC will be reduced, with a proportionately reduced FEV1

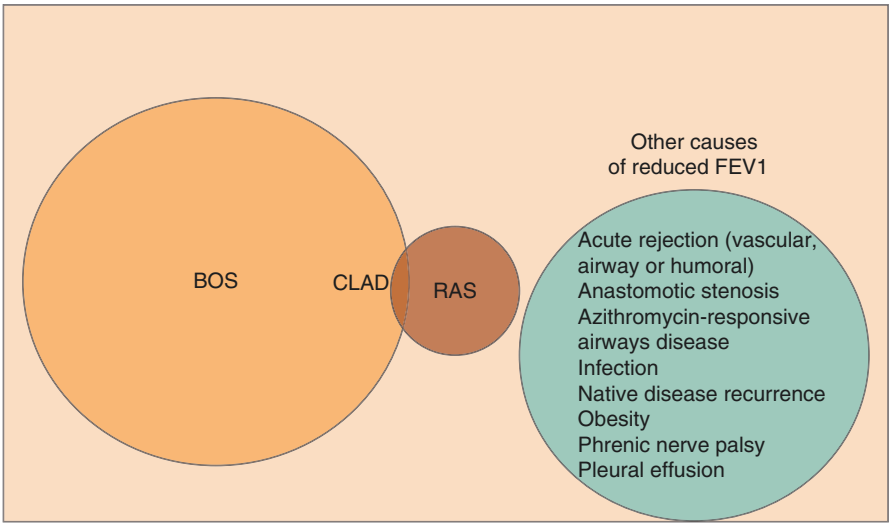


Fig. 11.2 Schematic framework for classifying causes of lung allograft dysfunction. In a patient presenting with a reduction in FEV1 after transplantation (typically a 10% fall is deemed significant) the initial approach is to exclude causes for a reduction other than chronic lung allograft dysfunction (CLAD). If these are excluded, CLAD (either the BOS or RAS variant) is diagnosed if there is at least a 20% fall in FEV1 compared to best post-transplant

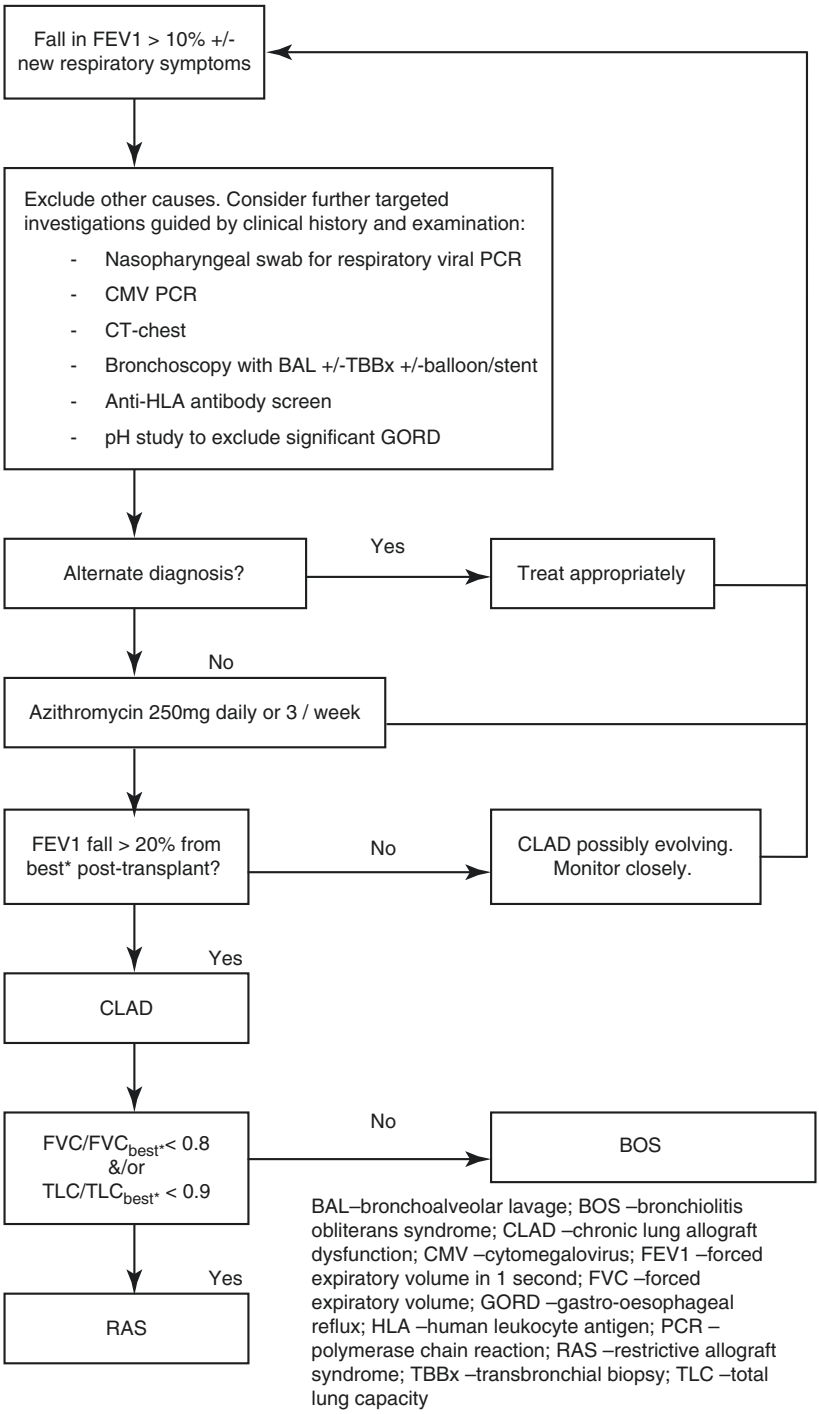


Fig. 11.3 Practical aproach to the further investigation and management of a lung transplant patient presenting with a fall in FEV1. Asterisk defined as the average of the two best FEV1s measured at least 3 weeks apart. For FVC and TLC the figure obtained on the same day is used

11.3 RAS and BOS

Although the term CLAD has not yet been formally adopted by the International Society for Heart and Lung Transplantation, it is now in common use in clinical transplant medicine and in the literature. Until a few years ago, patients with what we now refer to as CLAD would have received a label of BOS. Publications in 2011 by the Toronto group [2] and in 2014 by the Duke group [3] established the existence of a restrictive form of chronic lung transplant rejection, now generally referred to as RAS (restrictive allograft syndrome). The recognition of this new entity was the precipitant for the development of a new term to encompass all forms of chronic rejection—CLAD. BOS and RAS are subtypes of CLAD (Fig. 11.2). The Toronto group's definition of RAS is a total lung capacity (TLC) at the time of CLAD diagnosis <90% of the best post-transplant total lung capacity (TLC, which is further defined as the average of the two TLC measurements obtained at the time of the best two FEV1s) [2]. Since many programs do not routinely measure TLC, the Duke group arrived at a more broadly applicable definition of RAS—'Patients were considered to have FVC loss if the CLAD onset FVC/FVC_{Best} was less than 0.8, where FVC_{Best} was the average of the two FVC measurements that paired with the two best post-transplant FEV1 used in the CLAD calculation' [3]. A practical guide to diagnosing CLAD and differentiating RAS and BOS is provided in Fig. 11.3.

11.4 Pathogenesis of CLAD

CLAD is thought to result from repeated and/or persistent insults to the allograft, epecially the epithelium, with failed epithelial repair triggering a potent profibrotic response.Diverse epithelial injuries (cellular or antibody-mediated rejection (AMR); bacterial, viral or fungal infection; and exposure to non-specific irritants such as gastric contents, cigarette smoke or air pollution) have been implicated in CLAD pathogenesis, as has primary graft dysfunction. More recently microvascular injury leading to relative epithelial ischaemia, and antibodies to self-antigens such as K-α-1-tubulin and collagen V [4] have also been implicated (Fig. 11.4).

Failed epithelial repair may be related to the severity and/or persistence of the injury, but may also be related to the susceptibility of the donated epithelium to injury, and its capacity to repair. The fibrotic response is mediated by multipler mediators, but transforming growth factor β [5] and lysophosphatidic acid [6] appear to be promninent. It is currently unclear how this model for pathogenesis can manifest as distinct phenotypes (RAS and BOS).

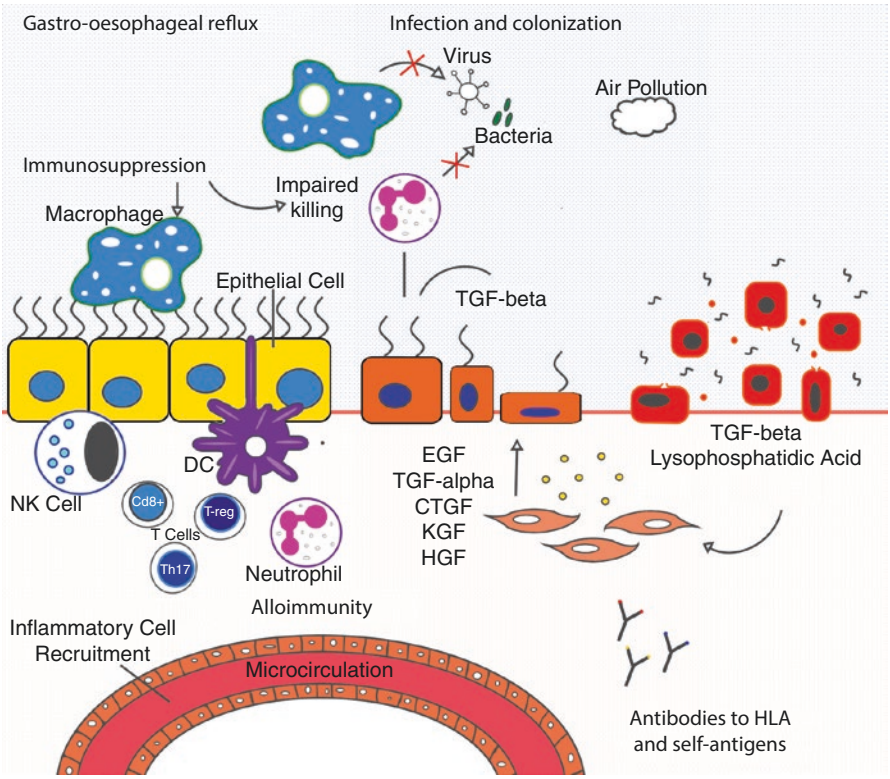


Fig. 11.4 Pathogeneis of CLAD. CLAD is thought to result from repeated or persistent insults to the allograft epithelium, with failed epithelial repair triggering a potent pro-fibrotic response. Diverse epithelial injuries (cellular or antibody-mediated rejection; bacterial, viral or fungal infection; and exposure to non-specific irritamnts such as gastric contents, cigarette smoke or air pollution) have been implicated in CLAD pathogenesis, with failed epithelial repair thought to be related to the severity or persistence of the injury and the susceptibility of the donated epithelium. Microvascular injury leading to relative epithelial ischaemia, and antibodies to self-antigens have also been implicated.The fibrotic response is mediated by multiplemediators, but transforming growth factor β and lysophosphatidic acid appear to be prominent. *CTGF* connective tissue growth factor, *DC* dendritic cell, *EGF* epidermal growth factor, *HGF* hepatocyte growth factor, *HLA* human leukocyte antigen, *KGF* kartinocyte growth factor, *NK cell* natural killer cell, *TGF-alpha* transforming growth factor alpha, *TGF-beta* transforming growth factor beta

11.5 Clinical Impact of CLAD

CLAD remains the predominant cause of post-transplant mortality after the first post-transplant year. Approximately 10% of patients develop CLAD each year, so that the prevalence of CLAD is approximately 10% at 1 year, 50% at 5 years and almost 100% after 10 years. Survival after CLAD onset is variable, but median survival is approximately 3 years. The RAS subtype of CLAD appears to have a worse prognosis than BOS. Despite the grim outlook for many patients with CLAD, it is not uncommon for patients with even aggressive disease to stabilise with an FEV1 around or just below 1 L.

11.6 Preventing CLAD

Since the prognosis once CLAD develops is poor, and as no treatments for established CLAD have been shown to be effective in well designed and powered trials, attention should focus on prevention. Whilst there have been no well controlled trials which have assessed the efficacy of preventative strategies, much is known about risk factors for CLAD development. Preventing or abrogating the impact of these risk factors on allograft function is likely to reduce CLAD incidence and hence improve post-transplant outcome.

One of the best described risk factors for subsequent CLAD is acute rejection, particularly of bronchioles ('B' grade rejection) [7], so although not proven, it makes intuitive sense that detecting and treating acute rejection should favourably impact on subsequent risk. The same principles apply to antibody-mediated rejection, although diagnosing AMR can be problematic as highlighted in Chap. 7. Since gastro-oesophageal reflux disease (GORD) is a well-described risk factor for CLAD, aggressively pursuing and treating GORD may be expected to improve outcomes. Similarly, detecting and treating viral (e.g. cytomegalovirus) and fungal (e.g. *Aspergillus*) infection favourably impacts on short term clinical outcomes, and may also impact on long-term outcomes.

Whilst it is likely that identifying these post-transplant complications and appropriately addressing them will reduce subsequent CLAD risk, arguably one of the most important risk factors for CLAD development and subsequent mortality is poor adherence to medication and medical/paramedical advice regarding post-transplant care. Although widely acknowledged as an important factor predicting outcome, this area remains poorly studied. Some of the most compelling evidence comes from studies investigating links between immunosuppressant blood levels and subsequent transplant outcome. Multiple observational studies, including in lung transplantation [8] have described a strong relationship between tacrolimus levels and, more importantly, variability in levels and clinical outcomes. In an Australian study, standard deviation of tacrolimus levels from 6 months post-transplant was the strongest risk factor for poor outcome [8]. It is likely that this association reflects poor adherence, and further that identifying the poorly adherent patient and intervening to improve adherence will favourably impact outcomes. It is possible that this may the most effective, and cost-effective, intervention of all. It is my practice now to actively assess tacrolimus variability by calculating standard deviation (SD) from 6 months post-transplant. Patients with an unacceptably high SD should be identified and investigation undertaken to understand why the SD is high. Possibilities include non-adherence (either missing doses or timing dosing poorly), gastroparesis, poor gastrointestinal absorption, taking tacrolimus with food (this reduces bioavailability) or co-prescribing medications which interfere with tacrolimus metabolism (e.g. azole antifungals).

Given this long list of risk factors, it is important that enough time is available at post-transplant clinic visits for each to be considered, and investigated and addressed if necessary. This approach should help protect patients visiting the clinic from subsequent CLAD development. A checklist of risk factors is provided in Table 11.2.

Table 11.2 Reducing CLAD risk—post-transplant clinic checklist

Risk factor	Investigation/diagnosis	Intervention
Acute cellular rejection	Monitor FEV1; bronchoscopy/ TBBx if >10% fall	Prednisolone/methylprednisolone. Review reasons for developing rejection (? Optimal dosing of tacrolimus, cell-cycle inhibitor, prednisolone)
Antibody-mediated rejection	Monitor FEV1; measure anti-HLA antibodies	Plasmapheresis/rituximab/intravenous immunoglobulin
Gastro-oesophageal reflux	Ask about symptoms when antacid treatment is interrupted; pH study	Fundoplication
CMV	Monitor peripheral blood viral load, especially in highest risk group (CMV—Recipient/+donor)	Valganciclovir
Fungal infection, especially *Aspergillus spp*	Bronchoscopy; CT chest	Voriconazole/posaconazole
Non-adherence	Direct questioning, especially high risk groups (adolescent/young adult; history of pre-transplant non-adherence; poor social supports)	Openly, non-confrontationally identify reasons for non-adherence and suggest remedies; motivational interviewing
High tacrolimus variability	Calculate tacrolimus standard deviation for the past 6 months	Identify possible reasons for high variability: – Non-adherence – Taking tacrolimus with food – Co-prescribing drugs which interfere with metabolism (e.g. azole antifungals—Can these be stopped?) – Gastroparesis/poor gastrointestinal absorption

11.7 Treating CLAD

Unfortunately the cupboard is bare when it comes to proven CLAD treatments. Although azithromycin has been reported to be of benefit (Fig. 11.3), this benefit is limited to a minority of patients with a predominance of neutrophils in bronchoalveolar lavage fluid [9] Whilst the fall in lung function can be reversed in this group, it is likely this condition is distinct from, or a precursor to true CLAD.

For established CLAD, there are a long list of interventions for which there are case reports, case series and retrospective observational studies, with a much shorter list of controlled trials. This evidence base has been well summarized in a recent systematic review by Benden et al. [10]. Whilst there are no good randomized controlled data supporting the efficacy of any treatment for CLAD, the evidence is strongest for extra-corporeal photophoresis, total lymphoid irradiation, Montelukast and aerosolized cyclosporine—see Benden et al. for more detail [10]. Deciding

which, if any, of these therapies may be trialled in a particular patient depends on local availability, risk of adverse effects and patient and physician preference. Supportive care—including vigilance for alternate causes of breathlessness and/or allograft dysfunction, supplemental oxygen therapy, psychological support and other measures targeted at symptom control is often more effective for this patient group.

11.8 Future Directions

Since established CLAD is a fibrotic condition, affecting bronchioles (BOS), lung parenchyma (RAS) or both, it is likely that anti-fibrotic treatments may be more effective than approaches involving augmentation of immunosuppression. The great strides currently being made in the management of idiopathic pulmonary fibrosis (IPF) are hence being observed with interest by the lung transplant community. Both pirfenidone (an antifibrotic drug which works through inhibition of TGFβ, and other as yet poorly described mechanisms) and nintedanib (a triple kinase inhibitor) have proven efficacy in IPF [11, 12]. A randomized trial of pirfenidone in CLAD (n = 80, NCT02262299) is ongoing in Europe with a planned completion date in 2019, whilst a small single arm study in RAS is also underway (n = 10, NCT03359863). A similar randomized trial for nintedanib in CLAD is planned to commence in 2018 (n = 80, NCT03283007). Newer antifibrotic agents which are in development for IPF, especially those targeting the lysophosphatidic acid pathway [6], may be of particular interest in CLAD. However, the tolerability of nintedanib, pirfenidone and even newer drugs and potential for drug interactions in lung transplant patients remains almost completely unknown.

Despite this promise, it is unlikely that established fibrosis in CLAD will be able to be reversed, nor will lost allograft function return. Attention should therefore be firmly directed to prevention of CLAD. As is the case for all transplant procedures, inducing immune tolerance to the allograft will be central to improving long-term outcomes. An allograft which is better tolerated is less likely to fail. At the same time the patient will require lower levels of immunosuppression to prevent acute rejection, so reducing side-effects. In these ways, inducing tolerance to the lung allograft will be key to preventing CLAD and improving long-term outcomes. However a first step to achieve this objective will be to develop much better measures of allograft tolerance. Our current tools for assessing the allograft (essentially lung function and transbronchial biopsy) are very crude—they only identify a problem after it has occurred and tell us little about how well (or how poorly) the patient is tolerating their graft. Understanding the mechanisms driving immunologic tolerance, and the cell-types most particularly involved, is likely to lead to better tools in the future. In this respect, of most interest are the regulatory group of T lymphocytes (Tregs). Traditional processing of allograft samples (e.g. bronchoalveolar lavage fluid and transbronchial biopsies), and even peripheral blood, does not differentiate between activated killer lymphocytes and ‘friendly’ tolerance-inducing Tregs. More

sophisticated tools based on flow cytometric technology and related emerging technologies will solve these problems and bring precision medicine to transplantation. Approaches to inducing tolerance which are under investigation involve adoptive transfer of Tregs in renal transplantation (the ONE study (NCT02091232)) and infusion of tolerogenic mesenchymal stromal cells in CLAD (the ASSIST CLAD study (NCT02709343)) [13].

Future, improved approaches to CLAD prevention will involve novel means of detecting and addressing the known risk factors highlighted above. Perhaps key amongst these is variability in exposure to immune suppressing agents, especially the calcineurin inhibitors. Some of the approaches and technologies which are likely to positively impact on this objective are already with us. More sophisticated methods for delivering stable levels of immune suppression—for example new formulations or new routes of administration of existing drugs; use of new technologies to avoid drug errors (e.g. the now widely available pharmacy Apps); and point of care kits for testing drug levels to empower the transplant patient with their care, could all contribute to improving outcomes. No doubt there will be incremental improvements in treatments and care which are able to address other CLAD risk factors. With so much on the horizon it is right to be optimistic about the future for transplant recipients.

References

1. Chambers DC, Yusen RD, Cherikh WS, et al. The Registry of the International Society for Heart and Lung Transplantation: thirty-fourth adult lung and heart-lung transplantation report-2017; focus theme: allograft ischemic time. J Heart Lung Transplant. 2017;36:1047–59.
2. Sato M, Waddell TK, Wagnetz U, et al. Restrictive allograft syndrome (RAS): a novel form of chronic lung allograft dysfunction. J Heart Lung Transplant. 2011;30:735–42.
3. Todd JL, Jain R, Pavlisko EN, et al. Impact of forced vital capacity loss on survival after the onset of chronic lung allograft dysfunction. Am J Respir Crit Care Med. 2014;189:159–66.
4. Hachem RR, Tiriveedhi V, Patterson GA, Aloush A, Trulock EP, Mohanakumar T. Antibodies to K-alpha 1 tubulin and collagen V are associated with chronic rejection after lung transplantation. Am J Transplant. 2012;12:2164–71.
5. DerHovanessian A, Weigt SS, Palchevskiy V, et al. The role of TGF-beta in the association between primary graft dysfunction and bronchiolitis obliterans syndrome. Am J Transplant. 2016;16:640–9.
6. Cao P, Aoki Y, Badri L, et al. Autocrine lysophosphatidic acid signaling activates beta-catenin and promotes lung allograft fibrosis. J Clin Invest. 2017;127:1517–30.
7. Glanville AR, Aboyoun CL, Havryk A, Plit M, Rainer S, Malouf MA. Severity of lymphocytic bronchiolitis predicts long-term outcome after lung transplantation. Am J Respir Crit Care Med. 2008;177:1033–40.
8. Gallagher HM, Sarwar G, Tse T, et al. Erratic tacrolimus exposure, assessed using the standard deviation of trough blood levels, predicts chronic lung allograft dysfunction and survival. J Heart Lung Transplant. 2015;34:1442–8.
9. Vanaudenaerde BM, Meyts I, Vos R, et al. A dichotomy in bronchiolitis obliterans syndrome after lung transplantation revealed by azithromycin therapy. Eur Respir J. 2008;32:832–43.
10. Benden C, Haughton M, Leonard S, Huber LC. Therapy options for chronic lung allograft dysfunction-bronchiolitis obliterans syndrome following first-line immunosuppressive strategies: a systematic review. J Heart Lung Transplant. 2017;36:921–33.

11. King TE Jr, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2014;370:2083–92.
12. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370:2071–82.
13. Chambers DC, Enever D, Lawrence S, et al. Mesenchymal stromal cell therapy for chronic lung allograft dysfunction: results of a first-in-man study. Stem Cells Transl Med. 2017;6:1152–7.

Chapter 12
Lung Transplantation for Interstitial Lung Disease

Monique Anne Malouf

12.1 Introduction

Interstitial lung disease (ILD) comprises a heterogeneous group of diffuse parenchymal lung disorders of more than 150 disease entities that are often associated with significant lung fibrosis [1–3] (Fig. 12.1). Idiopathic pulmonary fibrosis (IPF) is the most commonly diagnosed form of idiopathic interstitial pneumonia. Many of these disorders especially IPF, are subacute or chronic conditions which often lead to respiratory failure and death [4]. For many years, idiopathic pulmonary fibrosis was believed to be due to a chronic inflammatory response within the lung. However it is now believed to arise from an aberrant proliferation of fibrous tissue remodelling due to abnormal function and signalling of alveolar epithelial cells and interstitial fibroblasts [5, 6].The activation of cell signalling pathways through tyrosine kinases such vascular epithelial growth factors (VEGF) and fibroblast growth factors (FGF) plus platelet derived growth factor (PDGF) have all been implicated in the pathogenesis of the disease (Fig. 12.2) [7].

A comprehensive patient history taking is of crucial importance for the diagnosis of interstitial lung diseases. There are 4 main questions to be answered (1) when did the respiratory symptoms start? (2) How has the disease developed over time to the present? (3) The severity of symptoms at presentation? (4) Are there or have there been any exposures to etiologic agents known to cause ILD-such as smoking history, occupations, travel, hobbies, drug history and treatments e.g. radiation therapy? [8]. The disease chronology can be divided into 4 categories: (1) acute days to weeks; (2) subacute 4–12 weeks; (3) Chronic longer than 12 weeks and (4) episodic ie symptomatic and asymptomatic phases [2, 4, 9].

M. A. Malouf
The Lung Transplant Unit Xavier Level 4, St. Vincent's Hospital, Darlinghurst, NSW, Australia
e-mail: Monique.Malouf@svha.org.au

A. R. Glanville (ed.), *Essentials in Lung Transplantation*,
https://doi.org/10.1007/978-3-319-90933-2_12

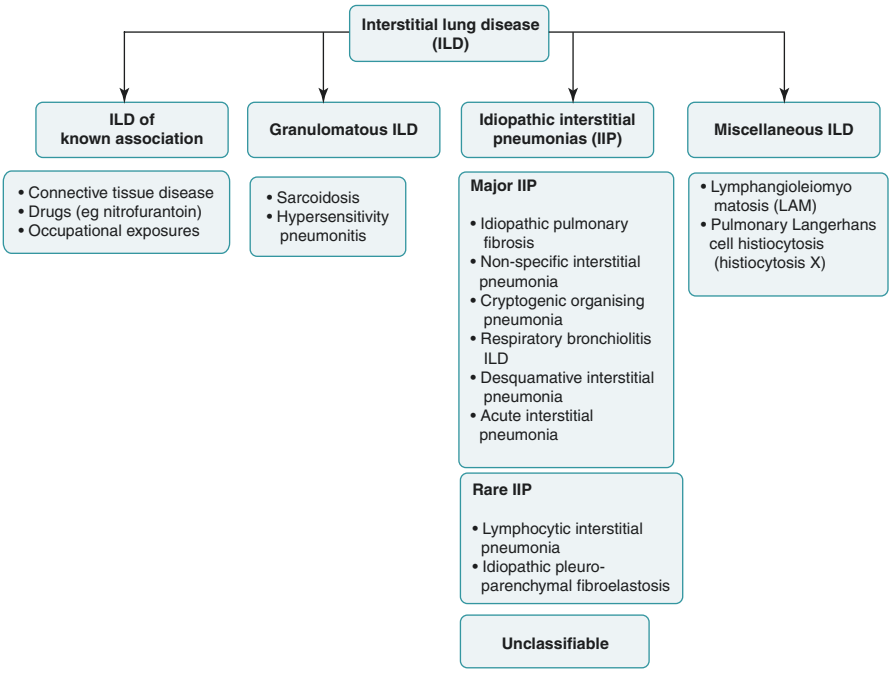


Fig. 12.1 Interstitial lung disease classification. Establishing an accurate diagnosis of ILD can be challenging for clinicians as there are more than 200 different subtypes. Over the past decade, ILDs have been reclassified in comprehensive international consensus statements. Reproduced with permission from The Royal Australian College of General Practitioners from Troy L, Corte T. Interstitial lung disease in 2015: Where are we now? Aust Fam Physician 2015;4(8):546–52

Assessment of Symptoms Dyspnoea with exertion or at rest is predominant in most ILDs [10, 11].Cough is the second most frequent symptom in patients with an ILD and ranges from minimal to very severe. A dry cough is very common in IPF and also to a lesser extent in sarcoidosis, hypersensitivity pneumonitis (HP) or organising pneumonia. Pleuritic pain and effusion in context of an ILD may indicate connective tissue disease (CTD). One should also ask if the patient experiences any rashes, joint pain, swelling, stiffness (>1 h in the morning), dry mouth, dry eyes or heartburn.

12.1.1 Physical Examination

On physical examination, oxygen saturations are often lower than normal on room air, which may be associated with peripheral or central cyanosis. Clubbing is present in 40% in of all ILDs and 60% with IPF. Inspection of the integument is very important ie skin thickening, acral necrosis, telangiectasia, sclerodactyly, narrowed oral aperture indicating scleroderma, rheumatoid arthritis features or nodules, Raynaud's phenomenon and dermatomyositis with heliotrope rash and Gottron's papules [12].

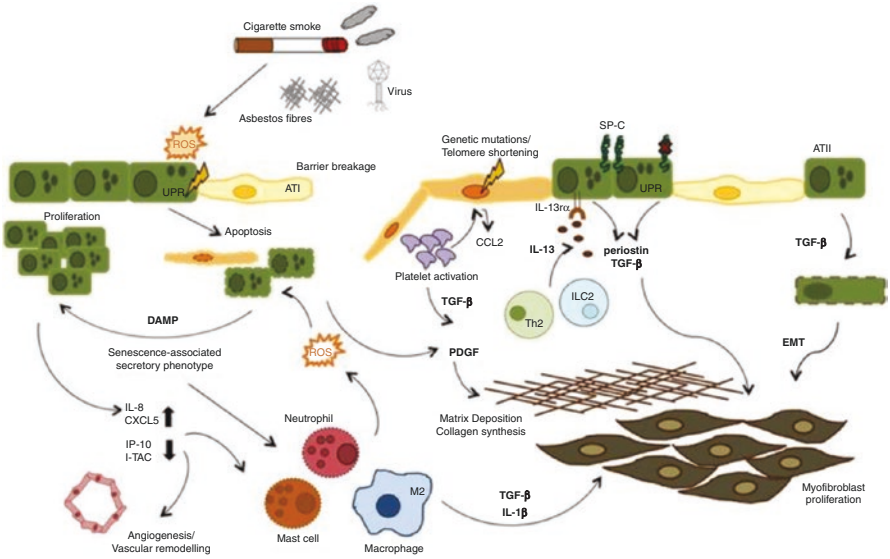


Fig. 12.2 This illustration demonstrates the complex pathways of airway remodelling which result from either genetic cellular mutations or exposure to external irritants and results in downstream dysregulation of various cytokine, chemokine, and molecular which favour an inflammatory response leading ongoing cellular damage and subsequently this phases into a fibroproliferative process which include fibroblast proliferation and collagen synthesis and extracellular matrix deposition

On auscultation of the lungs a fine "velcro like" inspiratory crackles will be heard, often bilaterally in more than 90% of patients with IPF and approximately 60% of patients with connective tissue associated ILDs. Crackles are less frequent in HP and sarcoidosis. Wheeze and inspiratory squeaks reflect bronchiolitis and/or bronchial obstruction and are associated with Churg-Strauss syndrome and rarely nonspecific interstitial pneumonia [2, 9].

CTDs that commonly cause ILDs include: rheumatoid arthritis, systemic sclerosis (scleroderma; SSc), idiopathic inflammatory myopathies, anti-synthetase syndrome, dermato/polymyositis, Sjögren syndrome and mixed connective tissue disease.

12.2 Radiology

The radiological appearance is a fundamental part of the assessment of ILDs as the appearances can be helpful in diagnosing an ILD. An abnormal chest X ray (CXR) is often the initial finding with loss of lung volume, diffuse reticulonodular infiltrate and ground glass changes. High resolution chest tomography (HRCT) allows more sensitive assessment of the type of ILD. Ragu G, Collard HR, Egan JJ et al. published that there were specific criteria used for the diagnosis of IPF, on HRCT which

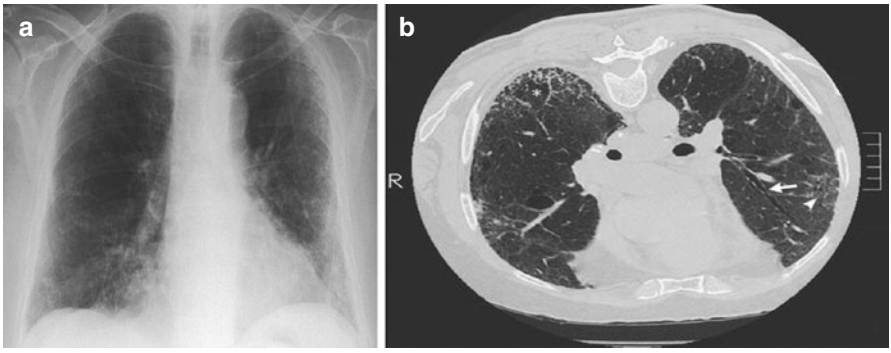


Fig. 12.3 Before lung transplant. (**a**) Chest x-ray showing idiopathic pulmonary fibrosis showing reticular-nodular changes and traction bronchiectasis. (**b**) High resolution CT images showing changes consistent with idiopathic pulmonary fibrosis. Imaging of the lung parenchyma should include views obtained with the patient lying prone to reduce gravitational effects on lower-lobe lung density. Overall there is a peripheral predominance with prominent irregular septal thickening (arrowhead), sub pleural honeycombing (asterisk), and a dilated airway, representing traction bronchiectasis (arrow). Open-lung biopsy confirmed pathological changes typical of usual interstitial pneumonia

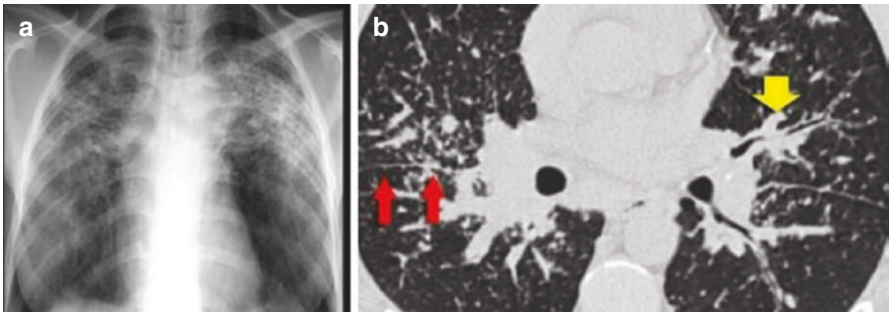


Fig. 12.4 (**a**) Chest x-ray showing typical features of sarcoidosis as seen by the upper lobe predominance and volume loss. Fibrosis leads to obliteration of pulmonary vessels which may lead to pulmonary hypertension. (**b**) High resolution computed tomography of the chest (HRCT) showing typical picture of sarcoidosis with hilar lymphadenopathy. Long standing sarcoidosis with pulmonary fibrosis with small nodules along bronchovascular bundles (yellow arrow) along fissure (red arrows) upper and mid-zone predominance

can be defined as definite, possible or inconsistent with IPF [4]. A definite diagnosis of IPF requires the HRCT chest to demonstrate all 4 UIP patterns—subpleural basal predominance, reticular abnormalities,honeycombing with or without traction bronchiectasis and no features inconsistent with this disorder (Fig. 12.3a, b).Possible UIP pattern requires all 3 out of 4 features—subpleural basal predominance, reticular abnormality and absence of features inconsistent with IPF—for example an upper lobe predominance, extensive ground glass changes (extent > reticular abnormality) and diffuse mosaic attenuation and air trapping [4]. The radiological features of sarcoidosis and hypersensitivity pneumonitis (HP) are described in Figs. 12.4 and 12.5.

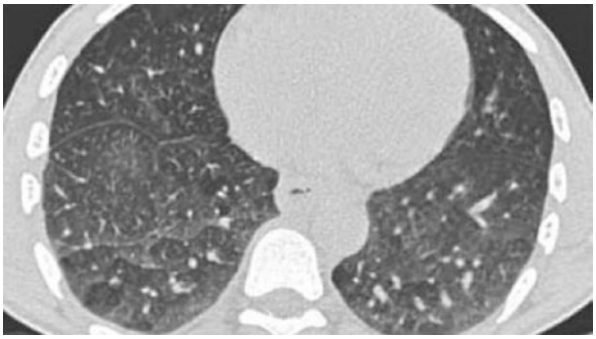


Fig. 12.5 HRCT chest showing typical features of hypersensitivity pneumonitis demonstrated by a mosaic pattern, and some secondary lobules demonstrating ground-glass opacity due to lung infiltration, whilst others are more lucent due to bronchiolitis and air trapping

12.3 Laboratory Tests

There are no specific blood tests for the diagnosis of an ILD but in the appropriate clinical setting the results may strongly support a specific diagnosis. Routine blood test should be done–full blood count, electrolytes, renal function, liver function tests, calcium, magnesium, phosphate, thyroid function tests, erythrocyte sedimentation rate C-reactive protein, and urinary sediment. To further evaluate for CTD a panel of tests are performed: antinuclear antibody, DsDNA, rheumatoid factor, serum angiotensin converting enzyme activity (ACE), anti CCP, c-ANCA p-ANCA, ENA differentiation Jo-1 or ScL-70 antibodies, Myositis,screen, creatine kinase activity (CK), myoglobin, aldolase, antiglomerular basement membrane antibody, specific serum IgG antibodies [13].

12.4 Lung Function

Patients with ILD should undergo comprehensive pulmonary function testing–spirometry, body plethysmography, measurement of diffusion capacity, and measurement of compliance. Lung function reflects the interstitial inflammation and scarring resulting in a restrictive ventilatory defect and impaired gas exchange reflected by abnormal capillary blood gas. While the forced vital capacity (FVC) may be quite low, the forced expiratory volume in 1 s divided by the forced vital capacity (FEV1/FVC) is often normal or greater than normal due to the increased elastic recoil pressure of the lung representing abnormally stiff and non-compliant lungs. Lung function demonstrates a low total lung capacity, low functional residual capacity and low residual volume. For example patients with an interstitial lung disease will have a restrictive pattern on their lung function tests ie FEV1/FVC ratio is $\geq$80% and TLC < 60% with significantly reduced diffusion capacity (see below example).The flow volume loop is moved further to the right compared to the normal flow volume loop (see green outline).They often have significant hypoxemia on room air and often desaturate further on exertion (Fig. 12.6).

		REF RANGE	PRE-BRONCH	
Lung Mechanics			Meas	%Ref
FVC	Liters	2.94 - 4.94	3.07	78
FEV1	Liters	2.23 - 3.91	2.46	80
FEV1/FVC	%	64 - n/a	80	
FEV1/SVC	%		80	
FEF25-75%	L/sec	1.55 - n/a	2.54	78
FEF50%	L/sec		4.62	110
PEF	L/sec	5.99 - 9.97	9.60	120
FET100%	Sec		8.02	
FIVC	Liters		3.08	
PIF	L/sec		4.68	
FEF/FIF50		<1.00	1.12	
PI max	cmH2O	39 - 111	94	125
PE max	cmH2O	75 - 167	85	70
MVV	L/min	90 - 168		
Lung Volumes (Plethysmography)				
VC	Liters	3.36 - 5.20	3.09	72
IC	Liters		1.90	59
ERV	Liters		1.19	110
FRC PL	Liters	2.55 - 4.53	2.02	57
Vtg	Liters		2.46	
RV	Liters	1.80 - 3.14	0.83	34
TLC	Liters	5.59 - 7.89	3.92	58
RV/TLC	%	30 - 48	21	
sGaw	L/s/cmH2O/L		0.212	96
Lung Diffusion Capacity (Single-Breath Hold)				
DLCO	mL/min/mmHg	21.7 - 36.2	7.6	26
DL Adj	mL/min/mmHg		7.6	
DLCO/VA	mL/min/mmHg/L	3.39 - 6.15	1.96	41
VA	Liters		3.87	
IVC	Liters		2.84	
Blood Gases				
FIO2	%		21.00	
pH			7.42	
PCO2	mmHg		41.0	
PO2	mmHg		69.5	
HCO3	meq/L		26.0	
BE			1.9	
Hb	gm/dL		14.9	
P(A-a)O2	mm/Hg		35.6	

Fig. 12.6 Full lung function demonstrating a severe restrictive defect due to an IPF

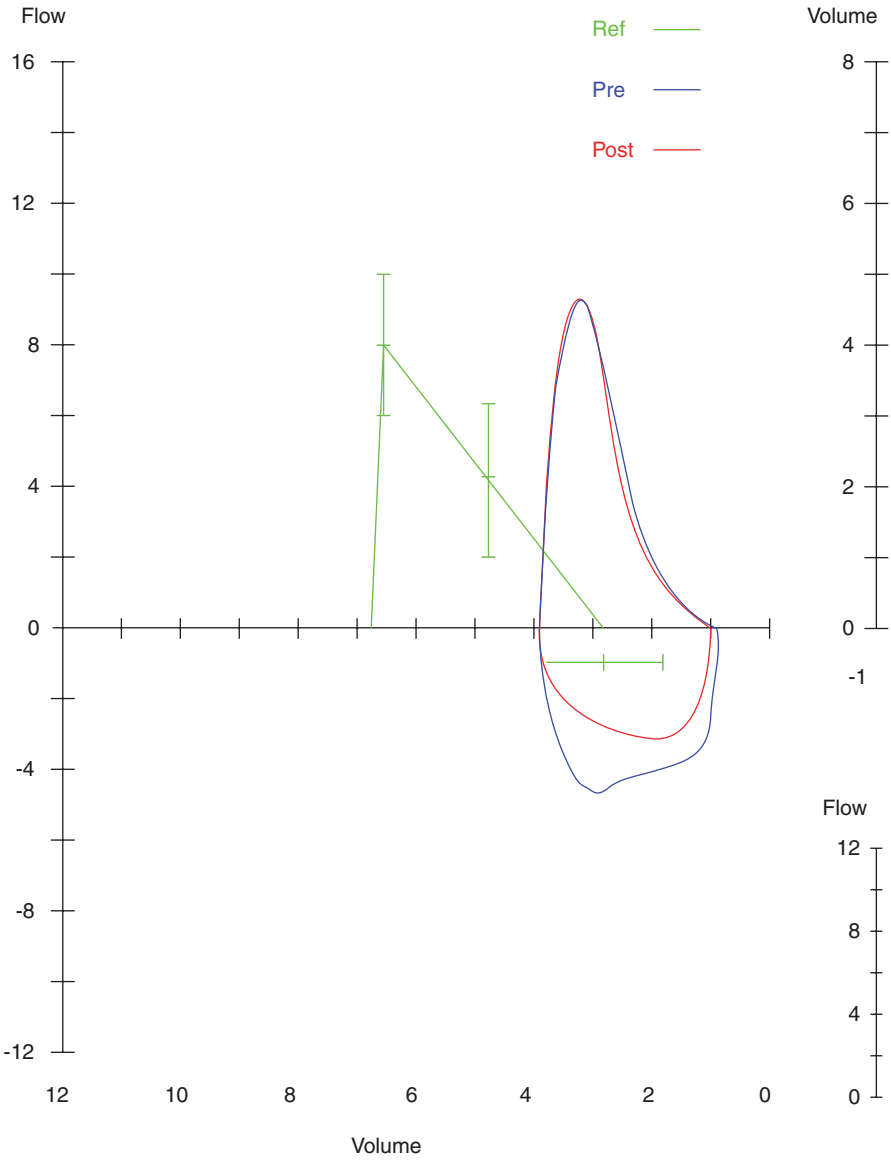


Fig.12. 6 (continued)

12.5 Confirmatory Diagnostic Testing

IPF is one, if not the most important disease to rule out for a patient with an ILD as this determines their prognosis, but making a diagnosis of IPF can be difficult. The accuracy and confidence of the diagnosis can be improved significantly with a multidisciplinary meeting which includes clinicians, radiologists and pathologists in centres that specialise in the care of these patients with this disease and this is now considered the gold standard for diagnoses [14]. When an experienced radiologist is confident that the pattern on HRCT is consistent with a usual interstitial pneumonitis (UIP) the patient can avoid an open lung biopsy (OLBX) (Fig. 12.7). However when characteristic pattern is absent then bronchoscopy, bronchoalveolar lavage (BAL),transbronchial lung biopsy (TBBX), endobronchial ultrasonography guided biopsy (EBUS) or an open lung biopsy may be required to make the diagnosis. Bronchoscopy and BAL is also useful to rule out an alternative diagnosis such as bacterial, viral and fungal infections. TBBx or EBUS can often diagnose conditions such as sarcoidosis (Fig. 12.8). Surgical lung biopsy nowadays is preferentially performed as a video-assisted thoracoscopic biopsy (VATS), which is most invasive diagnostic procedure for patients with possible IPF. It also assists in ruling out HP (Fig. 12.9) which can masquerade as IPF, until appropriate histology is obtained. However there may be sampling error and uniformity of disease pattern in advanced disease and histologic examination may not provide an answer [4].

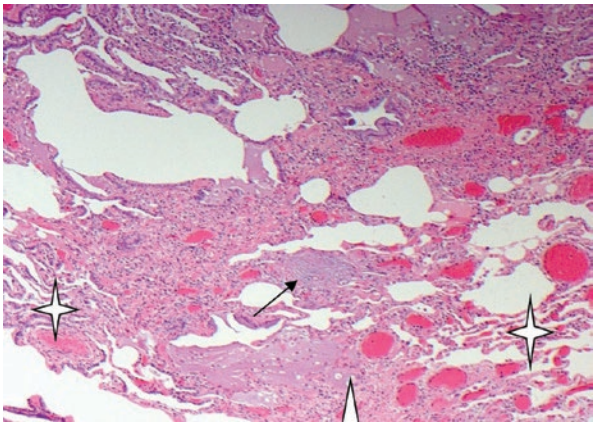


Fig. 12.7 Demonstrates features of IPF. Pathological heterogeneity exemplified by dense scarring adjacent to relative spared alveoli is characteristic of IPF. Sub pleural fibrosis (white arrow); fibroblastic foci visible as a nodule of spindle cells arranged in a linear fashion (black arrow) and adjacent normal alveolar septa (stars)

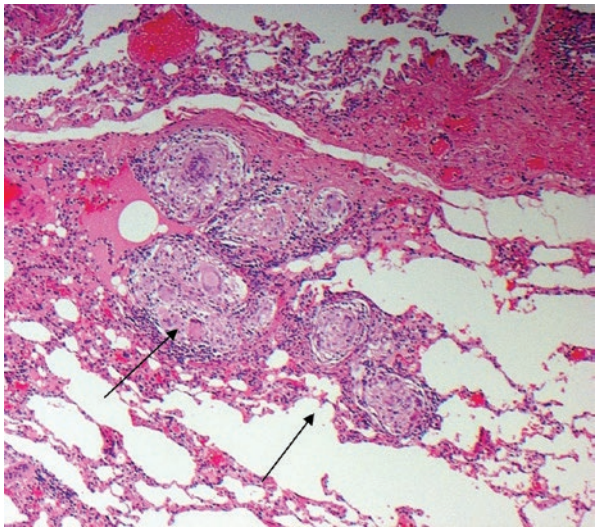


Fig. 12.8 Demonstrates features of sarcoidosis. Arrows showing non necrotising epithelioid granulomas with giant cells surrounded by concentric layers of fibrotic bundles

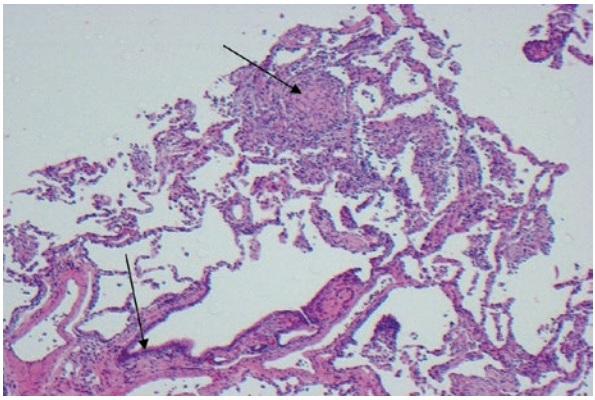


Fig. 12.9 Demonstrates features of hypersensitivity pneumonitis. The most striking and consistent feature is a cellular chronic interstitial pneumonia characterized by thickening of alveolar septa (interstitium) by an inflammatory infiltrate composed mainly of lymphocytes and plasma cells with occasional multinucleated giant cells

12.6 Treatment Options for ILD

The American Thoracic Society recognizes that supplemental oxygen and transplantation are the only suggested treatments for IPF. Prognosis of IPF is generally poor, retrospective cohort studies indicate a median survival of 2–3 years from diagnosis and only 20–30% survive 5 years after diagnosis. This underscores that these

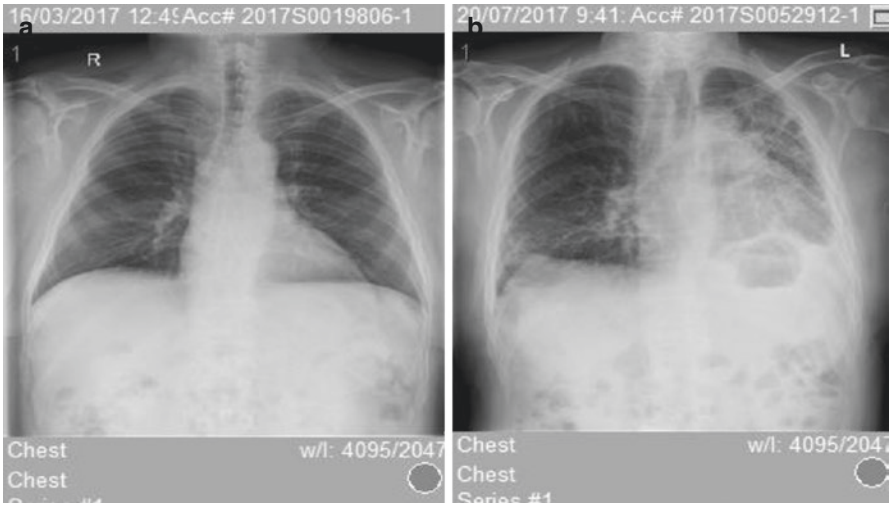


Fig. 12.10 Post lung transplant chest x-ray. (**a**) Bilateral lung transplant for idiopathic pulmonary fibrosis. (**b**) Single lung transplant of the right lung for idiopathic pulmonary fibrosis. There is significantly reduced lung volume on the left side as evidenced by the raised left hemi-diaphragm

patients should be referred for evaluation for transplantation immediately due to their high risk of mortality. Lung transplantation (LTx) is the only therapy that has been shown to prolong survival [4]. Recent worldwide changes in lung allocation of donor lungs, including the lung allocation score (LAS) in United States and within Europe have dramatically increased the lung transplant rates for ILD patients [15]. Only recently have there been available therapies such as Nintedanib and Pirfenidone for patients but within Australia these therapies are reserved for patients with a diagnosis of IPF which has been confirmed via a multi-disciplinary team meeting (MDT) [16–19] (Fig. 12.10).

12.7 Clinical Course of Disease

There appear to be several possible natural histories for patients with IPF. The majority of patients experience a slow but steady worsening of their disease [20]. Some patients remain stable, while others have an accelerated decline [21]. A minority of patients may experience unpredictable acute worsening of their disease, either from a secondary complication such as pneumonia, or from exacerbation of IPF [22]. This event may be fatal or may leave patients with substantially worsened disease. Other comorbid conditions may be subclinical or overt such as emphysema, pulmonary arterial hypertension, gastroesophageal reflux, obstructive sleep apnoea and obesity, which may have a negative impact on the disease course [22] but the relative frequency of each of these natural histories is unknown [4].

The failure rates of currently available treatments for advanced lung disease due to ILD, makes alternative therapeutic options necessary, hence referral to a lung transplant centre is recommended at the time of diagnosis.

ILD severe enough to warrant consideration of lung transplantation may be associated with collagen vascular diseases such as scleroderma and rheumatoid arthritis [23, 24]. Data regarding specific predictors of prognosis in this setting are limited. If the lung disease has not responded to appropriate treatment and there are no extrapulmonary contraindications to transplantation, it is reasonable to use similar guidelines to those proposed for idiopathic ILD [15].

The evidence reviewed here focuses on IPF as the most common and life threatening subtype of ILD, while recognising that fibrosing nonspecific interstitial pneumonia (NSIP) and other types of progressive ILD refractory to treatment may carry a similar prognosis.

Idiopathic pulmonary fibrosis (IPF) was the indication for the first successful isolated lung transplant (LTx) with long term survival, performed at the University of Toronto in1983 [25].Since then, patients diagnosed with an ILD, have emerged as one of the most common indications in selected patients for LTx replacing chronic obstructive pulmonary disease [26, 27].

12.8 Candidate Selection

When considering patients suitable for transplantation several factors must be borne in mind, however an important factor is that the patient should have exhausted all available medical and surgical options and thereby transplantation is their last hope of survival. With this in mind it is vital to consider the survival rates post-transplantation and the risks of the enormous procedure that the patient is undertaking thereby balancing the risk versus benefit ratio and ensuring that at the point of transplant listing the risk or survival outweighs the risks of the procedure itself. The current updated consensus adopted by the International Society for Heart and Lung Transplant (ISHLT) published in 2015, is that patients should have a predicted 2 year survival of less than 50% due to end stage pulmonary disease, with a likelihood of surviving for more than 90 days after lung transplantation. There should also be an 80% likelihood of having a 5 year post transplant survival from a general medical perspective provided adequate graft function [15].

Within the above mentioned consensus document from the ISHLT specific selection criteria must be met in order for a patient to be suitable for listing (Tables 12.1 and 12.2).

Relative contraindications have been breached in some cohorts with success. As a result careful patient selection in this group is paramount [15, 28]. A patient's age should not be the sole reason for them to be declined, however what is often the case is that due to a patient's advanced age there is an increased incidence of co-morbidities resulting in the patient not being considered suitable.

Table 12.1 Absolute contraindications to transplant—data from Weill D, Benden C, Corris PA et al. A consensus document for the selection of lung transplant candidates: 2014-an update from the pulmonary transplant council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2015:34(1):1–15

Absolute contraindications to lung transplantation
• A recent history of malignancy
– 2 year disease free interval (DFI) is desirable combined with low predicted risk of recurrence. e.g. non melanoma skin cancer that has been treated appropriately and a
– 5 year disease DFI for any haematological malignancy, sarcoma, melanoma, breast, bladder, kidney or prostate cancer
• Major organ system failure
• Un-correctable bleeding diathesis
• Active extra-pulmonary infections HIV or hepatitis B or C virus
• BMI >35
• Highly virulent organism
• Mycobacterium tuberculosis

Table 12.2 Relative contraindications to transplant—data from Weill D, Benden C, Corris PA et al. A consensus document for the selection of lung transplant candidates: 2014-an update from the pulmonary transplant council of the International Society for .Heart and Lung Transplantation. J Heart Lung Transplant 2015:34(1):1–15

Relative contraindications to lung transplantation
• Documented problems with adherence
• Poor rehabilitation potential
• Body mass index >30
• Unstable clinical condition ie shock or ventilator dependence
• Active substance abuse within the last 6 months
• Untreatable psychiatric conditions
• Absence of social support network
• Anatomically prohibitive chest or spinal deformity
• Mechanical ventilatory support or extra corporeal life support (ECLS)

12.8.1 Special Considerations: Telomere Abnormalities and Lung Transplantation

Telomerase mutations are the most common identifiable genetic cause of IPF [29]. The telomere defect also manifests in extrapulmonary disease such as cirrhosis, bone marrow failure, infection, renal dysfunction, a history of defective wound healing, rare drug reactions and non melanoma skin carcinomas. Patients with pulmonary fibrosis with mutations in the telomerase genes have a high rate of certain complications after lung transplant and require attention to specific complications that may be otherwise rare in other lung transplant recipients. Patients with this defect are at increased risk for post-transplant complications such as primary graft dysfunction (PGD) and CLAD. Lung transplant recipients uniformly required dose modification of immunosuppression for cytopenias reflecting limited underlying bone marrow reserves [30].

Timing of Referral Histopathological or radiographic evidence of usual interstitial pneumonitis (UIP) or fibrosing non-specific interstitial pneumonitis (NSIP), regardless of lung function. Abnormal lung function: forced vital capacity (FVC) less than 80% predicted or diffusion capacity of the lung for carbon monoxide (DLCO) <40% predicted; any dyspnea or functional limitation attributable to lung disease. Any oxygen requirement, even if only during exertion. For inflammatory interstitial lung disease (ILD), failure to improve dyspnea, oxygen requirement, and/or lung function after a clinically indicated trial of medical therapy [15].

Timing of Listing Decline in FVC >10% during 6 months of follow-up (note: a 5% decline is associated with a poorer prognosis and may warrant listing). Decline in DLCO >15% during 6 months of follow-up. Desaturation to <88% or distance <250 metre 6-min walk test or 450 m decline in 6-minute-walk distance over a 6-month period. Pulmonary hypertension on right heart catheterization or 2-dimensional echocardiography or hospitalization because of respiratory decline, pneumothorax, or acute exacerbation [15].

12.9 Single vs Bilateral Lung Transplantation

It is unclear whether BLT is superior to SLT transplantation in patients with underlying IPF and ILD [31]. Kaplan Meier survival curves analysing data from the ISHLT database shows that there is no difference in survival between the two groups (Figs. 12.11 and 12.12). However, the proportion of bilateral lung transplants (BLT) vs single lung transplants (SLT) procedures among IPF patients included in the ISHLT database has been steadily increasing since 1997, accounting for 70% of the total number of US LTx [33]. Lacking randomised controlled trials (RCT),it was necessary to consider observational studies and the pooled survival analysis of 3 observational studies, showed that there was no difference between patients who received single versus bilateral LTx (HR,47; 95% CI,0.19–1.17) [34–36].There was an increase incidence of postoperative graft dysfunction (PGD) grade for BLT vs SLT and further meta-analysis supported the above study's findings and unadjusted analysis suggested improved long term survival in BLT vs SLT. However after adjustment for patient characteristics the differences tended to disappear. Post-transplant % predicted FEV1% and freedom from bronchiolitis obliterans syndrome (BOS) were not statistically different for SLT vs BLT recipients [37].

12.10 Causes of Morbidity and Mortality

Long term outcomes after lung transplantation remain inferior to other solid organ transplants due to the development of chronic lung allograft dysfunction (CLAD) and infection. Primary graft dysfunction (PGD), infection and acute rejection are a

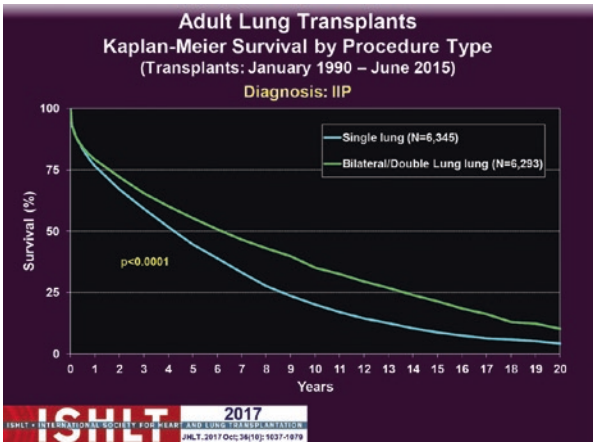


Fig. 12.11 Adult lung transplant survival 1990–2015. From the International Society for Heart and Lung Transplantation 2017 slide collection comparing survival of single versus bilateral lung transplant for IPF [32]

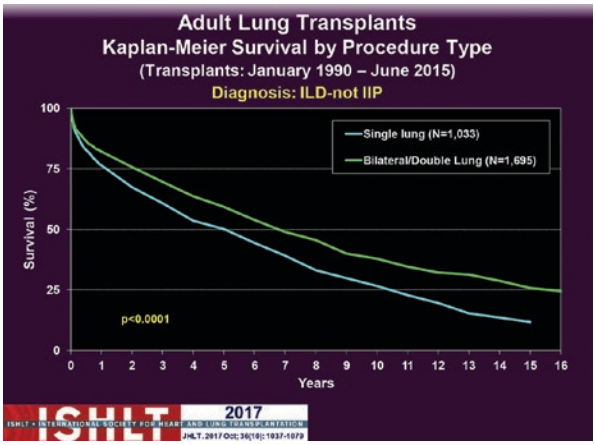


Fig. 12.12 Adult lung transplant survival 1990–2015. From the International Society for Heart and Lung Transplantation 2017 slide collection comparing survival of single versus bilateral lung transplantation in patients with ILD not IPF [32]

major cause of morbidity and death particularly in the first years of transplant. Infection occurs early and late mortality is often due to significant bacterial, viral or fungal infections particularly invasive fungal infections. Current 5 and 10 year survivals are 54% and 32% respectively, largely due to the development of obliterative bronchiolitis (OB), which is a progressive focal fibrotic and occlusive process of small airways, clinically apparent as bronchiolitis obliterans syndrome (BOS). BOS is the predominant phenotype of CLAD, while the other main phenotype is restrictive allograft syndrome (RAS). Despite rigorous pre-transplant evaluation and

selection, in recipients who survive >90 days, post-transplant survival is 5.7 years for all recipients and only 4.7 years for recipients with pulmonary fibrosis [38]. Treatment of CLAD is challenging because its' underlying pathogenesis is not well understood although addition of azithromycin and everolimus may slow the progression of OB. There are a number of complications that affect the allograft. ie acute rejection, anastomotic issues, antibody mediated rejection, viral infections, and aspiration due to gastroesophageal reflux. Patients are on lifelong immunosuppressive medications typically a calcineurin inhibitor, antimetabolite and prednisolone. These medications are used to prevent and treat rejection but they also cause increased morbidity and potentially mortality as there is an increased risk of the development of infections, diabetes, osteoporosis, chronic kidney disease and malignancy [39]. The development of CLAD approximates 20–25% per 3–5 years after transplant. Another risk factor for death after LTX was the earlier the date of transplantation for IPF, elevated wedge pressure and single lung transplant [34]. By 5–10 years and thereafter malignancy is a major cause of death by approximately10–15% per year, often due to the significant increase in the incidence of skin cancers [38].

Lung cancer rates are reported to be 20–25% higher compared to the general population with an incidence of 4.1%. Patients with ILD are at an increased risk of developing lung cancer. The incidence of bronchogenic carcinoma after lung transplant is approximately 0.25–4% 0.75 per 100 patient years. Collins et al. followed 2168 single lung transplant recipients (SLTx) and found that 24 or 1% developed cancer in the native lung [40] Dickinson et al. found that 7% of SLT developed lung cancer compared to 0% in bilateral lung transplant recipients (BLT). All were non-small cell malignancies [41]. There are sporadic cases reports of small cell lung cancer in both SLT & BSLT.

12.11 Coronary Artery Disease

IPF is the most common indication for LTx for ILD. Median age is 55–65 years with a male predominance. Consequently coronary artery disease (CAD) is a potential problem and/or contraindication. Challenges of considering lung transplant in this age group necessarily involves consideration of cardiovascular disease for patients with IPF [42, 43].

Consequently, investigation of the patient's cardiac status is very important to diagnose and manage CAD. These include tests to rule out ischemia such as an exercise stress test, Sestimibi or Persantin or Dobutamine stress test, CT coronary angiogram and finally coronary angiogram. If these investigations discover stenosis that cannot be managed medically, then if possible they will need to be managed either surgically or by stents. The decision may be to stent prior to LTX or perform coronary artery bypass surgery at the time of transplant. The use of bare metal stents (BMS) is preferred due to the fact that patients with drug eluting stents need to be on long term aspirin and clopidogrel for at least a year. BMS should be managed

with dual antiplatelet therapy (clopidogrel and aspirin) for a period of 3 months, after which clopidogrel may be ceased and it is generally safe to list the patient for LTx and continue aspirin long term.

12.12 Pulmonary Hypertension

Currently there are no clear indications to treat pulmonary hypertension (PHT) associated with ILD. Comorbid PHT is commonly seen in patients with IPF and contributes to a worsened clinical prognosis [22, 44]. To assess for PHT prior to transplant is very important. Initially, echocardiogram, a non-invasive diagnostic screening tool may be performed, but it may be inaccurate in estimating pulmonary haemodynamics. A right heart catheter often gives a more accurate appraisal for assessment. Initial studies focused on short term haemodynamics rather than long term patient outcomes, were not randomised to treatment or control arms or were retrospective analyses [45, 46]. A randomised control trial (RCT) was undertaken with the endothelin receptor antagonist Ambrisentan but showed no benefit either for pulmonary hypertension or survival, with a marked increase in adverse events [47]. Sildenafil (a phosphodiesterase inhibitor) was utilised in a trial of exercise performance in idiopathic pulmonary fibrosis trial (STEP-IPF), 180 patients with advanced IPF(DLco <35%),were randomised to either sildenafil 20 mg TDS or placebo for 12 weeks. There was no significant benefit of sildenafil and the study failed to reach clinical significance for the primary outcome for improvement in 6MWT of >20% after a 12 week period (10.1% vs 6.6% p = 039). However there were small benefits involving the secondary outcomes with improved shortness of breath, improved quality of life, improved DLco and improved arterial oxygen saturation at the end of the 12 week randomization in the sildenafil arm [48, 49]. A predefined subgroup in patients with documented right ventricular hypertrophy or right ventricular dysfunction, demonstrated significantly improvements with sildenafil on the primary outcome of 6 min walk distance. Sildenafil had no significant benefit on disease progression however there was improvement in quality of life and given that no other outcomes were significantly improved, no subgroup recommendation could be made for the use of sildenafil in patients with ILD with documented PHT [31].

The antifibrotic agentsPirfenidone and Nintedanib have been used as a bridge to transplant. The major side effects include weight loss while waiting for transplant. There was no difference in wound healing, in particular bronchial anastomosis, development of chronic lung allograft dysfunction or survival post-transplant [50].

12.13 Summary

Idiopathic pulmonary fibrosis is the most commonly diagnosed form of interstitial lung disease and usually fails to respond to medical therapy and carries a very poor prognosis with persistent and rapid decline in lung function, placing them at an

increased risk of mortality. Lung transplantation should therefore be considered early or at the time of diagnosis. Although LTx is not without its challenges, given that current treatment options are limited, it is the only therapy which can provide these patients with a reasonable chance of survival and improved quality of life.

Acknowledgment The author is grateful to the anatomical department of St. Vincent's hospital for graciously providing anatomical histology of the various interstitial lung diseases required for this chapter.

References

1. Leibow AA, Carrington CB. The interstitial pneumonia. In: Simon M, Potchen EJ, LeMay M, editors. Frontiers of pulmonary radiology. 1st ed. New York: Grune & Stratton; 1969. p. 102–41.
2. Travis WD, Costabel U, Hansell DM, et al. American Thoracic Society/European Respiratory Society: international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2002;165(2):277–304.
3. Troy L, Corte T. Interstitial lung disease in 2015: where are we now? Aust Fam Physician. 2015;44(8):546–52.
4. Raghu G, Collard HR. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011;183:788–824. https://doi.org/10.1164/rccm.2009.
5. Selman M, Pardo A. Idiopathic pulmonary fibrosis: an epithelial fibroblast cross talk disorder. Respir Res. 2002;3:3.
6. Gross TJ, Hunninghake GW. Idiopathic pulmonary fibrosis. N Engl J Med. 2001;345:517–25. https://doi.org/10.1056/NEJMra003200.
7. Carmelo A, Dunmore R, Sleeman MA, et al. The epithelium in idiopathic pulmonary fibrosis: breaking the barrier. Front Pharmacol. 2014;4:173.
8. Cooper JA Jr, White DA, Matthay RA. Drug induced pulmonary disease. Part 1: cytoxic drugs. Am Rev Respir Dis. 1986;133:321–40.
9. Bradley B, Branley HM, Egan JJ, et al. Interstitial lung disease guideline. Thorax. 2008;63(Suppl 5):v1–v58.
10. Raghu C, Mageto YN, Lockhart D, et al. The accuracy of the clinical diagnosis of new onset idiopathic pulmonary fibrosis. Chest. 1999;116:1168–74.
11. King TE Jr, Tooze JA, Schwatz MI, et al. Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. Am J Respir Crit Care Med. 2001;164:171–1181.
12. Gribbin J, Hubbard RB, Le Jeune I, et al. Incidence and mortality of idiopathic pulmonary fibrosis and sarcoidosis in the UK. Thorax. 2006;61:908–85.
13. Flaherty KR, King TE Jr, Raghu G, et al. Idiopathic interstitial pneumonia: what is the effect of a multidisciplinary approach to diagnosis? Am J Respir Crit Care Med. 2004;170:904–10.
14. Yang S, Raghu G, et al. Clinical evidence in diffuse parenchymal lung disease. Basel: Karger; 2007. p. 22–8.
15. Weill D, Benden C, Corris PA, et al. A consensus document for the selection of lung transplant candidates: 2014—an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2015;34(1):1–15.
16. Richeldi L, Costabel U, et al. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. N Engl J Med. 2011;365:1079–87.
17. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2071–82.
18. King TE Jr, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2083–92.

19. Jo HE. TSANZ position statement: treatment of idiopathic pulmonary fibrosis. Respirology. 2017;22:1436.
20. Ragu G. Idiopathic pulmonary fibrosis: a rational approach. Chest. 1987;92:148–54.
21. Selman M, Carrilo G, Estrada A, et al. Accelerated variance of idiopathic pulmonary fibrosis: clinical behavior and gene expression pattern. PLoS One. 2007;2:e48.
22. Mejia M, Carrilo G, Rojas-Serrano J, et al. Idiopathic pulmonary fibrosis and empysema: decreased survival associated with severe PAH. Chest. 2009;136:10–5.
23. Bongartz T, Nannini C, Medina-Velasquez YF, et al. Incidence and mortality of interstitial lung disease in rheumatoid arthritis:a population- based study. Arthritis Rheum. 2010;62:1583–91.
24. Bouros D, Wells AU, Nicholson AG, et al. Histopathologic subsets of fibrosing alveolitis in patients with systemic sclerosis and their relationship to outcome. Am J Respir Crit Care Med. 2002;165:1581–6.
25. Group TLT: Toronto Lung Transplant Group. Unilateral lung transplantation for pulmonary fibrosis. N Engl J Med. 1986;314(18):1140–5.
26. Christie JD, Edwards LB, Aurora P, et al. The registry of the International Society for Heart and Lung Transplantation: thirteenth official pediatric lung and heart-lung transplantation report—2010. The official report ISHLT. J Heart Lung Transplant. 2009;28(10):993–1006.
27. Yusen RD, Shearon TH, Qian Y, et al. Lung transplantation in USA 1999-2006. Am J Transplant. 2010;10(4 Pt 2):1047–68.
28. Timothy JG, Aranaoutakis GJ, et al. Lung transplant in idiopathic pulmonary fibrosis. Arch Surg. 2011;146(10):1204–9.
29. Armanios M. Telomeres and age relate disease: how telomere biology informs clinical paradigms. J Clin Invest. 2013;123:996–1002.
30. Silhan LL, Shah PD, Chambers DC, et al. Lung transplantation in telomerase mutation carriers with pulmonary fibrosis. Eur Respir J. 2014;44:178–87.
31. Raghu G, Rochwerg B, Zhang Y, et al. An official ATS/ERS/JRS/ALAT clinical practice guidelines: treatment of idiopathic pulmonary fibrosis. An update of the 2011 clinical practice guideline. Am J Respir Crit Care Med. 2015;192(2):e3–e19.
32. ISHLT Registry Report in the JHLT 2017;36(10):1037–79.
33. Kistler K, Nalysnk L, Rotella P, et al. Lung transplantation in idiopathic pulmonary fibrosis: a systemic review of the literature. BMC Pulm Med. 2014;14:139.
34. Force SD, Kilgo P, Neujahr DC, et al. Bilateral lung transplantation offers better long term survival, compared with single lung transplantation for younger patients with idiopathic pulmonary fibrosis. Ann Thorac Surg. 2011;91:244–9.
35. Mason DP, Brizzio ME, Alster JM, et al. Lung transplantation for idiopathic pulmonary fibrosis. Ann Thorac Surg. 2007;84:1121–8.
36. Neurohr C, Huppmann P, Thum D, et al. Potential functional and survival benefit of double over single lung transplantation for selected patients with idiopathic pulmonary fibrosis. Transpl Int. 2010;23:887–96.
37. De Oliveria NC, Osaki S, Maloney J, et al. Lung transplant for interstitial lung disease: outcomes for single versus bilateral lung transplantation. Interact Cardiovasc Thorac Surg. 2012;14:263–7.
38. Yusen RD, Edwards LB, Kucheryavaya AY, et al. The registry of the International Society for Heart and Lung Transplantation: thirty-first adult and heart lung transplant report—2014: focus theme: retransplantation. J Heart Lung Transplant. 2014;33(10):1009.
39. Newton CA, Kozlitina J, Lines JR, et al. Telomere length in patients with pulmonary fibrosis associated with chronic lung allograft and post-lung transplant survival. J Heart Lung Transplant. 2017;36(8):845–53.
40. Collins J, Kazerooni EA, Lacomis J, et al. Bronchogenic carcinoma after lung transplantation: frequency, clinical characteristics and imaging findings. Radiology. 2002;224:131–18.
41. Dickinson RP, Davis RD, Rea JB, et al. High frequency of bronchogenic carcinoma after single lung transplantation. J Heart Lung Transplant. 2006;25:1297–301.
42. Hubbard RB, Smith C, Le Jeune I. The association between idiopathic pulmonary fibrosis and vascular disease. A population-based study. Am J Respir Crit Care Med. 2008;178:1257–61. https://doi.org/10.1164/rccm.200805-725OC.

43. Kizer JR, Zisman DA, Blumenthal NP, et al. Association between pulmonary fibrosis and coronary artery disease. Arch Intern Med. 2004;164:551–5.
44. Lerreri CJ, Nathan SD, Barnett SD, et al. Prevalance and outcomes of pulmonary hypertension in advanced idiopathic pulmonary fibrosis. Chest. 2006;129:746–52.
45. Collard HR, Anstrom KJ, et al. Sildenafil improves walk distance in idiopathic pulmonary fibrosis. Chest. 2009;136:10–5.
46. Ghofrani HA, Wiedermann R, Rose F, et al. Sildenafil for treatment of lung fibrosis and pulmonary hypertension: a randomised controlled trial. Lancet. 2002;360:895–900.
47. Ragu G, Behr J, Brown KK, Artemis IPF Investigators*, et al. Treatment of idiopathic pulmonary fibrosis with ambrisentan: a parallel, randomised trial. Ann Intern Med. 2013;148:641–9.
48. Jackson RM, Glassberg MK, Ramos CF, et al. Sildenafil therapy and exercise tolerance in idiopathic pulmonary fibrosis. Lung. 2010;188:115–23.
49. Zisman DA, Schartz M, Anstrom KL, Idiopathic Pulmonary Fibrosis Clinical Research Network, et al. A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. N Engl J Med. 2010;363:620–8.
50. Delanote I, Wuyts WA, Yserbyt J, et al. BMC Pulm Med. 2016;16:156.

Chapter 13
Lung Transplantation for Obstructive Lung Diseases

Amy L. Rigby

13.1 Introduction

Obstructive lung disease is the most common indication for lung transplantation worldwide, comprising 36% of all lung transplants performed in the period 1995–2015 [1]. Of the obstructive lung diseases that are considered for transplantation, the most common by far is chronic obstructive pulmonary disease, which makes up 33% of all transplants [2], although other obstructive lung diseases considered for transplantation include α_1-antitrypsin deficiency (A1AT), lymphangioleiomyomatosis (LAM), and Langerhans cell histiocytosis (LCH) [3]. Unlike other indications for lung transplantation, the natural history of COPD is often more indolent than for other respiratory diseases for which transplants are performed [3, 4]. This makes the criteria for listing, and, in particular, the timing of listing, critical in this patient population. Unlike some other respiratory indications for transplantation, obstructive lung diseases also offer the potential consideration of single lung transplant (SLT) versus bilateral lung transplant (BLT).

13.2 Criteria for Transplantation in Obstructive Lung Diseases

Long term survival post-lung transplantation remains limited predominantly by chronic lung allograft dysfunction (CLAD), with median survival post-transplant for all transplant recipients of 5.7 years up to 2012, similar to that of the COPD-specific cohort [2]. Given the relatively indolent natural history of COPD, even in

A. L. Rigby
Lung Transplant Unit, St. Vincent's Hospital, Sydney, Darlinghurst, NSW, Australia
e-mail: Amy.Rigby@svha.org.au

A. R. Glanville (ed.), *Essentials in Lung Transplantation*,
https://doi.org/10.1007/978-3-319-90933-2_13

its advanced stages, this may be a shorter life expectancy than could be expected for these patients were they to not undergo transplantation. Recent studies, such as that by Casanova et al. in 2011, have found that progression of COPD is very heterogeneous, and only a small proportion of patients (14%) had progression of BODE index over the study period [5].

In 2006, Stavem et al. published a study of 219 consecutive patients who underwent lung transplantation for obstructive lung diseases, and found no evidence of survival benefit in this patient subgroup [6]. However, more recent studies have attempted to identify the subgroup of patients within the COPD cohort who are more likely to benefit. In earlier studies FEV_1 was used as a predictor for mortality and thus a low FEV_1 as an indication for transplantation [7]. However, despite its role in predicting severity in COPD, FEV_1 has not been shown to correlate with mortality, and it has since been shown that a composite assessment of several factors (namely body mass index, degree of airflow obstruction, dyspnoea, and exercise capacity, measured by 6 min walk distance) is far more accurate in predicting risk of death. This resulted in the development of the BODE index [8]. When Celli et al. first described this, patients with a BODE of 7–10 were shown to have a median survival of 3 years. Given that this is less than the median survival of lung transplant patients, the ISHLT guidelines recommended that patients with a BODE of 7–10 be considered for transplantation [9]. In 2010, Lahzami et al. reassessed the use of the BODE index as a means of identifying those patients who would benefit from transplantation, and found that those with a BODE of $\geq$7 lived longer after lung transplant than predicted by their BODE score [10]. Patients with a BODE of 5–6 should be referred to a transplantation centre [9]. Additional factors identified as negatively impacting upon survival in COPD patients include the presence of 3 or more exacerbations within a 1 year period, which affects mortality independently of the BODE score [11], and the presence of acute hypercapnic respiratory failure, which has a 43% 1 year mortality even if the acute hospitalisation is survived [12].

13.3 Transplantation for Obstructive Lung Diseases Other than Emphysema

13.3.1 α_1-Antitrypsin Deficiency (A1ATD)

A1ATD is the fourth most common indication for lung transplantation worldwide, making up 6% of all lung transplants [2, 13]. Patients with A1ATD often present with more severe disease and at an earlier age than those with emphysema secondary to smoking. However, the BODE index has been shown to predict mortality for this cohort of patients similarly well to those with COPD from smoking [14]. A retrospective analysis of data from the United Network for Organ Sharing (UNOS) database performed by Gulack et al. in 2015 did show a statistically significantly increased mortality up to 1 year in patients with A1ATD as compared with the COPD cohort; however, beyond 1 year this did not persist, and the difference was not evident in the more recent transplant patients [15]. In fact, data from the ISHLT Registry

demonstrates improved outcomes for the cohort of COPD patients with A1ATD, with a median survival of 6.7 years, in comparison to the median survival of 5.6 years in those patients with COPD without A1ATD [1]. However, it must be noted that these figures are not adjusted for factors such as the younger age of A1ATD patients. Although there have been theoretical concerns regarding the need for A1AT replacement therapy in these patients, there is no definitive evidence to support the use of augmentation therapy post-transplantation, and the management of this patient cohort post-transplant is no different from that of other COPD patients [4].

13.3.2 Lymphangioleiomyomatosis (LAM) (Fig. 13.1)

LAM is a rare, cystic lung disease almost exclusively affecting women, which generally results in progressive loss of lung function [3, 16]. It is an uncommon indication for lung transplantation, accounting for only 1% of transplants [1]. The progression of LAM is highly heterogeneous, with some patients demonstrating a 5–10% decline in FEV_1 per year, whilst others have a very slow loss of function [16]. Recent data demonstrates a 10-year survival of almost 90% in these patients [17] and the introduction of the mTOR inhibitors sirolimus and everolimus may further improve prognosis. There are currently no disease specific guidelines regarding timing of listing, and as such patients are generally considered for listing when there is evidence of severe and progressive impairment in pulmonary function, functional status, and quality of life [3]. Due to the recurrent pneumothoraces and, less commonly, chylous effusions that occur in these patients, many develop pleural adhesions that pose additional challenges during the perioperative period. However, despite the increased risk of intraoperative bleeding, this does not translate into an increase in early

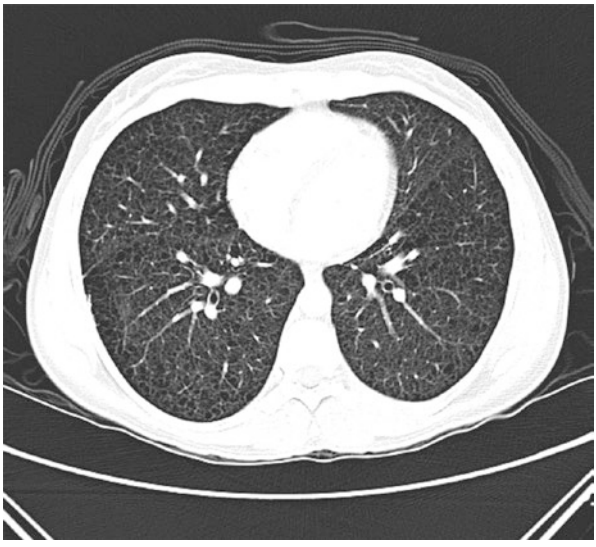


Fig. 13.1 Multiple small cysts throughout both lungs typical for LAM

mortality, with 1-year survival rates post-transplant of almost 80%, which compares favourably with overall survival rates reported by the ISHLT Registry in 2015 [18].

Renal angiomyolipomas are benign vascular tumours that occur in up to 50% of women with sporadic LAM; they are even more common in patients with LAM associated with tuberous sclerosis [3]. When they become large they may rupture or bleed, and occasionally may affect renal function. However, complications from bleeding are very rare [18] and as such renal angiomyolipomas do not generally represent a contraindication to transplantation [3].

The recurrence of LAM in the transplanted lungs does occur, at a rate of 5–10% [18, 19]. However, it does not necessarily appear to affect pulmonary function [18], and may only be detected at autopsy.

Despite the risk of recurrent pneumothoraces in the native lung of patients who undergo SLT, reported at over 5% in the European data presented by Benden et al. [18], patients undergoing SLT have comparable survival rates at 3–5 years post-transplant with those undergoing BLT [20], and individual considerations should be taken into account, including technical difficulties related to prior pleurodesis or pleurectomy and the patient's ability to undergo the longer bilateral procedure.

mTOR inhibitors have been used post-transplant in some LAM patients to treat extra-pulmonary complications and persistent chylothorax; however, the benefit is not clear, with Ussavarungsi et al. reporting only 2–7 patients treated with sirolimus post-transplant deriving a benefit [21]. This, in conjunction with the potential adverse effects associated with the mTOR inhibitors, suggests that widespread use of the mTOR inhibitors post-transplant for patients with LAM is not indicated.

13.3.3 Pulmonary Langerhans Cell Histiocytosis (LCH)

LCH is a rare disease that mainly affects young adults, with the vast majority being current or former smokers. It is characterised histologically by the accumulation of Langerhans and other inflammatory cells in the small airways with formation of nodular inflammatory lesions. As the disease progresses it results in lung destruction, cicatricial airway scarring and pulmonary vascular remodelling [22]. Pulmonary hypertension is a very common complication as the disease progresses (up to 90% by the time of transplant) and is associated with poor survival [22, 23]. LCH accounts for less than 1% of all lung transplants. Guidelines for listing are similar to those for other pulmonary conditions and include severely impaired lung function and functional status, hypoxemia requiring supplemental oxygen and moderate to severe pulmonary hypertension [3]. In the largest series of patients transplanted for LCH, by Dauriat et al. and published in 2006, survival rates were similar to the broader lung transplant population, with a 1-year survival of 77% and a 5-year survival of 57% [22]. Recurrence of pulmonary LCH after transplant does occur in up to 20% of patients but does not appear to adversely affect outcome [22]. Risk factors for recurrence include recommencement of smoking and extrapulmonary organ involvement.

13.4 Single versus Bilateral Transplantation

Up until the late 1980s, single lung transplant was favoured over bilateral transplant [3]. In 2015, 76% of lung transplants performed were bilateral [24]. However, in 1996 only 28% of lung transplants were bilateral [25]. There has been, and continues to be, significant debate regarding the putative survival benefit derived from bilateral transplantation for COPD. Initial studies favoured bilateral transplantation from a survival perspective [26]. However, more recent analyses have been less convincing. Concerns remain regarding functional outcomes and native lung complications. However, in an era where supply is far outstripped by demand, and utility and access to organs is critical, the debate continues as to the optimal choice of procedure for the obstructive lung diseases.

13.4.1 Survival

In 1997, Bavaria et al. studied 76 patients transplanted for COPD, and found that BLT conferred a survival advantage both perioperatively and up to 3 years post-transplant when compared to SLT [27]. This was in contrast to the preference at the time, when only 28% of lung transplants were bilateral [25]. This study, in addition to several other small retrospective studies, contributed to a gradual shift towards BLT, and in 2015 76% of lung transplants performed were BLT. The debate, however, is far from decided. Initial concerns regarding SLT centred on ventilation-perfusion mismatching and subsequent allograft failure with SLT [3, 27]. However, it has since been shown that, in the absence of allograft dysfunction, both ventilation and perfusion are preferentially directed toward the allograft [28, 29].

By 2001, Meyer et al. had published a large retrospective analysis of over 2000 lung transplant recipients and found that whilst BLT offered a survival advantage for patients aged under 50 (68% for BLT at 5 years compared with 44% for SLT) and for those aged 50–60 (60% for BLT at 5 years compared with 40% for SLT), this advantage was not seen in the patients aged over 60 [30].

This was supported by a study by Thabut et al., published in 2006, in which almost 10,000 patients from 1987 to 2006 were analysed; and although bilateral transplantation conferred a survival advantage (6.41 years for BLT versus 4.59 years for SLT), again this advantage was not seen in the older patient population (over 60 years) [24]. Finally, a study by Nwakanma et al. in 2006 of recipients aged over 60 years again found that there was no statistically significant survival benefit in either short- or medium-term mortality (to 5 years) in COPD patients undergoing SLT versus BLT [31].

Selection bias may confound some of the reported results, as SLT is often performed on patients who have greater comorbidities.

13.4.2 Functional Outcomes

As expected, both SLT and BLT result in significantly improved FEV_1. It has consistently been demonstrated that FEV_1 and 6-min walk test (6MWT) distance improve to a greater extent following BLT [25, 32–34]. Following SLT, FEV_1 on average increases 40–60%, whereas the FEV_1 following BLT is generally greater than 80% predicted [32, 33]. However, it is important to note that 6MWT distance is not adjusted for age, and in some of the studies patients receiving SLT were statistically older than those receiving BLT; thus this variation may be accounted for by an age-related reduction in functional capacity.

Several studies have not demonstrated any difference in occurrence of and survival from bronchiolitis obliterans syndrome (BOS) between SLT and BLT [35, 36]. In contrast, a retrospective review by Hadjiliadis et al. of 225 COPD patients undergoing lung transplantation demonstrated an increased incidence of BOS in patients who underwent SLT, and increased survival after diagnosis of BOS in BLT patients [37]. It must be noted that BLT patients generally have a higher baseline FEV_1 than SLT patients, and so a 20% reduction in FEV_1 from baseline (the definition of BOS) necessitates a larger absolute reduction in the BLT cohort—a potential confounder to the findings.

13.4.3 Native Lung Complications *(Fig. 13.2)*

Native lung complications have been reported in 15–50% of patients undergoing SLT, and may be associated with significant morbidity and mortality [38, 39]. The major concerns regarding the native lung in SLT are native lung hyperinflation (NLH) and carcinoma of the native lung.

13.4.3.1 Native Lung Hyperinflation (NLH)

NLH may occur in the immediate post-operative period or more insidiously months to years after transplant. Although radiographic acute NLH (mediastinal shift and diaphragmatic flattening on X-ray) has been seen in up to one third of patients, symptomatic or clinically severe acute NLH is much less common; in a study of 51 SLT patients by Weill et al. only 8 were symptomatic (resulting in haemodynamic or respiratory failure requiring inotropic support or independent lung ventilation), and 2 severely so. Although the patients who developed acute NLH had longer lengths of stay and longer mechanical ventilation, overall survival was not adversely affected—neither in the short- nor longer-term (up to 3 years) [35]. Conversely, a prospective study by Angles et al. of 34 emphysematous patients who underwent lung transplantation (14 SLT and 20 BLT) found a much higher rate of acute NLH (64%). In keeping with other studies, acute NLH contributed to increased length of ICU stay and prolonged mechanical ventilation, but not to increased mortality per se. However,

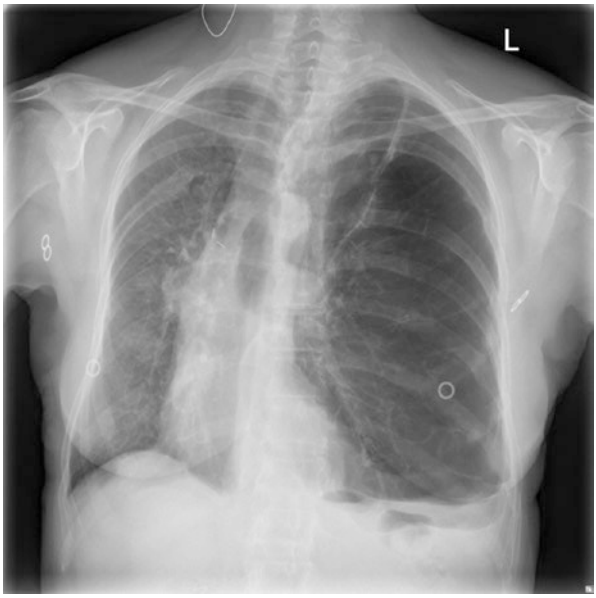


Fig. 13.2 Hyperinflation of the native lung on the left with mediastinal shift, 24 years after right single lung transplantation

the prolonged stay was thought to contribute to an increased incidence of infectious complications in the SLT recipients, with an overall mortality in the SLT of 50% [40]. Risk factors for acute NLH may include early graft dysfunction, which is thought to increase the difference in compliance between the native lung and the allograft, prolonged positive-pressure ventilation, and severe bullous emphysema in the native lung [41]. Early extubation or ventilation allowing prolonged expiration will generally prevent symptomatic acute NLH; if severe, independent lung ventilation may be undertaken and will usually result in rapid clinical improvement [41].

Chronic NLH presents with insidious dyspnoea months to years after transplantation. FEV_1 is reduced and imaging demonstrates mediastinal shift and compression of the transplanted lung [41]. Despite radiological evidence of NLH, which is reasonably common, clinically significant chronic NLH is less common and thus other causes of loss of lung function and dyspnoea must be considered. These include infection and the development of obliterative bronchiolitis. If chronic NLH is thought to be responsible for the symptoms, a number of surgical procedures may be successful in alleviating dyspnoea and improving exercise tolerance, including bullectomy (in the presence of large bullae) and unilateral lung volume reduction surgery [42].

13.4.3.2 Malignancy in the Native Lung

COPD, with its close association with cigarette exposure, is strongly associated with an increased risk of bronchogenic carcinoma. Thus one of the concerns associated with single lung transplantation is the development of carcinoma within the native lung. Dickson et al. found that the presence of a native lung was the strongest

risk factor for developing lung cancer after transplantation [43]. King et al. reported on 180 SLT recipients, and found that 14% developed significant native lung complications; of these, one-third were malignancies in the native lung [44]. The prevalence of bronchogenic carcinoma in patients transplanted for COPD is around 3.5% [45, 46]. In a study by Yserbyt et al. of 494 lung transplant recipients, almost 9% of the 101 SLT recipients developed bronchogenic carcinoma of the native lung, whereas only 1% of the 393 BLT patients developed this complication over the 10 year study period. Of the 13 patients diagnosed with bronchogenic carcinoma, 4 had local disease and the remainder loco-regionally advanced or metastatic disease. Survival is generally poor, although those with local disease at the time of diagnosis (T1N0M0 and T2N0M0) had much better survival (median 21 months) than those with loco-regionally advanced or metastatic disease (median 6 months) [45].

13.4.3.3 Infectious Complications

Despite concerns over infectious complications in the native lung, mortality related to these infections is rarely reported [38, 39]. Mal et al. retrospectively reviewed 46 consecutive patients who underwent SLT and found that 12 episodes of infection in the native lung occurred; however only 2 were fatal, and a further 21 episodes of bacterial pneumonia occurred in 16 patients in the transplanted lung [38]. From the available data it appears that although infection may occur within the native lung, it can often be managed successfully.

13.4.4 Organ Allocation

In an era when organ demand far exceeds donation rates and patients die whilst awaiting lung transplant, consideration must be given not only to the individual patient but to overall utility and access to a scarce and valuable resource. This is a strong argument for the judicious use of SLT in appropriate patients.

13.5 Outcomes of Transplantation for Obstructive Lung Diseases in Comparison to Other Indications

Patients transplanted for obstructive lung diseases tend to have lower post-operative mortality rates than those transplanted for other indications, both in the early post-operative period and in the following years. The exception to this is the subgroup of patients with A1ATD. In the most recent ISHLT Registry data, lung recipients transplanted for COPD without A1ATD or cystic fibrosis had an unadjusted mortality at 3 months after transplant of 8–9%, whereas those transplanted for idiopathic interstitial pneumonia (IIP), interstitial lung disease-not IIP and COPD with A1ATD had

a mortality rate of 11–12% [1]. Many diagnoses (e.g., ILD-not IIP, sarcoidosis, non-CF bronchiectasis, pulmonary hypertension including idiopathic pulmonary artery hypertension, retransplant) had worse 1-year mortality than COPD without A1ATD [1]. With respect to 5-year mortality, those transplanted for cystic fibrosis or LAM/tuberous sclerosis had a lower risk of death than those transplanted for COPD without A1ATD. In the 10-year mortality model, only those transplanted for LAM/tuberous sclerosis had a lower risk of death than those transplanted for COPD without A1ATD [1].

13.6 Summary and Conclusions

There are limited options available to patients with advanced obstructive lung diseases. Despite its variable course, chronic obstructive pulmonary disease remains the cause for much morbidity and mortality, and is the most common indication for lung transplantation worldwide. Overall, the obstructive lung diseases offer favourable postoperative mortality rates when compared to transplantation for other indications. However, this population does present its own considerations and challenges, specifically: the timing of listing, for which the use of multivariable indices such as the BODE index provide much needed guidance; and the decision about whether to undertake single versus bilateral transplantation in this subset of patients. At present the literature seems to support bilateral lung transplant for patients aged under 60, whilst those over 60 may well benefit equally from single lung transplantation, thus offering greater use of the available donor pool. As the outcomes for patients undergoing lung transplantation improve overall and the demographics continue to change it remains vital to pursue further data with regards to these considerations and to refine the criteria that lead to optimal outcomes for the patients seeking transplantation for obstructive lung diseases.

References

1. Yusen RD, Edwards LB, Dipchand AI, et al. The registry of the International Society for Heart and Lung Transplantation: thirty-third adult lung and heart-lung transplant report-2016; focus theme: primary diagnostic indications for transplant. J Heart Lung Transplant. 2016;35(10):1170–84.
2. Yusen RD, Edwards LB, Kucheryavaya AY, International Society of Heart and Lung Transplantation, et al. The registry of the International Society for Heart and Lung Transplantation: 31st adult lung and heart-lung transplant report - 2014; focus theme: retransplantation. J Heart Lung Transplant. 2014;33(10):1009–24.
3. Shah RJ, Kotloff RM. Lung transplantation for obstructive lung diseases. Semin Respir Crit Care Med. 2013;34:288–96.
4. Lane CR, Tonelli AR. Lung transplantation in chronic obstructive pulmonary disease: patient selection and special considerations. Int J Chron Obstruct Pulmon Dis. 2015;10:2137–46.

5. Casanova C, de Torres JP, Aguirre-Jaime A, et al. The progression of chronic obstructive pulmonary disease is heterogeneous: the experience of the BODE cohort. Am J Respir Crit Care Med. 2011;184(9):1015.
6. Stavem K, Bjørtuft O, Borgan O, Geiran O, Boe J. Lung transplantation in patients with chronic obstructive pulmonary disease in a national cohort is without obvious survival benefit. J Heart Lung Transplant. 2006;25(1):75–84.
7. Celli BR. Predictors of mortality in COPD. Respir Med. 2010;104(6):773–9.
8. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnoea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004;350(10):1005–12.
9. Weill D, Benden C, Corris PA, et al. A consensus document for the selection of lung transplant candidates: 2014 - an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2015;34(1):1–15.
10. Lahzami S, Bridevaux PO, Soccal PM, et al. Survival impact of lung transplantation for COPD. Eur Respir J. 2010;36:74–80.
11. Soler-Cataluna JJ, Martinez-Garcia MA, Sanchez LS, Tordera MP, Sanchez PR. Severe exacerbations and BODE index: two independent risk factors for death in male COPD patients. Respir Med. 2009;103:692–9.
12. Connors AF Jr, Dawson NV, Thomas C, et al. Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments). Am J Respir Crit Care Med. 1996;154:959–67.
13. Tanash H, Riise G, Hansson L, Nilsson P, Piitulainen E. Survival benefit of lung transplantation in individuals with severe α_1-anti-trypsin deficiency (PiZZ) and emphysema. J Heart Lung Transplant. 2011;30(12):1342–7.
14. Thabut G, Mornex JF, Pison C, et al. Performance of the BODE index in patients with α_1-antitrypsin deficiency-related COPD. Eur Respir J. 2014;44(1):78–86.
15. Gulack BC, Ganapathi AM, Speicher PJ, Chery G, Snyder LD, Davis RD, Hartwig MG. Survival after lung transplant in alpha-1-antitrypsin deficiency recipients compared to other forms of chronic obstructive pulmonary disease. J Heart Lung Transplant. 2015;34(4):S243–4.
16. Taveira-DaSilva AM, Pacheco-Rodriguez G, Moss J. The natural history of lymphangioleiomyomatosis: markers of severity, rate of progression and prognosis. Lymphat Res Biol. 2010;8(1):9–19.
17. Oprescu N, McCormack FX, Byrnes S, Kinder BW. Clinical predictors of mortality and cause of death in lymphangioleiomyomatosis: a population-based registry. Lung. 2013;191(1):35–42.
18. Benden C, Rea F, Behr J, et al. Lung transplantation for lymphangioleiomyomatosis: the European experience. J Heart Lung Transplant. 2009;28(1):1–7.
19. Reynaud-Gaubert M, Mornex JF, Mal H, et al. Lung transplantation for lymphangioleiomyomatosis: the French experience. Transplantation. 2008;86(4):515–20.
20. Kpodonu J, Massad MG, Chaer RA, et al. The US experience with lung transplantation for pulmonary lymphangioleiomyomatosis. J Heart Lung Transplant. 2005;24(9):1247–53.
21. Ussavarungsi K, Hu X, Scott JP, et al. Mayo clinic experience of lung transplantation in lymphangioleiomyomatosis. Respir Med. 2015;109(10):1354–9.
22. Suri HS, Yi ES, Nowakowski GS, Vassallo R. Pulmonary Langerhans cell histiocytosis. Orphanet J Rare Dis. 2012;7:16.
23. Dauriat G, Mal H, Thabut G, et al. Lung transplantation for pulmonary Langerhans cell histiocytosis: a multicenter analysis. Transplantation. 2006;81(5):746–50.
24. ISHLT transplant registry quarterly reports. 30 Dec 2016.
25. Thabut G, Christie JD, Ravaud P, et al. Survival after bilateral versus single lung transplantation for patients with chronic obstructive pulmonary disease: a retrospective analysis of registry data. Lancet. 2008;371(9614):744–51.
26. Trulock EP. Lung transplantation for COPD. Chest. 1998;113:269S–76S.
27. Bavaria JE, Kotloff R, Palevsky H, et al. Bilateral versus single lung transplantation for chronic obstructive pulmonary disease. J Thorac Cardiovasc Surg. 1997;113(3):520–7.

28. Levine SM, Anzueto A, Peters JI, et al. Medium term functional results of single-lung transplantation for endstage obstructive lung disease. Am J Respir Crit Care Med. 1994;150(2):398–402.
29. Malk H, Andreassian B, Pamela F, et al. Unilateral lung transplantation in end-stage pulmonary emphysema. Am Rev Respir Dis. 1989;140(3):797–802.
30. Meyer DM, Bennett LE, Novick RJ, Hosenpud JD. Single vs bilateral, sequential lung transplantation for end-stage emphysema: influence of recipient age on survival and secondary end-points. J Heart Lung Transplant. 2001;20(9):935–41.
31. Nwakanma LU, Simpkins CE, Williams JA, et al. Impact of bilateral versus single lung transplantation on survival in recipients 60 years of age and older: analysis of United Network for Organ Sharing database. J Thorac Cardiovasc Surg. 2007;133(2):541–7.
32. Gerbase MW, Spiliopoulos A, Rochat T, Archinard M, Nicod LP. Health-related quality of life following single or bilateral lung transplantation: a 7-year comparison to functional outcome. Chest. 2005;128(3):1371–8.
33. Gaissert HA, Trulock EP, Cooper JD, Sunaresan RS, Patterson GA. Comparison of early functional results after volume reduction or lung transplantation for chronic obstructive pulmonary disease. J Thorac Cardiovasc Surg. 1996;111(2):296–306.
34. Sundaresan RS, Shiraishi Y, Trulock EP, et al. Single or bilateral lung transplantation for emphysema? J Thorac Cardiovasc Surg. 1996;112(6):1485–94.
35. Weill D, Torres F, Hodges TN, Olmos JJ, Zamora MR. Acute native lung hyperinflation is not associated with poor outcomes after single lung transplant for emphysema. J Heart Lung Transplant. 1999;18(11):1080–7.
36. Pochettino A, Kotloff RM, Rosengard BR, et al. Bilateral versus single lung transplantation for chronic obstructive pulmonary disease: intermediate term results. Ann Thorac Surg. 2000;70(6):1813–8.
37. Hadjiliadis D, Davis RD, Palmer SM. Is transplant operation important in determining post-transplant risk of bronchiolitis obliterans syndrome in lung transplant recipients? Chest. 2002;122(4):1168–75.
38. Mal H, Brugiere O, Sleiman C, et al. Morbidity and mortality related to the native lung in single lung transplantation for emphysema. J Heart Lung Transplant. 2000;19(2):220–3.
39. Horvath J, Dummer S, Loyd J, Walker B, Merril WH, Frist WH. Infection in the transplanted and native lung after single lung transplantation. Chest. 1993;104:681–5.
40. Angles R, Tenorio L, Roman A, Soler J, Rochera M, de Latorre FJ. Lung transplantation for emphysema. Lung hyperinflation: incidence and outcome. Transpl Int. 2005;17:810–4.
41. Ahya VN, Kawut SM. Noninfectious pulmonary complications after lung transplantation. Clin Chest Med. 2005;26(4):613–22.
42. Venuta F, de Giacomo T, Rendina EA, et al. Thoracoscopic volume reduction of the native lung after single lung transplantation for emphysema. Am J Respir Crit Care Med. 1998;157(1):292–3.
43. Dickson RP, Davis RD, Rea JB, Palmer SM. High frequency of bronchogenic carcinoma after single-lung transplantation. J Heart Lung Transplant. 2006;25:1297–301.
44. King CS, Khandar S, Burton N, et al. Native lung complications in single-lung transplant recipients and the role of pneumonectomy. J Heart Lung Transplant. 2009;28(8):851–6.
45. Yserbyt J, Verleden GM, Dupont LJ, et al. Bronchial carcinoma after lung transplantation: a single-center experience. J Heart Lung Transplant. 2012;31:585–90.
46. Arcasoy SM, Hersh C, Christie JD, et al. Bronchogenic carcinoma complicating lung transplantation. J Heart Lung Transplant. 2001;20(10):1044–53.

Chapter 14
Lung Transplantation for Pulmonary Arterial Hypertension

Helen Whitford

Whilst pulmonary arterial hypertension is the indication for lung transplantation in less than 5% of recipients [1] it reflects the spectrum of complex decision making involved in this field with timing of referral and listing as well as the complex operative and peri-operative management required [2].

14.1 Definitions

Pulmonary hypertension (PH) is the pathophysiological consequence of a number of heart and lung conditions resulting in elevated pressures in the right heart. PH is defined haemodynamically as a mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg as assessed by right heart catheterisation (RHC) [3].

Pulmonary arterial hypertension (PAH) is the term used to describe the group of patients with PH who have pre-capillary disease (ie: in the lung pulmonary vasculature), in the absence of parenchymal lung disease and chronic thromboembolic disease. PAH is defined haemodynamically as mPAP ≥25 mmHg, pulmonary artery wedge pressure (PAWP) ≤15 mmHg and a pulmonary vascular resistance (PVR) >3 Wood units [3].

PAH can be associated with a number of conditions (Table 14.1).

PH associated with parenchymal lung disease is classified in a different group (Group 3 PH). The presence of PH is associated with poorer prognosis in these patients, but should be considered separately and will not be covered in this chapter.

H. Whitford
Department of Respiratory Medicine, The Alfred Hospital, Melbourne, VIC, Australia

Monash University, Clayton, VIC, Australia
e-mail: H.Whitford@alfred.org.au

A. R. Glanville (ed.), *Essentials in Lung Transplantation*,
https://doi.org/10.1007/978-3-319-90933-2_14

Table 14.1 This table represents a clinical classification of PAH according to the presence or absence of known associations

Clinical classification of pulmonary arterial hypertension
1.1 *Idiopathic*
1.2 *Heritable*
1.2.1 *BMPR2 mutation*
1.2.2 *Other mutations*
1.3 *Drugs and Toxins induced*
1.4 *Associated with*:
1.4.1 Connective tissue disease
1.4.2 Human immunodeficiency virus (HIV) infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.5 Schistosomiasis
1′. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis
1′.1 *Idiopathic*
1′.2 *Heritable*
1′.2.1 EIF2AK4 mutation
1′.2.2 Other mutations
1′.3 *Drugs and Toxins induced*
1′.4 *Associated with*:
1′.4.1 Connective tissue disease
1′.4.2 HIV infection
1.″ *Persistent pulmonary hypertension of the newborn*

Adapted from Galiè et al. [4]

14.2 Historical Perspective

The first specific medical therapy for PAH became available in the 1990s in the form of a continuous intravenous infusion of epoprostenol [5, 6]. Prior to this the only available therapy in patients without acute vaso-reactivity was lung transplantation. Patients with acute vaso-reactivity may do well in the long term on calcium channel blockers [7].

The first successful transplant for this condition was a heart lung transplant performed in 1981 [8]. Subsequent to this it became apparent that the right ventricle would recover completely and rapidly if the pulmonary vasculature was normalised [9]. In the interests of organ utility isolated lung transplantation has become the procedure of choice for PAH.

The options of single lung, bilateral lung and heart lung transplantation for PAH are all reported in the literature [10]. At present most centres favour bilateral lung

transplant, with heart lung transplant being reserved for those patients with complex congenital heart disease [1, 11].

14.3 Timing of Referral and Listing for Lung Transplantation in PAH

Despite significant advances in the medical management of pulmonary arterial hypertension (PAH) in the last 15 years, the median survival from the time of diagnosis remains low at 7–9 years. As a result lung transplantation remains an essential treatment option for selected patients with this diagnosis.

High waiting list mortality has been reported in PAH (20–30%) [12], however if timing of referral and listing is optimised it can be very low [13].

Current European Society of Cardiology/European Respiratory Society guidelines on PAH recommend assessing eligibility for lung transplantation if there is inadequate response to initial monotherapy or initial combination therapy, and referral for lung transplantation if there is inadequate response to maximal medical therapy [4].

The consensus document for the selection of lung transplant candidates 2014 is more specific (Table 14.2).

Although there are these guidelines the exact timing of referral and listing for lung transplantation remains difficult in this group. A number of risk assessment tools have been developed to try and address this.

Table 14.2 This table is a summary of the current recommendations from the International Society of Heart and Lung Transplantation for the timing of referral and listing for lung transplantation

Timing of referral	Timing of listing
• NYHA functional class III or IV during escalating therapy • Rapidly progressive disease • Use of parenteral targeted PAH therapy • Known or suspected pulmonary veno-occlusive disease (PVOD) or pulmonary capillary haemangiomatosis	• NYHA functional class III or IV during despite a trial of at least 3 months of combination therapy including prostanoids • Cardiac index <2 L/min/m^2 • Mean right atrial pressure >15 mmHg • 6 min walk distance <350 m • Development of significant: – Haemoptysis – Pericardial effusion – Or signs of progressive right heart failure

Adapted from Weill et al. [14]

Table 14.3 Risk assessment in Pulmonary Hypertension with expert opinion generated variables to estimate the risk of death in a one year period

Determinants of prognosis* (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	Hish risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope'
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 mL/min/kg (>65% prod.) VE/VCO_2 slope <36	Peak VO_2 11–15 mL/min/kg (35–65% prod.) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 mL/min/kg (<35% prod.) VE/VCO_2 slope ≥45
NT-proBNP plasma levels	BNP <50 ng/L NT-proBNP <300 ng/L	BNP 50–300 ng/L NT-proBNP 300–1400 ng/L	BNP >300 ng/L NT-proBNP >1400 ng/L
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 L/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 L/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 L/min/m^2 SvO_2 <60%

From Galiè et al. [4]

[b]Occasional syncope during brisk or heavy exercise, or occasional orthostatic syncope in an otherwise stable patient

*Repeated episodes of syncope even with little or no regular physical activity

14.3.1 The Concept of Risk Stratification

The goal in the therapy of PAH is to achieve low risk of clinical worsening or death. Medical therapy is targeted towards this goal with double and triple combinations. The recent ERS/ESC guidelines [4] have attempted to provide a tool to assess risk in PAH, utilising the common variables used to assess patients with PAH. These factors reflect symptoms, exercise capacity and right ventricular function (Table 14.3).

This tool has been validated by Kylhammar et al. using the Swedish PAH registry and showed that being in the low risk group was associated with improved survival [15].

Other tools to assess risk have also been developed, such as the French Registry equation [16] and the REVEAL (Registry to Evaluate Early and Long-term PAH Disease Management) registry risk score [17]. All can be used to assist in deciding timing of referral and listing for lung transplantation in PAH.

14.4 Lung Transplantation and Specific Subsets of PAH

14.4.1 Pulmonary Veno-Occlusive Disease (PVOD) and Pulmonary Capillary Haemangiomatosis (PCH)

Once thought to be distinct entities, the pathological findings of pulmonary venous obstruction and capillary proliferation are now felt to reflect a spectrum disease [18]. These disorders confer the risk of pulmonary oedema with the use of PAH specific therapies [19], as increased pulmonary arterial flow reaches obstructed veins. The response to therapy is also poor and a diagnosis of PVOD or PCH should result in immediate referral for transplantation in eligible patients.

The diagnosis of PVOD/PCH is not always clear cut and many patients are diagnosed with PAH. The definitive diagnosis is a pathological one and lung tissue cannot be safely obtained in patients with severe PAH. Clinical suspicion should be raised if there is disproportionate hypoxia, digital clubbing and crackles on auscultation of the chest (all features which are uncommon in PAH). High resolution CT chest findings suggestive of PVOD/PCH are the presence of mediastinal lymphadenopathy, sub-pleural thickened septal lines and centrilobular ground glass opacities [20].

14.4.2 PAH Secondary to Congenital Heart Disease (PAH-CHD)

PAH is a common complication of CHD, mainly in patients with uncorrected left to right cardiac shunts. This abnormal flow through the pulmonary vasculature results in endothelial dysfunction and vascular remodelling. Eventually with a progressive increase in the right sided pressures there can be reversal of the shunt and the development of Eisenmenger's syndrome [21].

Patients with simple shunts can be treated with isolated bilateral lung transplantation with repair of the shunt [22]. There is some evidence however, for improved survival in ventricular septal defects treated with heart-lung transplantation rather than lungs alone [23].

Transplantation for complex CHD requires heart and lung transplantation. These procedures are often extremely complex and there are very few performed each year worldwide.

The timing of transplantation in CHD is even more difficult as the survival of this group is significantly better than that of idiopathic PAH [24].

14.4.3 PAH Related to Scleroderma

PAH affects 5–12% of patients with a diagnosis of scleroderma [25], and is one of the major causes of morbidity and mortality in this group [16, 26]. Patients with PAH related to scleroderma have a worse prognosis than those with idiopathic PAH [16].

Patients with scleroderma have multiple co-morbidities related to the disease adding to the complexity of lung transplantation [27]. The diagnosis itself should not be an absolute contraindication to lung transplantation, but a multi-disciplinary discussion regarding the gastrointestinal, renal, cardiac and cutaneous manifestations of scleroderma should be considered prior to undertaking transplantation in this group [28].

14.5 Outcomes Post Lung Transplantation for PAH

Early survival following lung transplantation has been historically worse in patients transplanted for PAH than for other indications such as COPD, IPF and cystic fibrosis [29]. However, if patients survive 1 year, survival in the longer term is extremely good [29]. The main reason reported for early mortality is the development of primary graft dysfunction [30] (Fig. 14.1).

A number of reasons for an increased incidence of primary graft dysfunction in PAH have been postulated. The first of these is the increased endothelial sheer stress caused by the very well trained right ventricle now pumping against much reduced vascular resistance resulting in the development of pulmonary oedema [31]. The second postulated reason which has become accepted as the likely mechanism is the

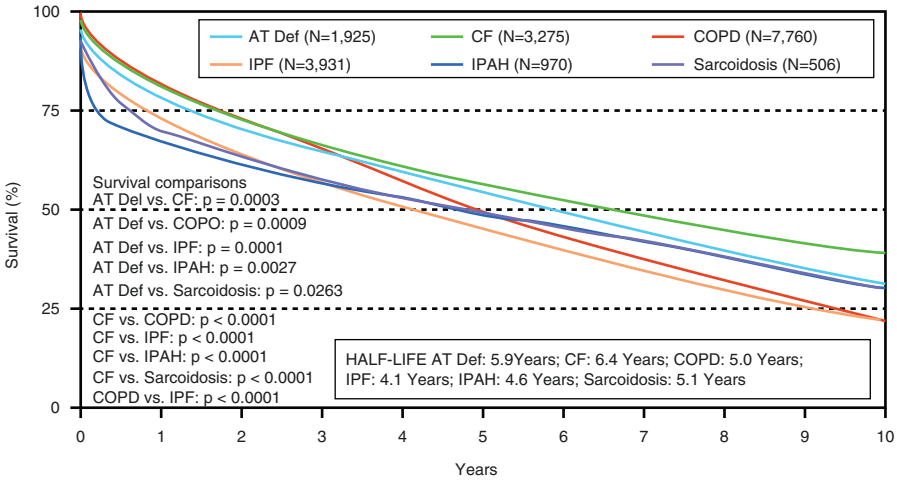


Fig. 14.1 Survival Curves for different disease categories after lung transplantation

presence of severe diastolic dysfunction of the chronically under filled left ventricle [32]. In the early post-operative period the "deconditioned" left ventricle is unable to handle the normal pre load now delivered to it through lungs with normal pulmonary vascular resistance. This leads to the development of pulmonary oedema and a diagnosis of primary graft dysfunction.

In PAH patients who survive the first 3 months after lung transplantation the outcomes are excellent and only secondary to that seen in patients with cystic fibrosis [29].

14.6 Peri-Operative Management

With careful planning, and timely assessment and listing of patients with PAH for lung transplantation it is hoped that the transplant will proceed smoothly. This is not always the case and additional support prior to, during and post transplantation may be necessary.

14.6.1 Veno-Arterial Extracorporeal Membrane Oxygenation (VA-ECMO)

ECMO has been used in a number of situations around the lung transplant process.

1. As a bridge to transplant.
   Mechanical ventilation prior to lung transplantation has been associated with poor outcomes particularly in patients with PAH. The Hannover group have reported a number of cases bridged to transplant on VA-ECMO with the patient extubated and able to participate in exercise [33].
2. Prior to induction of anaesthesia
   Induction of anaesthesia results in a significant fall in systemic blood pressure and can precipitate circulatory collapse in patients with severe PAH [34]. Institution of awake femoral-femoral VA- ECMO or cardiopulmonary bypass (CPB) is now standard for many patients undergoing lung transplantation for severe end stage PAH.

   There are reports of improved outcome using VA-ECMO rather than CPB intra-operatively as it requires lower doses of heparin and does not have a venous reservoir leading to a reduced incidence of bleeding and potentially a lower incidence of PGD [35].
3. Post lung transplantation
   Early following lung transplantation for severe PAH the left ventricle is unable to tolerate the normal preload. Use of ECMO post-operatively for a minimum of 5 days is recommended by the Hannover group, who report excellent outcomes using this strategy [32]. It is also advocated that the patients are extubated and able to participate in rehabilitation whilst the left ventricle remodels [32].

14.6.2 Bleeding Complications

Intra-operative and post-operative bleeding is a major cause of morbidity in lung transplantation for PAH. Many patients with long standing disease have large bronchial collateral vessels which need to be ligated at the time of transplantation and also the use of CBP or ECMO increases this risk. Patients receiving IV epoprostenol prior to transplant are at additional risk due to the anti-platelet effects of this medication [36].

As a result of the bleeding risk which can be compounded by the use of post-operative ECMO an alternative strategy to manage the impaired filling of the left ventricle is to allow the patient to remain sedated with excellent analgesia for a number of days. LV dysfunction with the development of pulmonary oedema generally occurs when the patient increases their heart rate in the setting of pain or agitation.

14.7 Conclusion

Lung transplantation for PAH is challenging.

Excellent outcomes can however be achieved with careful selection of candidates and the attention to the timing of referral and listing.

Peri-operative management is complex with LV dysfunction and bleeding playing major roles. Strategies to deal with these complications have been developed and excellent early and long term outcomes can be achieved [13, 32].

References

1. Yusen RD, et al. The registry of the International Society for Heart and Lung Transplantation: thirty-third adult lung and heart-lung transplant report-2016; focus theme: primary diagnostic indications for transplant. J Heart Lung Transplant. 2016;35(10):1170–84.
2. Andersen KH, et al. Pulmonary hypertension as a risk factor of mortality after lung transplantation. Clin Transpl. 2016;30(4):357–64.
3. Hoeper MM, et al. Definitions and diagnosis of pulmonary hypertension. J Am Coll Cardiol. 2013;62(25 Suppl):D42–50.
4. Galiè N, et al. ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2015;37(1):67–119.
5. Barst RJ, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. N Engl J Med. 1996;334(5):296–301.
6. Rubin LJ, et al. Treatment of primary pulmonary hypertension with continuous intravenous prostacyclin (epoprostenol). Results of a randomized trial. Ann Intern Med. 1990;112(7):485–91.
7. Sitbon O, et al. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. Circulation. 2005;111(23):3105–11.

8. Reitz BA, et al. Heart-lung transplantation: successful therapy for patients with pulmonary vascular disease. N Engl J Med. 1982;306(10):557–64.
9. Kramer MR, et al. Recovery of the right ventricle after single-lung transplantation in pulmonary hypertension. Am J Cardiol. 1994;73(7):494–500.
10. Pielsticker EJ, Martinez FJ, Rubenfire M. Lung and heart-lung transplant practice patterns in pulmonary hypertension centers. J Heart Lung Transplant. 2001;20(12):1297–304.
11. Olland A, et al. Should we perform bilateral-lung or heart-lung transplantation for patients with pulmonary hypertension? Interact Cardiovasc Thorac Surg. 2013;17(1):166–70.
12. Schaffer JM, et al. Transplantation for idiopathic pulmonary arterial hypertension: improvement in the lung allocation score era. Circulation. 2013;127(25):2503–13.
13. Levvey BJ, et al. Donation after circulatory determination of death lung transplantation for pulmonary arterial hypertension: passing the toughest test. Am J Transplant. 2015;15(12):3208–14.
14. Weill D, et al. A consensus document for the selection of lung transplant candidates: 2014—an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2015;34(1):1–15.
15. Kylhammar D, et al. A comprehensive risk stratification at early follow-up determines prognosis in pulmonary arterial hypertension. Eur Heart J. 2017.
16. Humbert M, et al. Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. Eur Respir J. 2010;36(3):549–55.
17. Benza RL, et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). Circulation. 2010;122(2):164–72.
18. Lantuejoul S, et al. Pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis: a clinicopathologic study of 35 cases. Am J Surg Pathol. 2006;30(7):850–7.
19. Humbert M, et al. Pulmonary edema complicating continuous intravenous prostacyclin in pulmonary capillary hemangiomatosis. Am J Respir Crit Care Med. 1998;157(5 Pt 1):1681–5.
20. Montani D, et al. Pulmonary veno-occlusive disease: clinical, functional, radiologic, and hemodynamic characteristics and outcome of 24 cases confirmed by histology. Medicine (Baltimore). 2008;87(4):220–33.
21. Wood P. The Eisenmenger syndrome or pulmonary hypertension with reversed central shunt. Br Med J. 1958;2(5099):755–62.
22. Choong CK, et al. Repair of congenital heart lesions combined with lung transplantation for the treatment of severe pulmonary hypertension: a 13-year experience. J Thorac Cardiovasc Surg. 2005;129(3):661–9.
23. Waddell TK, et al. Heart-lung or lung transplantation for Eisenmenger syndrome. J Heart Lung Transplant. 2002;21(7):731–7.
24. Galie N, et al. Management of pulmonary arterial hypertension associated with congenital systemic-to-pulmonary shunts and Eisenmenger's syndrome. Drugs. 2008;68(8):1049–66.
25. Avouac J, et al. Prevalence of pulmonary hypertension in systemic sclerosis in European Caucasians and metaanalysis of 5 studies. J Rheumatol. 2010;37(11):2290–8.
26. Hachulla E, et al. Risk factors for death and the 3-year survival of patients with systemic sclerosis: the French ItinerAIR-Sclerodermie study. Rheumatology (Oxford). 2009;48(3):304–8.
27. Bernstein EJ, et al. Survival of adults with systemic sclerosis following lung transplantation: a nationwide cohort study. Arthritis Rheumatol. 2015;67(5):1314–22.
28. Launay D, et al. Lung and heart-lung transplantation for systemic sclerosis patients. A monocentric experience of 13 patients, review of the literature and position paper of a multidisciplinary Working Group. Presse Med. 2014;43(10 Pt 2):e345–63.
29. Christie JD, et al. Registry of the International Society for Heart and Lung Transplantation: twenty-fifth official adult lung and heart/lung transplantation report—2008. J Heart Lung Transplant. 2008;27(9):957–69.
30. Diamond JM, et al. Clinical risk factors for primary graft dysfunction after lung transplantation. Am J Respir Crit Care Med. 2013;187(5):527–34.
31. Halldorsson AO, et al. Controlled reperfusion prevents pulmonary injury after 24 hours of lung preservation. Ann Thorac Surg. 1998;66(3):877–84; discussion 884-5.

32. Tudorache I, et al. Lung transplantation for severe pulmonary hypertension—awake extracorporeal membrane oxygenation for postoperative left ventricular remodelling. Transplantation. 2015;99(2):451–8.
33. Fuehner T, et al. Extracorporeal membrane oxygenation in awake patients as bridge to lung transplantation. Am J Respir Crit Care Med. 2012;185(7):763–8.
34. Pilkington SA, Taboada D, Martinez G. Pulmonary hypertension and its management in patients undergoing non-cardiac surgery. Anaesthesia. 2015;70(1):56–70.
35. Ius F, et al. Lung transplantation on cardiopulmonary support: venoarterial extracorporeal membrane oxygenation outperformed cardiopulmonary bypass. J Thorac Cardiovasc Surg. 2012;144(6):1510–6.
36. Akagi S, et al. High frequency of acute adverse cardiovascular events after lung transplantation in patients with pulmonary arterial hypertension receiving preoperative long-term intravenous prostacyclin. Int Heart J. 2017;58(4):557–61.

Chapter 15
Common Infections Following Lung Transplantation

Deborah J. Marriott and C. Orla Morrissey

15.1 Bacteria Including Mycobacteria and Nocardia

15.1.1 Introduction

Infection accounts for around 35% of all deaths in the first year after transplantation with bacterial pathogens responsible for approximately half of all infections [1].

The risk of infection following lung transplantation is determined by a number of factors including:

- physical factors such as denervation of the allograft resulting in a reduced cough reflex and anastomotic site stenosis with distal infection
- the 'net state of immunosuppression'—the result of all factors including host immune system, anti-rejection immunosuppressive therapy and concomitant viral infections such as cytomegalovirus that contribute to a patient's risk of infection
- epidemiological exposure to organisms, including donor-derived infections, community acquired infections, travel related infections and healthcare associated infections
- the use of prophylactic antimicrobial agents in the post-transplant period

D. J. Marriott
Department of Infectious Diseases and Clinical Microbiology, St. Vincent's Hospital, Sydney, Darlinghurst, NSW, Australia

Medical School, University of New South Wales, Sydney, NSW, Australia

C. Orla Morrissey (✉)
Department of Infectious Diseases, Alfred Health and Monash University, Melbourne, VIC, Australia
e-mail: o.morrissey@alfred.org.au

A. R. Glanville (ed.), *Essentials in Lung Transplantation*,
https://doi.org/10.1007/978-3-319-90933-2_15

15.1.2 Bacterial Infection: The Basics

Bacteria are defined by their morphology or shape and size. Most pathogenic bacterial species are spherical (cocci) or rod-shaped (bacilli) and may exist as single cells (for example many of the common bacilli such as Pseudomonas and Stenotrophomonas) or in a variety of characteristic patterns such as *S. pneumoniae* (pairs of lancet shaped cocci), *S. aureus* (large clusters of cocci forming 'bunches of grapes') and Streptococci (long chains of cocci).

Whilst molecular diagnostic techniques such as polymerase chain reaction (PCR) are increasingly important the basis of much microbiological diagnosis remains the characteristic appearance of the organism on a glass microscope slide when stained with dyes under a variety of conditions. Common stains include the Gram stain, first described by HC Gram in 1884 but still in everyday use, the Ziehl-Neelsen or acid-fast stain for mycobacteria and the modified Ziehl–Neelsen stain for nocardia. The Gram stain divides bacteria into Gram positive or Gram negative depending on the ability of the cell wall to prevent decolourisation after staining with crystal violet. It is important to remember that bacteria such as *S. aureus* and *Pseudomonas* species are not stained by the Ziehl-Neelsen stain and conversely mycobacteria cannot be seen on a Gram stain. Culture techniques also differ with mycobacteria often unable to grow on conventional agar plates, requiring special growth media and prolonged culture periods. Therefore if mycobacterial infection is suspected the request form for the sample must specify 'mycobacterial culture' so the appropriate investigations are performed by the laboratory.

The laboratory diagnosis of important bacteria in the setting of lung transplantation is summarised in Table 15.1.

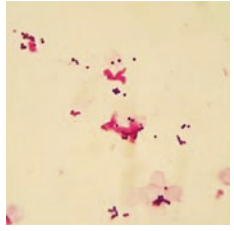
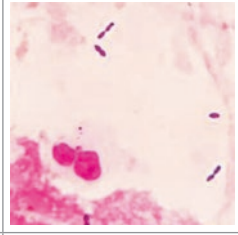
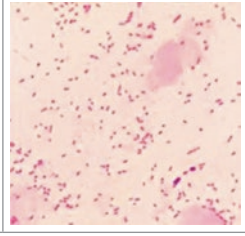
15.1.3 What You Need to Know: A Brief Summary of Important Bacteria in Lung Transplantation

15.1.3.1 *Staphylococcus aureus*

Clinical Features

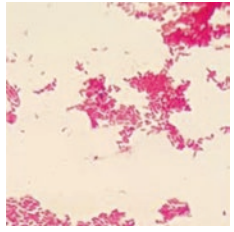
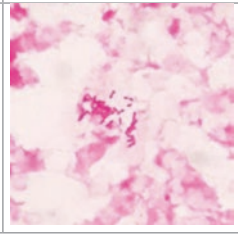
S. aureus is a common colonizer of the upper respiratory tract and skin, and is isolated with increased frequency from the sputum of patients with cystic fibrosis although the frequency decreases with age [2]. *S. aureus* can be acquired from the donor, the recipients own bacterial flora or the hospital environment as a healthcare associated infection, and is responsible for a wide range of health care-associated infections such as ventilator-associated pneumonia, bactereamia, and surgical site infections. Isolates of *S. aureus* are characterised according to their susceptibility to methicillin, an anti-staphylococcal penicillin. Methicillin susceptible *S. aureus*

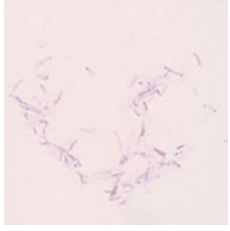
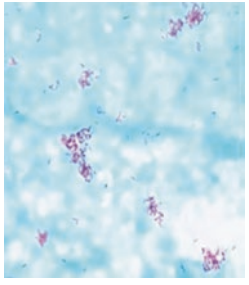
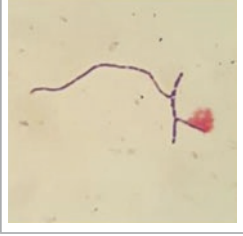
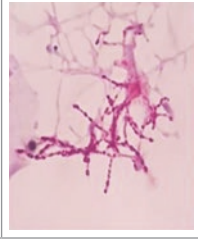
Table 15.1 Laboratory diagnosis of important bacteria

Important organisms	Gram stain appearance	Ziehl–Neelsen stain	Modified Ziehl–Neelsen stain	Polymerase chain reaction
Staphylococcus aureus		Not applicable	Not applicable	Rapid detection of the presence of *S. aureus* and differentiation between MSSA and MRSA
Streptococcus pneumoniae		Not applicable	Not applicable	Urinary antigen test for rapid diagnosis of systemic illness (not PCR based)
Haemophilus influenzae		Not applicable	Not applicable	Not in routine use

(continued)

Table 15.1 (continued)

Important organisms	Gram stain appearance	Ziehl–Neelsen stain	Modified Ziehl–Neelsen stain	Polymerase chain reaction
Pseudomonas aeruginosa		Not applicable	Not applicable	Not in routine use
Burkholderia cepacia complex		Not applicable	Not applicable	Not in routine use. Utilised in some specialist laboratories for rapid differentiation between species

Mycobacteria species	May appear as 'non-staining' or colourless rods against the background 		Not applicable	PCR directly on clinical sample for rapid diagnosis of tuberculosis and differentiation from other mycobacterial species. Also performed for rapid identification of *M. tuberculosis* from culture
Nocardia species		Not applicable		Not in routine use

Photographs courtesy of Thomas Cawsey and Maisie Cao, Department of Microbiology, St. Vincent's Hospital, Sydney

(MSSA) is more common in community acquired infections whereas methicillin resistant *S. aureus* (MRSA) occurs with greater frequency in hospital acquired infections.

The largest study of *S. aureus* following lung transplantation was a retrospective single centre study conducted over a 5 year period [3]. *S aureus* infection developed in 109 of 596 lung transplant (18%) recipients within 90 days of transplantation. MSSA (62%) was more common than MRSA (38%) but the proportion of MRSA infections increased over time. Pneumonia (48%) was the most common infection, followed by tracheo-bronchitis (26%), bacteremia (12%), intrathoracic infections (7%), and skin/soft tissue infections (7%). Infected patients required longer hospital and intensive care unit stays ($p < 0.0001$ for both) but the 30- and 90-day mortality rates were low (7% and 12%, respectively). However infected patients had higher rates of rejection (both acute and chronic) at 1 ($p = 0.048$) and 3 years ($p = 0.002$), and higher mortality at 1 ($p = 0.058$) and 3 years ($p = 0.009$).

Treatment

MSSA

- dicloxacillin or flucloxacillin
- cefazolin or cephalothin for penicillin allergic patients (note—there is 5–10% risk of anaphylaxis in patients with documented penicillin anaphylaxis)
- clindamycin is often prescribed for deep infections because it exhibits good tissue penetration. However it is a bacteriostatic antibiotic and should only be administered to patients with *S. aureus* bacteraemia following specialist advice

MRSA

- vancomycin with appropriate therapeutic drug monitoring (TDM)
- Teicoplanin—TDM not available in most centres. Standard dosing may be inadequate, especially for bacteraemia
- Linezolid—superior to vancomycin for MRSA pneumonia. Toxicity may occur with long-term administration unless TDM is undertaken
- some isolates may be susceptible to clindamycin, cotrimoxazole and doxycycline. However these agents should not be used to treat bacteraemia

Infection Control

MSSA: no specific measures required.

MRSA: patients are usually placed on contact precautions (gown or apron, glove and careful hand hygiene as per 5 moments for hand hygiene) and may be isolated in a single room or cohorted with other colonised patients to prevent spread to ~~other~~ non-identified colonised patients.

15.1.3.2 *Haemophilus influenzae*

Clinical

Haemophilus influenzae is an important respiratory pathogen. In patients with cystic fibrosis it often causes infection early in life but is replaced by other organisms such as *Pseudomonas spp*. over time [4]. In contrast, patients undergoing lung transplantation for other indications may be colonized with *H. influenzae* at any stage of life. Post-transplant infection with *H. influenzae* is relatively uncommon. This is at least in part because of the wide spread practice of the administration of azithromycin and trimethoprim/sulphamethoxazole as prophylactic agents in the post-operative period. Both these antimicrobial agents have activity against *H. influenzae* thereby reducing the frequency of infection.

Treatment

- approximately 25% of *H. influenzae* isolates are susceptible to ampicillin
- ampicillin resistant isolates are generally susceptible to augmentin, cefuroxime and third generation cephalosporins (cefotaxime, ceftriaxone)
- cephalexin is ineffective

Infection Control

No specific infection control measures required other than standard precautions and hand hygiene.

15.1.3.3 *S. pneumoniae*

Like *H. influenzae S. pneumoniae* is an important respiratory pathogen which is uncommon in the setting of lung transplantation, again in part because of the impact of antimicrobial prophylaxis with trimethoprim/sulphamethoxazole and azithromycin. After lung transplantation a reduction in an important component of the immune system, serum immunoglobulins, is common occurring in up to 63% of lung transplant recipients [5]. It is likely that this increases the risk and frequency of severe pneumococcal infection.

Treatment

- *S. pneumoniae* is generally susceptible to penicillin
- penicillin resistant *S. pneumoniae* pulmonary infection can usually be successfully treated with penicillin as the concentration achieved in the lung is sufficient to exceed the threshold for efficacy
- alternative treatment options for penicillin resistant *S. pneumoniae* causing meningitis or blood-stream include third generation cephalosporins and vancomycin

Infection Control

No specific infection control measures required other than standard precautions and hand hygiene.

15.1.3.4 *Pseudomonas aeruginosa*

Pseudomonas aeruginosa is a Gram negative bacillus which commonly colonises the airways of patients with cystic fibrosis but is also found in other patients proceeding to lung transplantation, for example those with chronic obstructive pulmonary disease. In many centres Pseudomonas is the most common cause of post-transplantation bacterial infection. Prolonged pre-transplant therapy with a variety of antibiotics frequently results in highly resistant organisms colonizing the patient at the time of transplantation.

Laboratory reports may refer to 'mucoid Pseudomonas' isolated from a specimen. Mucoid Pseudomonas develops under certain environmental conditions following infection with non-mucoid species. The thick polysaccharide capsule gives the organism a 'wet' appearance when growing on an agar plate in the laboratory but more importantly renders the organism more resistant to immunological defense mechanisms such as phagocytosis and to standard anti-Pseudomonas therapy.

Treatment

- guided by laboratory susceptibility testing, especially in patients with extensive prior antibiotic exposure
- susceptibility testing of mucoid strains is less reliable than standard strains
- commonly used antibiotics include aminoglycosides (gentamicin, tobramycin, amikacin), antipseudomonal beta-lactams (piperacillin-tazobactam, ceftazidime, cefepime), ciprofloxacin and meropenem. Colistin may occasionally be required for extremely resistant organisms

Infection Control

Contact precautions are generally reserved for patients with multi-drug resistant *Pseudomonas aeruginosa.*

15.1.3.5 *Stenotrophomonas maltophilia*

Stenotrophomonas maltophilia is a Gram negative bacillus which is increasingly recognized as an important pathogen of the airways in the setting of lung transplantation. The organism is widespread in the environment, found in soil, water and animal and plant material. Treatment is complicated by the multi-drug resistance.

Treatment

- trimethoprim-sulphamethoxazole is the treatment of choice although resistance is increasingly described
- ciprofloxacin is active against approximately 50% of laboratory isolates

Infection Control

- no specific infection control requirements other than standard precautions and hand hygiene.

15.1.3.6 *Burkholderia cepacia* Complex

Burkholderia species are Gram negative bacilli closely related to Pseudomonas species (in fact they were previously called *Pseudomonas cepacia* and you will sometimes see this referred to in older literature). In the setting of cystic fibrosis and lung transplantation, the clinically important species belong to the *Burkholderia cepacia* complex (Bcc), a group of 17 genetically closely related organisms. However it has been recently recognised that not all Bcc are equally pathogenic. The most important organisms include *B. cenocepacia* (previously named Bcc genomovar III) and *Burkholderia multivorans* (previously Bcc genomovar 2) which account for up to 97% of all *Burkholderia cepacia* complex isolates from patients with cystic fibrosis [6]. One of the most feared organisms is *Burkholderia cenocepacia* which can be an aggressive pathogen that is transmissible between patients and can cause epidemics.

Recent studies have suggested that *B. cenocepacia* is associated with poor outcome and is a contraindication to transplantation in many centres. Therefore accurate detection and identification of *Burkholderia species* prior to transplantation is absolutely essential: a false positive result can lead to exclusion from the transplantation waiting list whereas a false negative result can lead to poor transplantation outcome and possible cross infection between patients if appropriate infection control measures are not put in place.

Treatment

There is no standard treatment that can eliminate Bcc. Eradication of Bcc is extremely difficult as many species of Bcc, particularly *B. cenocepacia*, are intrinsically resistant via a variety of resistance mechanisms to numerous antimicrobial agents including the aminoglycosides (gentamicin, tobramycin), most antipseudomonal beta-lactam antibiotics (piperacillin-tazobactam, cefepime, ceftazidime) and colistin. Rapid development of resistance may occur during therapy [6]. In a study of a large number of Bcc isolates, 2621 strains of *Burkholderia cepacia* complex isolated from 1257 cystic fibrosis patients were tested. Resistance to all available antimicrobial agents was demonstrated in 18% of isolates with the most active

agents, minocycline, meropenem, and ceftazidime inhibiting 38%, 26%, and 23% of strains, respectively [7]. The use of combination antimicrobial therapy to overcome these issues has not usually been successful.

Infection Control

Bcc can be spread to susceptible patients by:

- person to person contact
- contact with contaminated surfaces or objects
- exposure to Bcc in the environment

Contact precautions and isolation (see MRSA) may be implemented in hospital. Alternately, patients colonised with Bcc should not be housed next to an immunosuppressed patient.

15.1.4 Mycobacterial Infection

Mycobacteria are bacteria forming their own genus within the phylum Actinobacteria. Over 190 species have been identified but not all are pathogenic (that is have the potential to cause infection in humans). Mycobacteria are slender, curved rods that, unlike most bacteria, are acid fast (see preceding section). In addition, they are resistant to alkalis and dehydration meaning they can survive for long periods in the environment. The cell wall contains complex waxes and glycolipids. They multiple very slowly on special media and some clinical isolates can take 4–6 weeks to grow. Based on their growth rate, catalase and niacin production and pigmentation in light or dark conditions mycobacteria are classified as *Mycobacterium tuberculosis* complex (*M. tuberculosis, M. bovis, M. africanum, M. microtii*) and non-tuberculous mycobacterium (NTM). Molecular techniques (e.g. PCR) can now readily differentiate between them.

15.1.4.1 *Mycobacterium tuberculosis* (TB)

M. tuberculosis is transmitted from person to person. The incidence in transplant recipients is much higher than in the general population [8]. The most common cause in the transplant population is reactivation of latent infection but other causes include unrecognised transmission in the donor lungs (that is donor-derived), especially in countries where TB is endemic, and primary infection after transplantation [9]. The median time to infection from lung transplantation is 3.5 months (earlier than in renal transplant recipients) but donor-derived infections usually occur earlier, often within the first month post-lung transplant [8].

Risk factors include prior residence in an endemic country, history of untreated TB, a chest x-ray which shows evidence of old healed TB, augmented immunosup-

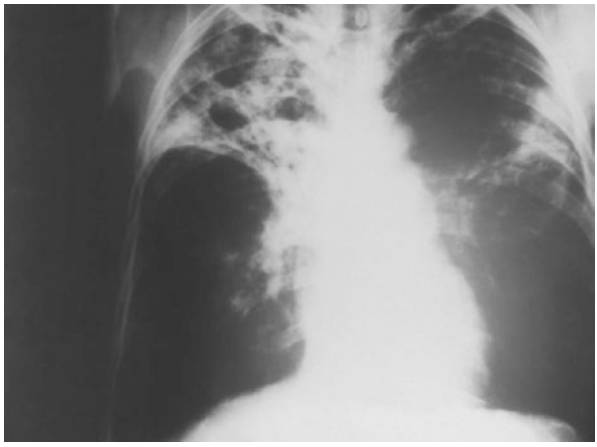


Fig. 15.1 Chest x-ray showing bilateral *Mycobacterium tuberculosis*. Courtesy of the Public Health Image Library, Center for Disease Control and Prevention

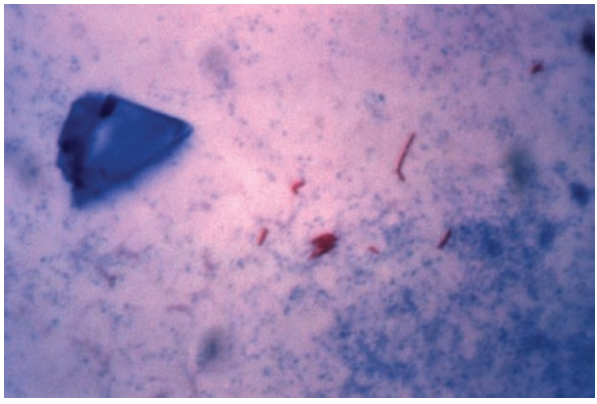


Fig. 15.2 Mycobacterium tuberculosis detected in a sputum smear using Ziehl-Neelsen stain (×1000 magnification). Courtesy of the Public Health Image Library, Center for Disease Control and Prevention

pression for rejection, use of T-cell depleting agents for immunosuppression and recipient age.

The lung is the most common site of infection but in up to 33% extra-pulmonary or disseminated TB can occur with unusual presentations (e.g. skin ulcers, abscesses, tenosynovitis) [9]. Fever is a very common presenting complaint as are night sweats and weight loss [9]. Instead of the classical cavity that is seen on chest x-ray in immunocompetent patients, in lung transplant recipients focal infiltrates, miliary pattern, nodules or pleural effusions are more common (Fig. 15.1) [9].

The diagnosis of active TB can be challenging in lung transplant recipients with sputum samples commonly stain and culture negative. Bronchoalveolar lavage (BAL) with the fluid sent for acid fast bacilli (AFB) staining (Fig. 15.2) and culture is ideal. PCR testing is useful to decrease the time to diagnosis given cultures are slow to grow. Biopsy of skin lesions, abscesses, soft tissue lesions or other accessible extra-pulmonary sites for AFB staining, culture, histology and/or PCR can assist in the diagnosis of extra-pulmonary TB.

Treatment

Guidelines exist for the treatment of active TB; however, there are a few specific things to note in the lung transplant setting [10–12].

- a rifamycin-based regimen (rifampicin is the most common drug used in this group) is strongly preferred because of its sterilizing capacity and ability to prevent the emergence of resistance
- rifamycins interact with immunosuppressant agents. Dose adjustments will be required at initiation and cessation with close monitoring of levels of immunosuppressant drugs whilst receiving a rifamycin
- some centres prefer rifabutin for use in the transplant setting as it has less impact on drug metabolism than rifampicin
- for localised non-severe infection and no suspicion of isoniazid resistance a fluoroquinolone could be substituted for the rifamycin with the duration extended to 12–18 months depending on the number of drugs used. Otherwise a rifamycin agent should be used in the regimen.
- the minimum duration is 6 months but some experts prefer a minimum of 9 months in the transplant setting. Longer treatment is required for severe or disseminated infection or for infection involving the central nervous system and/or bone and joint and in pulmonary disease with ongoing AFB detectable in sputum (>2 months)
- streptomycin should not be used in the lung transplant setting because of the associated high-risk of nephrotoxicity.
- immunosuppressive agents used to prevent rejection may only require minimal or no dose reduction. This is because immune reconstitution inflammatory syndrome (IRIS) can occur even when the immunosuppressant agents are not dose-reduced as the anti-TB treatment can reverse some of the immunosuppressive effects of TB.

Screening for latent TB (prior exposure to *M. tuberculosis* which can reactivate and cause clinical disease) needs to be performed pre-transplant in all lung transplant candidates. Two tests are available, namely, the tuberculin skin test (TST) and the interferon-gamma release assay (IGRA). The IGRA is used in most centres. Screening algorithms are available [10, 13]. As the risk of reactivation and severe infection is increased in transplant recipients and the annual risk of active TB with a positive TST is 7.4%, there is a good argument for latent TB treatment. The optimal timing for latent TB treatment is pre-transplant. Latent TB should be treated if:

- the initial or boosted TST produces induration of ≥5 mm or a positive IGRA;
- prior history of untreated latent TB; or
- receipt of an organ from a donor known to have untreated latent TB.

Isoniazid (with oral pyridoxine) is the treatment of choice and has a low risk of toxicity. Rifampicin for 16 weeks or isoniazid in combination with rifapentine for 12 weeks are alternative regimens, but only pre-transplantation because of drug interactions.

Infection Control

As already stated person-to-person transmission of TB can occur. The major route is by inhalation of airborne particles. There are a number of factors that increase the risk of transmission of airborne particles including presence of untreated active pulmonary or laryngeal TB, cavitary disease, smear positivity and short time to positive *M. tuberculosis* culture. A number of procedures can also increase the risk of dispersal of airborne particles including intubation and bronchoscopy. Patients with extra-pulmonary TB are not contagious; however, concomitant pulmonary or laryngeal TB needs to be excluded firstly. Immunocompromised patients with extra-pulmonary TB should be presumed to have pulmonary TB until proven otherwise.

There are numerous international and national TB control guidelines on which hospitals base infection control programs for TB [14]. If TB is suspected or untreated:

- the patient must be managed in airborne isolation rooms with negative pressure ventilation
- masks must be worn by health-care workers when in contact with the patient and by the patient when he/she leaves the room
- when TB is excluded the patient can be removed from isolation
- for patients with confirmed TB isolation can be discontinued when the patient is receiving treatment, demonstrates a clinical response and has three negative AFB smears from sputum
- close liaison with the institutional Infection Control Team is essential in cases of suspected or untreated TB.

15.1.4.2 Non-tuberculous Mycobacterium (NTM)

Common NTM affecting lung transplant recipients include *M. avium* complex, *M. kansasii* and *M. abscessus.* These are environmental organisms so infection usually occurs via acquisition from an environmental reservoir and not person to person transmission. Healthcare-associated infection from contaminated medical devices can occur and person-to-person transmission has been described with *M. abscessus* [15, 16].

Risk factors for infection include cystic fibrosis as an underlying disease, the isolation of a NTM (particularly *M. abscessus*) pre-transplant and the use of rabbit anti-thymocyte globulin. Median time to onset is later when compared with TB (1 year). The lungs are most commonly affected but cutaneous, soft tissue and

disseminated infection can be seen, especially with *M. abscessus*, *M. chelonae* and *M. kansasii* [17]. With disseminated disease constitutional symptoms (e.g. sweats, tiredness, weight loss) predominate [18]. The most common radiological features seen are fibrocavitary and cavitary, nodules, bronchiectasis, tree-in-bud, and large opacities (>2 cm) [19].

Diagnosis is very challenging as these are environmental organisms and it is difficult to determine whether isolation of these organisms reflects contamination/colonization or true infection. Guidelines for diagnosis exist for NTM [20]. Factors such as organism burden, specific species, clinical signs and symptoms and radiological features all need to be considered when determining infection category and whether or not to treat.

Treatment

Treatment is similar to the immunocompetent population. A multi-drug regimen is used (see Table 15.2); however, similar to TB a few specific points need to be considered in the transplant setting.

- susceptibility testing should be performed to direct initial and maintenance regimens.
- clarithromycin can increase serum levels of calcineurin inhibitors and rapamycin agents via the cytochrome (CYP) 3A4 pathway so with the initiation and cessation of clarithromycin the immunosuppressant agents may need dose adjustment. Close monitoring of immunosuppressant concentrations is required.
- the issues outlined above for rifamycin use in TB treatment also apply to the treatment of NTM.
- the duration of treatment is longer than for the immunocompetent population. The minimum is usually 12 months after last positive culture; but lifelong suppressive therapy may be needed in some patients.
- reduction of immunosuppression needs to be considered.
- surgical resection may be required if:

Table 15.2 Treatment regimens for commonly encountered *non-tuberculous mycobacteria* post-lung transplantation

Organism	Treatment regimens
M. avium intracellulare	Clarithromycin (or azithromycin), rifampicin (or rifabutin) and ethambutol (consider adding amikacin in fibrocavitary or severe nodular/bronchiectatic disease)
M. kansasii	Isoniazid, rifampicin, ethambutol (rifampicin resistance—high dose isoniazid and ethambutol, trimethoprim-sulphamethoxazole and streptomycin)
M. abscessus	Amikacin, cefoxitin and clarithromycin (or azithromycin) (very resistant organisms or disseminated disease consider adding a carbopenem, tigecycline or linezolid) [1]

- large abscesses are present
- there is a large burden of disease
- focal disease not responding to therapy
- the patient cannot tolerate therapy.

M. abscessus is a particular problem in the lung transplant setting. It is increasing in incidence and can cause disseminated infection post-lung transplant which can be very difficult to eradicate. It is also resistant to many of the available antimicrobial agents and drug-related toxicity has been detected in up to 44% post-lung transplantation [21, 22]. Treatment is complicated and prolonged.

In some centres isolation of *M. abscessus* in a lung transplant candidate is considered as a strong relative contra-indication to transplantation [23]. Other centres have determined that transplantation of patients with pre-transplant isolation of *M. abscessus* is possible with the precautions outlined in Table 15.3 [24, 25]. Currently, expert opinion indicates that transplantation in those with pre-transplant isolation of *M. abscessus* should be decided on a case-by-case basis.

Infection Control

As NTM are ubiquitous in the environment, transmission is usually from an environmental source. In addition, NTM are resistant to chlorine and have the ability to form bio-films. As a result infection control measures are directed at ensuring adequate disinfection of hospital equipment, rigorous and repeated surface cleaning and high-quality water supply. Ongoing environmental surveillance in the hospital setting and close liaison with institutional Infection Control and Engineering Teams is critical to prevent outbreaks of NTM, particularly in the setting of construction.

Table 15.3 Current recommendation for management of pre-transplant *M. abscessus* into the post-transplant period

Recommendations
Ensure meet the ATS criteria for disease
Commence triple antimicrobial therapy (according to susceptibility patterns)
Intra-operatively Use a clam-shell approach Irrigate the pleural cavity after removal of native lungs with betadine or amikacin Change surgical gloves prior to insertion of allograft Complete hilar and mediastinal lymphadenectomy
Continue therapy post-transplant for a minimum of 6 weeks Exact duration is dependent on surveillance bronchoscopy results. If the 6 week surveillance bronchoscopy is negative for *M. abscessus* culture then stop, if it is positive then continue
Consider switching to indefinite prophylaxis with inhaled amikacin, oral ciprofloxacin and oral clarithromycin
Regular examination of wounds, skin and soft tissue for signs of disseminated infection

ATS American Thoracic Society
Adapted from Lobo et al. [16] and Robinson et al. [17]. Courtesy of Dr. Orla Morrissey and Dr. Hannah Bills

There are some evidence in the literature that *M. abscessus* has been associated with person-to-person transmission but other studies have indicated that this may not be the case [26, 27]. Careful assessment of each institution's epidemiology will assist in deciding if patients with *M. abscessus* require airborne isolation or simply rigorous cleaning of the environment [28]. Recently *M. chimera* contamination of heater-cooler units used in cardiac surgery has been reported resulting in cases of surgical-site and disseminated infection worldwide. New enhanced decontamination strategies have been developed and ongoing surveillance is required to ensure that these remain effective [29].

15.1.4.3 *Nocardia*

Nocardia are ubiquitous, saprophytic, gram-positive bacteria that belong to the aerobic actinomycetes group. They are partially acid-fast rods that grow slowly in branching chains resembling fungal hyphae. There are more than 80 species but most infections in humans are caused by *Nocardia asteroides sensu stricto*, *N. farcinica, N. nova, and N. brasiliensis*.

Infections with *Nocardia* are increasing in lung transplant recipients [30]. Whilst widespread throughout the world infections with *Nocardia* have the highest frequency in dry windy climates which facilitate aerosolisation and dispersal. Infections mostly occur in the first year after lung transplantation but are rare within the first month unless it is donor-derived infection. Risk factors include corticosteroids (particularly in the preceding 6 months), and augmented immunosuppression (high median calcineurin inhibitor levels in the preceding 30 days) [30]. Rituximab use and hypogammaglobulinaemia have also been associated with an increased risk of developing *Nocardia* infection as has the use of alemtuzumab for treatment of allograft rejection [31–33].

Inhalation is the most common route of infection therefore the lungs are most commonly affected. Dissemination to other organs, particularly the skin and central nervous system (CNS) has been reported in 50% of cases. The skin can also be infected by direct inoculation, especially if the lung transplant recipient is involved in outdoor activities. The most common signs and symptoms are fever, weight loss, cough, pleuritic chest pain and dyspnoea. Chest imaging frequently shows irregular nodular lesions which may be cavitary (Fig. 15.3) [34]. Other features include diffuse infiltrates or consolidation with associated pleural effusions.

Diagnosis is by microscopy, culture and histological examination of respiratory specimens (most particularly bronchoalveolar lavage fluid [BAL]) or biopsy tissue (e.g. skin or brain tissue). *Nocardia* grows on non-selective media forming characteristic white and chalky colonies. If there is a suspicion that the infection may be *Nocardia* inform your diagnostic laboratory as the specimens require longer incubation for the growth of *Nocardia* and in samples with mixed growth (that is multiple organisms [particularly sputum]) *Nocardia* may be obscured. Selective media can be used to improve the yield of *Nocardia* growth (e.g. Thayer-Martin). *Nocardia* has characteristic features on gram stain (see Fig. 15.4). In tissue *Nocardia* appears as gram positive branching and beaded rods with surrounding pyogenic inflammatory

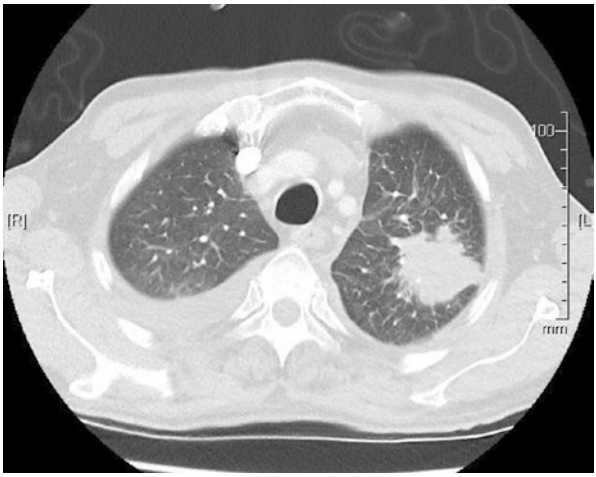


Fig. 15.3 Large nodule of *Nocardia* infection in a solid-organ transplant recipient

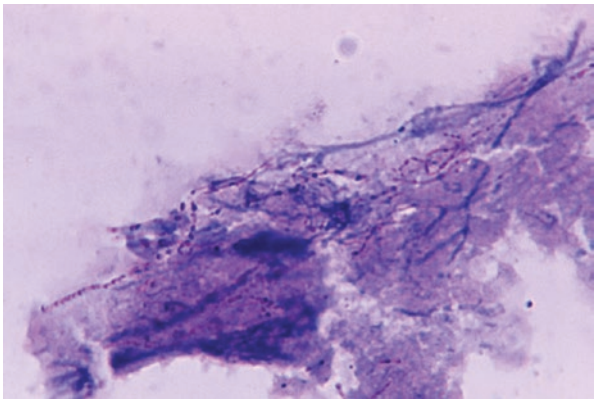


Fig. 15.4 Characteristic microscopic features of *Nocardia*. Courtesy of the Public Health Image Library, Center for Disease Control and Prevention

reaction. It is important to determine the species and susceptibility profiles as different species have different susceptibility profiles. This information is very useful in determining the treatment regimen.

Treatment

Antibiotics are the mainstay of treatment. The site(s) and burden of infection, the species and the potential drug-drug interactions all determine the antimicrobial regimen to be used for treatment [35].

- mild pulmonary infection—trimethoprim-sulfamethoxazole (TMP-SMX) for 6–12 weeks
- severe pulmonary infection (no CNS involvement)—parenteral treatment with TMP-SMX plus amikacin

- CNS infection-parenteral treatment with TMP-SMX plus imipenem
- multi-organ infection including the CNS—intravenous (IV) amikacin added to the regimen of IV TMP-SMX and imipenem.
- meropenem may be used instead of imipenem as the former is less likely to precipitate seizure activity. Sensitivity to meropenem must be demonstrated in the laboratory before use [36].
- linezolid has excellent in vitro activity against Nocardia and has been used with success in treatment; therefore linezolid may be used as part of a multi-drug regimen [37, 38].
- if the patient has a TMP-SMX allergy desensitisation should be performed if possible.

Parenteral treatment is continued for 3–6 week followed by oral therapy for 6–9 months. Oral agents that are commonly used include TMP-SMX, minocycline and/or amoxicillin-clavulanate. Surgery may be required in cases of cerebral nocardiosis or large soft tissue abscesses not responding to treatment, empyema or mediastinal fluid collections and for pulmonary nocardiosis that is complicated by pericarditis. Consideration should be given to reducing immunosuppression especially in cases with severe disease or those progressing on anti-microbial treatment. Indefinite secondary prophylaxis is also recommended as the immunosuppression cannot be fully reversed.

Infection Control

There are no reports of person-to-person transmission of Nocardia in the literature. As Nocardia are ubiquitous environmental organisms, acquisition is mostly from an environmental source. Similar to NTM infection control measures in the hospital setting for Nocardia are directed at disinfection of equipment and surfaces and ensuring high-quality water supply. Ongoing surveillance is required to prevent outbreaks, particularly in the setting of construction.

15.2 Fungal Infections

15.2.1 Introduction

Fungal infections are a significant problem in lung transplant recipients occurring in 8.6% and causing death in up 39.5% of those infected [39, 40]. The majority of infections are caused by *Aspergillus* and *Candida* species. *Cryptococcus* is the third most common cause of fungal infection. The fungi that cause mucormycosis (e.g. *Rhizopus* species), *Scedosporium,* and *Fusarium* are emerging and are associated with very high mortality rates (60.5%); thus, increasing emphasis is placed on early recognition, diagnosis and treatment [40]. *Histoplasma*, *Coccidioides* and *Blastomyces* species are important for those who live in or have previously resided

in or visited endemic areas. *Pneumocystis jirovecii,* whilst infrequent, can cause significant morbidity and mortality.

The risk factors for infection are very similar to those described above for bacterial infection. In addition, fungal infections have been implicated in triggering the development of chronic rejection (that is, chronic lung allograft dysfunction [CLAD]) [41].

Fungi are a major problem in lung transplant recipients. The importance of thinking about fungi in any lung transplant recipient suspected of having infection cannot be over-estimated. Early diagnosis and treatment is critical to optimising outcomes. Prophylaxis may reduce the impact of fungal infections in lung transplant recipients but issues such as drug intolerance and drug-drug interactions and the emergence of resistance may complicate treatment and reduce overall efficacy.

15.2.2 Microbiology

Fungi can be a single cell or complex multicellular organisms. Fungi are mainly found in soil or on dead plant matter. They can be divided up into yeasts, multicellular filamentous moulds and dimorphic fungi. Yeasts are small, lemon-shaped single cells that are around the size of red blood cells. They multiply by budding a daughter cell off from the original parent cell. Multicellular filamentous moulds are made up of very fine threads known as hyphae. They grow from the hyphal tips and divide repeatedly along their length creating long and branching chains. Some of the hyphal branches grow into the air and spores form on these aerial branches. These spores can be carried by the wind, rain or insects to new habitats where they can germinate to start growing and producing new hyphae. The process of infection is mimicked in immunosuppressed individuals where the conidia (spores) are inhaled and with impaired immune defence mechanisms the conidia (spores) can germinate and uncontrolled hyphal growth can occur. Dimorphic fungi are fungi that can exist as yeast or mould. A prime example of a dimorphic fungus is *Penicillium marneffei,* a human pathogen that exists as a mould at room temperature but as yeast at human body temperature.

15.2.2.1 *Aspergillus* Species

Aspergillus fumigatus is the most common of all *Aspergillus* species [42]. Other species that can cause infection in the lung transplant setting include *A. flavus, A. terreus, A. niger* and *A. nidulans* [42]. The importance of identifying *A. terreus* is that it has a different susceptibility profile to the other *Aspergillus species*. It is resistant to amphotericin B [43].

Aspergillus species commonly cause 4 types of infection in lung transplant recipients:

- *Aspergillus* colonisation

- Tracheobronchial aspergillosis
- Invasive pulmonary aspergillosis (IPA) (also known as *Aspergillus* pneumonia)
- Disseminated invasive aspergillosis (IA).

15.2.2.2 *Aspergillus* Colonisation

Aspergillus colonization is defined as the detection of *Aspergillus* in respiratory secretions by culture, PCR or by the detection of *Aspergillus* galactomannan (a cell wall protein) in the absence of any symptoms, lesions in the airways seen on bronchoscopy or new changes seen on chest x-ray or computed tomography (CT) scan [44, 45]. *Aspergillus* colonization has been detected pre-transplant in 8–59% of patients (most commonly in cystic fibrosis [CF] patients) and is a risk factor for post-transplant IPA and CLAD [3, 7]. Post-transplant colonization is found in 30–40% [45].

Treatment

Some centres give antifungal agents to all lung transplant recipients (immediately post-transplant for 4–6 months) to minimize *Aspergillus* colonization and its complications [45, 46]. With the use of universal prophylaxis the time to *Aspergillus* colonisation has lengthened from 3.2 months to 6.8 months post-lung transplant [47, 48]. Other centres only give antifungal treatment (for 3 months) once *Aspergillus* is detected [45, 46]. This is known as the pre-emptive strategy. It is not known which strategy is best.

15.2.2.3 Tracheobronchial Aspergillosis

Tracheobronchial aspergillosis is defined as the detection of *Aspergillus* in respiratory secretions by culture, PCR or the detection of *Aspergillus* galactomannan with new lesions demonstrated on bronchoscopy including patches of redness (erythema), ulceration, necrosis or pseudomembranes but with no changes detected on chest x-ray or CT scan [44, 45]. The patient may be asymptomatic or may present with symptoms such as fever, cough, wheeze and/or hemoptysis [49]. It occurs in the majority of patients in the first 3 months post-lung transplant [47]. The importance of tracheobronchial aspergillosis is that the lung transplant recipient is at risk of progressing to IPA or disseminated IA [47].

Treatment

- the treatment of choice is voriconazole. Alternative agents include amphotericin B, posaconazole and itraconazole

- combine with nebulized amphotericin B for a direct local effect [50].
- repeated bronchoscopic debridement particularly in those with large amounts of necrotic debris [51]
- stenting occasionally required to maintain a patent airway

The duration of treatment is dependent on the severity of the initial infection, degree of immunosuppression and response to therapy but should be given until the lesions have completely healed and potentially life-long in those with bronchial anastomotic involvement.

15.2.2.4 Invasive Pulmonary Aspergillosis and Disseminated Invasive Aspergillosis

Proven IPA is defined as evidence of parenchymal (lung tissue) invasion by *Aspergillus* hyphae or positive culture from sterile lung tissue alone or with signs/symptoms such as fever, abnormal white cell count, new onset purulent sputum or change in the character or quantity of sputum or respiratory secretions, new onset or worsening cough, dyspnoea, tachypnoea, pleural rub, crackles or bronchial breath sounds. Probable IPA is defined as signs/symptoms (as above) and new or progressive and persistent infiltrate, consolidation, cavitation or nodules and detection of *Aspergillus* in respiratory secretions by culture, PCR or the detection of *Aspergillus* galactomannan (single positive for bronchoalveolar lavage [BAL] or 2 positives for sputum) (Fig. 15.5) [44, 45]. Average time to development is 6 months [52].

In disseminated IA, respiratory disease can be associated with infection in the sinuses, orbits and central nervous system (CNS). Other sites where *Aspergillus* can rarely cause infection include skin, bones, eyes (endophthalmitis), in the intra-abdominal cavity or retroperitoneum (e.g. abscess) and in the pericardium [42, 47].

Treatment

- voriconazole is the treatment of choice [53]
- an echinocandin (anidulafungin, caspofungin, micafungin) can be added for synergy in those with extensive disease or who are very unwell (e.g. hypoxic at presentation) [53]
- treatment of disseminated disease is the same as for IPA and as for IPA treatment continues until complete resolution

It is important to remember that when giving voriconazole (or other azole antifungal agents) in lung transplant recipients there are significant interactions with the immunosuppressant (e.g. tacrolimus, cyclosporine and sirolimus). Dose adjustments of the immunosuppressants are required at initiation and cessation of voriconazole (or other azole) and regular monitoring of serum immunosuppressant levels is required.

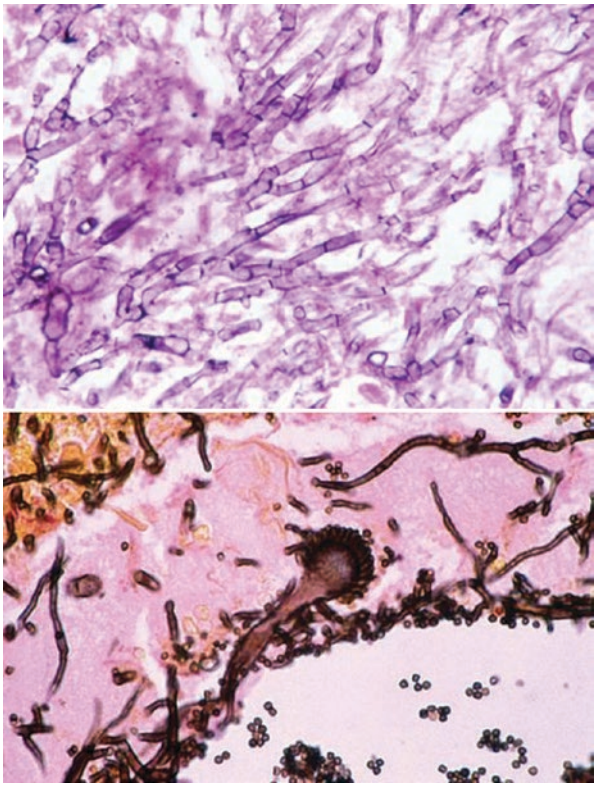


Fig. 15.5 Aspergillosis of the lung. Lung biopsy tissues stained with methenamine silver. With permission from A/Prof. David Ellis and Dr. Sarah Kidd. From Mycology Online, University of Adelaide, South Australia

Infection Control

No specific infection control measures required.

15.2.2.5 *Candida* Species

The most common infection type seen with *Candida* species is candidaemia (infection in the bloodstream; Fig. 15.6). This is most common during the first month post-transplant and is usually related to the recent surgery, intensive care unit stay and broad-spectrum antibiotic use peri-transplant. Tissue infections can also occur and include infected pleural effusion, pleural space infection, infection of the incision sites and bronchial anastomotic site infections [50, 54]. *Candida* species are frequently isolated from the mouth, pharynx, sputum and BAL specimens but almost never spread to invade the lung tissue. Universal prophylaxis targeting *Candida* species during the first month post-transplant have been shown to be effective [55]. However, universal prophylaxis may be associated with the emergence of resistant *Candida* strains [56].

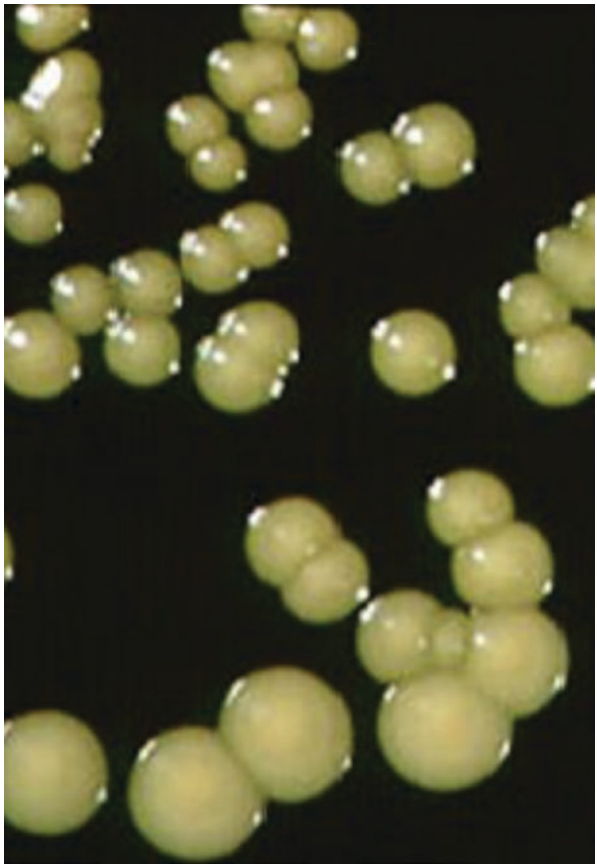


Fig. 15.6 A positive blood culture showing typical moist colonies. With permission from A/Prof. David Ellis and Dr. Sarah Kidd. From Mycology Online, University of Adelaide, South Australia

Candidaemia can manifest as fever or as severe sepsis (e.g. hypotension, tachycardia, requirement for inotrope support). Invasive candidiasis is related to the site of the infection. For example, if disseminated to the skin invasive candidiasis cause skin pustules or to the eye results in endophthalmitis. Blood cultures are still the gold-standard for the diagnosis of candidaemia; therefore a blood culture is required for all patients in whom candidaemia is suspected. In patients with invasive candidiasis a biopsy of the relevant tissues for staining, culture and histological examination is useful. Some centres have access to beta-D-glucan testing. This non-culture based assay detects a cell wall protein of *Candida* species and is a useful as an additional test (in addition to blood cultures and biopsy) in some patients, particularly those with intra-abdominal candidiasis.

Treatment

- echinocandin or liposomal amphotericin B for the treatment of candidaemia and serious Candida infection [45].

- once the *Candida* is detected and the sensitivity profile is known antifungal therapy can be altered [45]. If the isolate is sensitive to fluconazole then a change to this agent is recommended [45]
- if *Candida* is causing symptomatic infection of the urinary tract an echinocandin is not recommended as it has poor penetration into the urinary tract [45]. In this setting, fluconazole (if the isolate is sensitive) or amphotericin B and 5-flucytosine in combination (if the isolate is fluconazole-resistant) is recommended [45].

Infection Control

No specific infection control requirements.

15.2.2.6 *Cryptococcus*

Cryptococcus causes infection in 2% of lung transplant recipients. The most common site of cryptococcal infection is the lung (Fig. 15.7) but disseminated infection can also occur with a predilection to the central nervous system. Skin involvement including cellulitis [57] and infection transmitted in the donor lungs has also been described. The median time to infection onset is 190 days.

In addition to the usual diagnostic tests of culture and biopsy cryptococcal antigen assay is very useful as it is sensitive and specific and can be used to monitor disease treatment response.

Pre-transplant cryptococcosis has been described and is not a contra-indication to transplantation so long as disease control has been achieved with no positive cultures and cryptococcal antigen level is declining. Fluconazole is continued throughout the transplant procedure and for a minimum of 6 months post-transplantation.

Immune reconstitution inflammatory syndrome (IRIS) is common with treatment of cryptococcal infection (5–14%) [58] and manifests as an apparent flare of

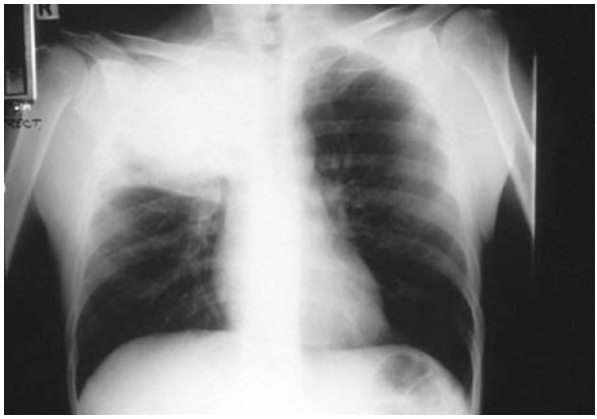


Fig. 15.7 X-ray showing pulmonary cryptococcal infection involving the right upper lobe. With permission from A/Prof. David Ellis and Dr. Sarah Kidd. From Mycology Online, University of Adelaide, South Australia

infection including worsening of clinical and radiological manifestations of the infection, negative microbiology and no other explanation. It is most likely with CNS infection. Discontinuation of calcineurin inhibitors is a pre-disposing factor. It is recommended that calcineurin inhibitors are only dose-reduced and not ceased to minimise the risk of IRIS.

Treatment

The antifungal agents used depend on the site and burden of infection, indicating that diagnosis/exclusion of CNS disease by CT scan or MRI scan of head, a lumbar puncture for culture and cryptococcal antigen testing and CT of chest to determine extent of disease is critically important.

- CNS infection, disseminated infections or severe lung disease—liposomal amphotericin B and 5-flucytosine for a minimum of 2 weeks followed by fluconazole at high dose for 8 weeks and fluconazole at lower doses from 6 months to 1 year is recommended.
- small volume pulmonary disease—fluconazole alone for 6–12 months is recommended [59].

Infection Control

No specific infection control requirements.

15.2.2.7 Mucormycosis

The most common manifestation is pulmonary infection or infection of the CNS and sinuses but gastrointestinal infection (likely through ingestion) has also been described [60]. The cumulative incidence is 0.07% and it accounts for 2% of all fungal infections. Risk factors for infection include renal failure, diabetes and prior voriconazole and/or caspofungin use [61].

Mucormycosis is particularly associated with tissue infarction and necrosis due to invasion of the tissue blood vessels with the growing hyphae (Fig. 15.8). The fungi also spread rapidly along tissue planes. Both these factors contribute to the high mortality rates of up to 87% seen with this infection.

Treatment

In view of the aggressive nature of the fungus and high mortality rate treatment requires a multi-pronged approach.

- anti-fungal therapy

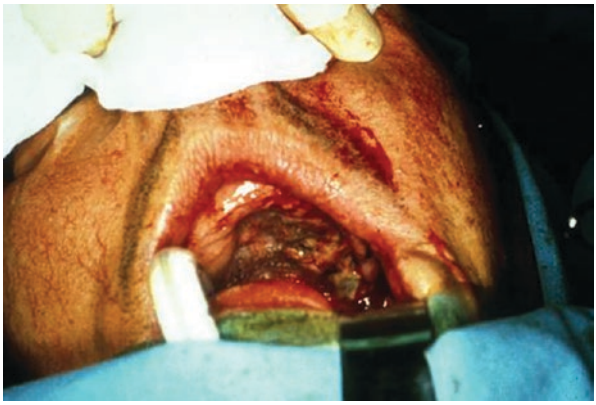


Fig. 15.8 Mucormycosis involving the palate. With permission from A/Prof. David Ellis and Dr. Sarah Kidd. From Mycology Online, University of Adelaide, South Australia

  - first-line therapy is liposomal amphotericin B.
  - caspofungin can be added if the infection is severe.
  - posaconazole or isavuconazole can be given as maintenance therapy or if the patient in intolerant of liposomal amphotericin B.
- surgical debridement of all the necrotic tissue (Fig. 15.8),
- reduction of immunosuppression
- reversal of underlying factors (e.g. diabetes mellitus)

Infection Control

No specific infection control measures required.

15.2.2.8 *Scedosporium* Species

Scedosporium is an environmental organism that is recognised worldwide but has a higher incidence in specific geographical areas such as Spain, The Middle East and Australia. It is a common fungus in floods, tsunamis and tornados resulting in a risk for transmission if the donor drowned [62]. It is commonly isolated from CF patients pre-transplant. Risk factors for invasive *Scedosporium* disease post-transplant include pre-transplant colonisation, prior receipt of amphotericin B and augmented immunosuppression. *Scedosporium* is prone to disseminate and can be detected in blood cultures unlike other moulds such as *Aspergillus*.

In lung transplant recipients *Scedosporium* mainly causes colonisation with invasive infection occurring in about 25%. The most common clinical manifestations of invasive disease include pneumonia, mediastinitis, fungaemia or disseminated disease [63].

Progression to invasive disease is more likely in those with pre-transplant isolation; thus, if *Scedosporium* is isolated prior to transplantation it should be treated [63].

Treatment

- *Scedosporium* is innately resistant to many of the available antifungal agents including amphotericin B.
- *S. apiospermum* is sensitive to some of the azole antifungal agents, particularly voriconazole
- a combination of voriconazole and terbinafine may be the only option against *S. prolificans* (now known as *Lomentospora prolificans*) [63].

Infection Control

No specific infection control measures required.

15.2.2.9 *Fusarium* Species

Fusarium accounts for <1% of all invasive fungal disease in solid organ transplant patients with lung transplant recipients most commonly affected. Like *Scedosporium* whilst *Fusarium* occurs worldwide it has a higher incidence in some countries such as in Brazil, where the incidence of *Fusarium* is second only to *Aspergillus.* Infection usually occurs within a year of transplantation and most commonly affects the lungs. Outcome is poor with a 67% mortality rate.

Treatment

Voriconazole is the most effective agent.

Infection Control

No specific infection control measures required.

15.2.2.10 Endemic Fungi

Histoplasma is endemic to the states bordering the Ohio River Valley and the lower Mississippi River, USA but it has also been detected in Montana and Idaho. Other countries and regions where it has been isolated include Canada, Mexico, Central and South America, parts of eastern and southern Europe, Africa, eastern Asia and

Australia. Pulmonary and disseminated infections are the most common manifestations post-transplant. Infection can range from asymptomatic to severe. The diagnosis is made by using a combination of serology (antigen and antibody), culture of respiratory secretions and biopsy with histological examination of the affected tissue [64].

Routine screening pre-transplant is not recommended. Serial monitoring or the administration of prophylaxis is recommended in those who had active infection prior to transplantation [65].

Treatment

- mild disease—itraconazole
- more severe infection—amphotericin B [66]

Infection Control

No specific infection control measures required.

15.2.2.11 Coccidiodomycosis

Coccidioides are fungi that endemic to the Southwest of the United States particularly the San Joaquin Valley, and the Sonoran desert of southern California, Arizona and northern Mexico. In the lung transplant recipient these fungi can cause severe pneumonia or disseminated infection. Disseminated infection is most commonly characterized by skin, bone and joint lesions and/or meningeal involvement. Diagnosis is established by serological testing, culture or histopathology.

Pre-transplant assessment is required and includes a detailed past history [65]. Any history of residence or travel to an endemic area requires evaluation with serological testing and chest x-ray [65]. Any transplant candidate with past infection requires assessment by a specialist infectious diseases physician for clearance for transplantation [65]. In the case of active infection transplantation is deferred until the infection is quiescent (on radiology, clinically and serologically) [65].

Treatment

- focal pneumonia can be treated with fluconazole
- diffuse disease is treated initially with amphotericin B until clinical response followed by fluconazole or itraconazole
- coccidioidal meningitis is treated with fluconazole

Infection Control

No specific infection control measures required.

15.2.2.12 Blastomycosis

Blastomyces is endemic to parts of eastern North America, particularly northern Ontario, south-eastern Manitoba, Quebec, south of the St. Lawrence River, parts of the Appalachian mountains and the interconnected eastern mountain chains, the west bank of Lake Michigan, the state of Wisconsin and the entire Mississippi River including the valleys of the major tributaries (e.g. Ohio River). It also occurs in Africa, the Arabian Peninsula and the Indian subcontinent. Similar to *Histoplasma* and *Coccidioides* it causes pneumonia and skin involvement (with verrucous or wart-like lesions) and is also common in the transplant recipient. Diagnosis is made by culture of sputum, BAL or tissue or by histopathological examination of biopsy tissue.

Pre-transplant assessment includes symptom assessment and chest radiography for those who live in endemic areas [65]. Prophylaxis is given on a case by case basis.

Treatment

- liposomal amphotericin B until clinical improvement followed by oral itraconazole

Infection Control

No specific infection control measures required.

15.2.2.13 *Pneumocystis jirovecii*

Pneumocystis jirovecii was previously classified as a protozoan but with modern molecular techniques it has recently been reclassified as a fungus [67]. It was previously named *P. carinii* (which infects rats) but has been renamed *P. jirovecii* as this is the species that infects humans [68, 69].

If prophylaxis is not universally administered 5–15% of all solid organ transplant recipients develop *P. jirovecii* pneumonia (PJP) with the highest incidence occurring in the lung and heart-lung transplant recipients [70]. Most centres administer PJP prophylaxis and as a result very few cases are now seen. The most important risk factor for PJP is corticosteroid use in combination with other immunosuppressive agents [71]. There are no good data as to a dose and duration

of corticosteroids to decide when to give prophylaxis. The period of highest risk is the first 6 months post lung transplantation but most centres recommend indefinite prophylaxis [72].

Previously, patients presented in respiratory failure with fever and a dry cough but as the awareness of the significance of the infection has increased and as more sensitive diagnostic tests have been developed diagnosis is made earlier when the disease in mild or indolent (that is less severe cough and dyspnoea). Chest x-ray or CT scan of thorax usually demonstrates diffuse bilateral infiltrates. It is important to make a microbiological diagnosis so obtaining a respiratory specimen (induced sputum or ideally a BAL) is best. A lung biopsy is rarely required. The best test is PCR although it is very sensitive so false positive results can occur. Serum beta-D-glucan testing may be a useful adjunct if available [73].

Treatment

- trimethoprim-sulfamethoxazole (TMP-SMX) 15–20 mg/kg (based on the trimethoprim component) intravenously or orally in 3–4 divided doses daily is recommended as first-line treatment
- if the patient is allergic to TMP-SMX desensitization should be performed where possible
- if TMP-SMX cannot be used the alternative include TMP in combination with dapsone, primaquine in combination with clindamycin, atovaquone or intravenous pentamidine
- adjunctive corticosteroids are recommended if arterial blood gases show a partial pressure of oxygen of $\leq$70 mmHg

Like the treatment of PJP the first-line agent for prophylaxis is TMP-SMP but at lower doses (1 double-strength tablet 3 times a week or a single-strength tablet daily). Alternatives include dapsone, atovaquone or aerosolized pentamidine.

Infection Control

Several clusters or outbreaks of PJP have been reported, particularly in renal transplant patients. In some of these clusters or outbreaks person-to-person transmission was postulated as the cause [74]. Consequently hospitalised patients with PJP should not be placed in the same room as other immunocompromised patients. Otherwise standard precautions apply [75].

This review clearly illustrates that fungi are a major problem in lung transplant recipients. The importance of thinking about fungi in any lung transplant recipient suspected of having infection cannot be under-estimated. Early diagnosis and treatment is critical to optimising outcomes. Prophylaxis may reduce the impact of fungal infections in lung transplant recipients but issues such as drug intolerance and drug-drug interactions and the emergence of resistance may complicate and reduce its overall efficacy. Further multicentre research is required to determine the optimal prophylactic strategies for lung transplant recipients.

15.2.3 Viruses and Lung Transplantation

Viruses are organisms that are much smaller than bacteria and are unable to be detected on routine microscopy. They are only able to survive and replicate within a living cell, using the chemical machinery of that cell to reproduce. Viruses contain either deoxyribonucleic acid (DNA) or ribonucleic acid (RNA). Important DNA viruses in the setting of transplantation include the Herpesvirus family whilst the RNA viruses include most significant respiratory pathogens. Viral infection, either primary or following reactivation of latent virus, remains an important cause of morbidity and mortality following lung transplantation.

Viral culture is extremely laborious and difficult and is restricted to specialist laboratories. Increasingly the diagnosis of viral infection is made by PCR of peripheral blood or affected tissue with PCR available for all the members of the herpesvirus family listed below.

15.2.4 The Herpesvirus Family

The members of the Herpesvirus family are:

- Herpes simples 1 and 2 (HSV-1 and HSV-2)
- Varicella (Herpes) zoster (VZV)
- Cytomegalovirus (CMV)
- Epstein-Barr virus (EBV)
- Human herpesvirus 6 (HHV6)
- Human herpesvirus 7 (HHV7)
- Human herpesvirus 8 (HHV8)

EBV and HHV8 are both recognised as oncogenic or cancer-inducing viruses whereas CMV has immunomodulatory properties. The Herpesviruses all exhibit the phenomenon of latency where the virus lies dormant after initial infection and reactivates causing a variety of clinical presentations during periods of altered immunity.

15.2.4.1 Herpes Simplex Type 1 and 2

HSV-1 and HSV-2 cause oral and genital ulceration but occasionally cause disseminated infection, particularly in the immunocompromised host. As a rule, HSV-1 causes 80% of oral infection and 20% of genital ulceration whereas HSV-2 is responsible for 20% of oral infection and 80% of genital infection. Infection may be primary, which can be severe, or reactivation from the site of latency in the neurons. The incidence of prior infection increases with age and varies according to socio-economic status, race and country of residence, with 50–96% of the general population having antibodies to HSV-1 and therefore at risk of reactivation [76, 77].

The most common manifestation of HSV-1 and HSV-2 in lung transplant recipients are mucocutaneous ulcers involving either the oral cavity or genital tract. Less commonly, pneumonia, hepatitis or encephalitis may result from viral reactivation.

The introduction of acyclovir in the 1980s marked the first highly effective antiviral therapy and resulted in a significant reduction in morbidity and mortality from post-transplant HSV infections. The incidence of HSV-1 and HSV-2 has fallen dramatically since ganciclovir, an anti-CMV agent with activity against HSV, has been widely used as prophylaxis against CMV infection in the transplant setting.

Treatment

- acyclovir/valaciclovir/famciclovir
- suppressive therapy may be appropriate for frequent recurrences
- the development of resistant virus is uncommon

Infection Control

Standard precautions apply to patients with active HSV lesions; however contact precautions may apply in healthcare settings if lesions are not covered and for 3 days post initiation of treatment or until crusting occurs. If HSV is disseminated contact precautions required until lesions are dried and crusted. Immunocompromised staff should not care for patients. Infected staff in high risk clinical areas require urgent review for leave/ redeployment.

15.2.4.2 Varicella Zoster Virus

VZV primary infection results in chicken pox. The virus then lays dormant in neural tissue prior to reactivating as shingles, in particular during periods of immunosuppression. Shingles may follow a single nerve pathway or dermatome, may involve multiple dermatomes or the virus may disseminate involving a variety of organs including the liver, lungs, brain and spinal cord.

Approximately 90% of adults in Australia and the United States have antibody against VZV indicating prior infection. However, the incidence of antibody positivity varies between geographic areas with the incidence lower in tropical regions. Patients who do not have antibodies to VZV should be considered for vaccination prior to transplantation. As the vaccine is a live vaccine it should not be administered after transplantation as there is insufficient safety data in immunosuppressed transplant recipients [78].

Treatment

- high dose acyclovir/valaciclovir/famciclovir
- ganciclovir
- potential role for zoster immune globulin

Infection Control

Contact precautions for patients with active VZV lesions and for 3 days post-initiation of treatment or until crusting occurs.

15.2.4.3 Epstein Barr Virus

EBV is the causative agent of infectious mononucleosis (glandular fever), a common infection in the general population. It is also associated with the development of two cancers, nasopharyngeal carcinoma and Burkitt's lymphoma. Like other herpesviruses, EBV is associated with latent infection; in the case of EBV, B lymphocytes in the blood and lymphoid tissue which sets the scene for lymphoproliferative disorders.

In the setting of transplantation, EBV has a clearly established role in the pathogenesis of post transplantation lymphoproliferative disorder (PTLD) with up to 90% of cases associated with EBV latent infection. PTLD is a spectrum of disease caused by the abnormal proliferation of lymphoid cells, with clinical manifestations varying from asymptomatic to tissue infiltration and/or focal masses in a variety of organs. Figure 15.9 is a PET-CT scan from a patient with PTLD and demonstrates the widespread involvement that can occur. Diagnosis is made by excisional biopsy and histological examination. High levels of EBV DNA measured by PCR in peripheral blood provide supportive evidence.

Treatment

- reduce the level of immunosuppression
- no good data to support a role for antiviral therapy (acyclovir, ganciclovir)
- immunomodulatory agents such as anti CD20 (rituximab)
- resection of localised lesions

Infection Control

No specific precautions are required.

15.2.4.4 Cytomegalovirus (CMV)

CMV infection is defined as the detection of CMV replication (usually by PCR to detect CMV DNA or RNA in plasma or whole blood) regardless of the clinical presentation or symptoms. As with other herpesviruses, CMV infection may be

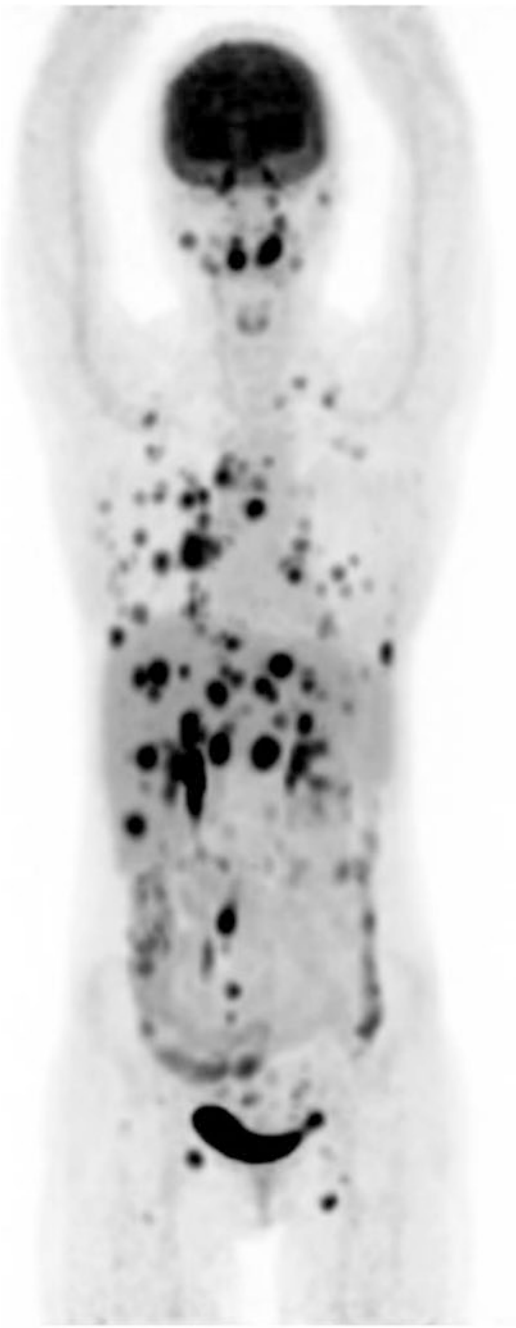


Fig. 15.9 PET-CT scan of a patient with extensive PTLD (the dark areas on the scan represent deposits of EBV-related PTLD). Image courtesy of Professor Allan Glanville

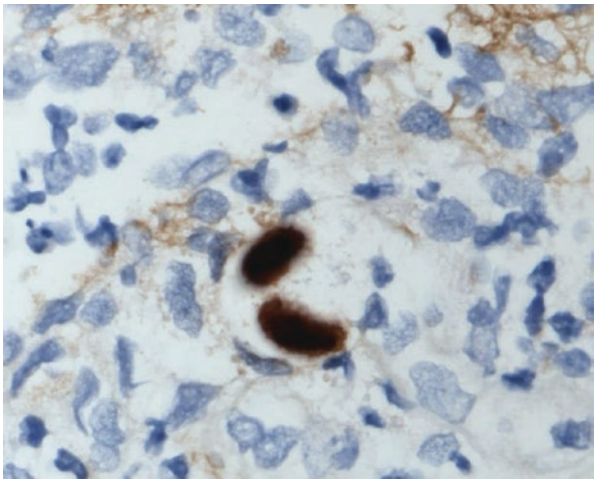


Fig. 15.10 CMV inclusion body in a gut biopsy from a patient with CMV enteritis. Image courtesy of Dr. Wade Barrett, St. Vincent's Hospital, Sydney

primary, donor-derived or reactivation of latent infection. The CMV status of donor (D) and recipient (R) is abbreviated to D+ (donor CMV seropositive), D− (donor seronegative) R+ (recipient CMV seropositive) and R− (recipient seronegative). Possible combinations include D+/R−, D−/R−, D−/R+ and D+/R+. Primary CMV infection is most likely in the setting of D+/R− whilst reactivation can occur in D−/R+ and CMV superinfection with a different strain can be seen in D+/R+.

The effects of CMV infection may be due to either direct tissue damage to a variety of organs (e.g. colitis) or indirect effects on the graft and the immune system (e.g. induce CLAD). Figure 15.10 demonstrates the 'owl's eye' appearance of CMV inclusion bodies in the bowel of a patient with CMV enteritis.

There are two approaches to the prevention of CMV disease.

- prophylaxis strategy—prescribing anti-CMV drugs for a defined period after transplantation (usually 6–12 months).
- pre-emptive therapy—treatment with anti-CMV drugs only when the plasma or blood CMV PCR becomes positive during regular monitoring

The choice of strategy varies between transplant centres and will in part be determined by the ability to rapidly and regularly perform CMV PCR on blood or plasma. In the setting of lung transplantation the prophylaxis strategy is the most frequent approach. In addition, high risk D+/R− patients are more likely to receive prolonged CMV prophylaxis.

Treatment

Despite the various approaches to prevent CMV disease, active infection occurs in up to 30% of transplant recipients [79]. Treatment options include:

- intra-venous ganciclovir
- oral valganciclovir
- CMV immunoglobulin
- reduction in immunosuppression

Treatment failure due to the development of resistant virus is well recognised and may in part be due to sub-therapeutic dosing of ganciclovir/valganciclovir. Resistance may be detected by specific testing for genetic mutations, the most common of which are UL97 and UL54.

Options to treat resistant CMV disease include alternative and experimental drugs such as:

- foscarnet
- cidofovir
- leflunomide
- brincidofovir
- maribavir
- letermovir

Infection Control

No specific infection control measures required.

15.2.4.5 Human Herpesvirus 6

HHV-6 is very common in the community with approximately 95% of the general population demonstrating serological evidence of prior infection [80]. As with other herpesviruses it remains latent after primary infection and frequently reactivates after transplantation. However the significance of reactivation is uncertain as it is not reliably associated with any specific clinical syndrome. Infection is most commonly asymptomatic but encephalitis, hepatitis, gastro-duodenitis and pancytopenia have been described. CMV prophylaxis does not appear to prevent HHV-6 reactivation [81].

Treatment

There is limited clinical treatment data available but ganciclovir, valganciclovir and foscarnet appear to have activity against HHV-6 in laboratory testing. There may be a role for reduction of immunosuppression.

Infection Control

No specific infection control measures required.

15.2.4.6 Human Herpesvirus 7

Like HHV-6, HHV-7 infection is very common in the community and reactivation can occur following transplantation. However the clinical importance of this is uncertain with no syndromes regularly associated with this virus. For this reason most laboratories do not perform PCR for HHV-7.

Treatment

There is minimal anecdotal data and no controlled trials for the treatment of HHV-7 although anti-CMV drugs such as ganciclovir, foscarnet and cidofovir may be effective.

Infection Control

There are no specific infection control procedures required.

15.2.4.7 Human Herpesvirus 8

Along with EBV, HHV-8 is an oncogenic or cancer-causing herpesvirus. Clinical manifestations include Kaposi's sarcoma (KS), body cavity lymphoma and Castleman's disease, a rare lymphoproliferative disorder. The prevalence of HHV-8 varies greatly, from 0 to 5% in North America and Northern Europe to up to 70% in regions of sub-Saharan Africa and the southern Mediterranean where the virus is endemic [82].

Previously recognized as an uncommon malignancy of elderly Mediterranean men, African children, and Ashkenazi Jews, KS became the most common neoplasm of patients with HIV infection with an incidence >20,000 times that of the general population [83]. Seropositive transplant recipients have a small risk of reactivation of latent virus and donor-derived infection has been infrequently reported. KS is the most common manifestation and body cavity lymphoma and Castleman's disease are rare presentations of HHV-8.

Diagnosis of HHV-8 reactivation is generally by PCR whilst KS, body cavity lymphoma and Castleman's disease require histological diagnosis.

Treatment

Antiviral drugs do not appear to be clinically effective. The mainstay of treatment includes:

- reduction of immunosuppression or reversal of underlying immune deficiency
- chemotherapy
- rituximab for Castleman's disease

Infection Control

No specific infection control procedures required.

15.2.4.8 Respiratory Viruses

Respiratory viruses circulate within the community with seasonal and geographic variability. Serious complications are uncommon in the non-immunocompromised host but in the setting of lung transplantation respiratory virus infections are associated with secondary bacterial infections, acute rejection and chronic graft dysfunction. Increased susceptibility to respiratory viruses in lung transplant recipients is multifactorial and includes immunosuppression, impaired cough reflex, poor mucociliary clearance, altered lymphatic drainage and the direct exposure of the lung allograft to the environment.

A prospective study compared 50 lung transplant recipients with respiratory virus infection with 50 uninfected recipients and demonstrated that those with a respiratory virus infection had a greater risk of acute rejection, bronchiolitis obliterans syndrome and death [84].

Important respiratory viruses include:

- respiratory syncytial virus (RSV)
- influenza
- parainfluenza
- human metapneumovirus (hMPV)
- coronavirus/rhinovirus
- adenovirus

Respiratory viral infections are common in lung transplantation. A recent study of 112 lung transplant recipients over a 2 year period found an infection rate of 19.3% with 61% having one or more viral infections over the study period [85]. Asymptomatic carriage was uncommon (<10%) and was mainly associated with coronavirus/rhinovirus. The hospitalisation rate was 50% for influenza and parainfluenza and 16.9% for other viruses.

Infection control precautions for respiratory viruses include droplet precautions (single room, mask, gown and gloves for room entry) until asymptomatic and hand hygiene as per 5 moments. Staff should not come to work if they have a respiratory illness and unwell visitors should not be allowed patient contact. Chemoprophylaxis may be administered to patients following exposure where appropriate (see below for specific viruses).

Many microbiology laboratories perform a respiratory pathogen PCR diagnostic panel which includes the common respiratory viruses such as Influenza A, Influenza B, Enterovirus, Rhinovirus, Coronavirus, hMPV, Parainfluenza, Adenovirus, RSV and non-viral organisms including *Bordetella pertussis, Bordetella parapertussis, Mycoplasma pneumoniae* and *Pneumocystis jirovecii.* Testing is generally performed on nose and throat swabs (both required), a nasopharyngeal aspirate or bronchial washings.

15.2.4.9 Respiratory Syncytial Virus

Like many respiratory viruses, RSV is seasonal with a winter predominance. In healthy adults RSV is usually associated with mild, self-limited infection but in lung transplant recipients RSV can cause bronchiolitis, pneumonia and respiratory failure with a significant acute mortality up to 20% [86] and decline in lung function associated with the subsequent development and progression of bronchiolitis obliterans syndrome (BOS) [87]. RSV has also been associated with acute rejection but a recent prospective study failed to confirm this finding [85].

Treatment

Ribavirin is a nucleoside analogue with broad range of activity against many RNA viruses and, despite a lack of randomised trial data, is the cornerstone of treatment for RSV. Ribavirin can be administered in 3 ways:

- oral
- intra-venous
- aerosolised (negative pressure room and specific equipment required)

Advice regarding administration and dosing regimen should be sought as ribavirin has significant toxicity (primarily haematological), is teratogenic and has a very long half-life.

Infection Control

Standard and droplet precautions required. Patients should be managed in a single room.

15.2.4.10 Influenza

Influenza is a seasonal virus with the greatest incidence of infections during the winter months, although it is detectable year-round in the community. The two most frequent types are influenza A followed by influenza B. Influenza viruses characteristically undergo ‘antigenic drift’ or minor annual changes in the surface glycoprotein that allows reinfection due to inadequate immunity. Every 10 years or so ‘antigenic shift’ occurs secondary to the reassortment of genes between species. Major outbreaks of influenza occur at this time as there is little immunity present in the community.

The rate of influenza is higher after lung transplantation than other solid organ transplants [88] and may be community acquired, nosocomial or donor-derived infection. Complications such as viral and bacterial pneumonia occur more frequently than in the general population. Annual vaccination of transplant recipients,

transplant candidates and their families is strongly recommended although the antibody response may be impaired in immunosuppressed patients [89].

Treatment

Treatment should be initiated in all transplant patients with suspected or proven influenza and ceased if an alternative diagnosis is made. Therapeutic options include:

- oseltamivir (oral, influenza A and B)
- zanamivir (inhaled, influenza A and B)
- amantadine (oral, influenza A only)
- rimantadine (oral, influenza A only)

Chemoprophylaxis should be offered to patients known to be exposed to influenza virus either in the hospital or the community setting.

Infection Control

Droplet and standard precautions for duration of symptoms or until 3 days of active influenza treatment.

15.2.4.11 Parainfluenza Viruses

Parainfluenza viruses (PIV) consist of a group of 4 serotypes, PIV 1–4, which circulate year-round in the community and cause a variety of clinical presentations from the 'common cold' to bronchiolitis and pneumonia. PIV 3 has been associated with large hospital outbreaks of infection due to person-to-person transmission, especially in haematology wards, with mortality rates up to 30% in outbreaks [90]. In lung transplant recipients PIV infection can lead to loss of lung function and bronchiolitis obliterans syndrome. Figure 15.11 shows extensive interstitial pneumonia in a patient with severe PIV infection.

Treatment

There are no randomised studies of antiviral therapy. However there are reports published primarily in the haematology setting suggesting ribavirin, either orally or intravenously administered, may be effective treatment. A small single centre study of RSV and PIV in lung transplant recipients indicated that 33% of lung transplant patients with lower respiratory tract paramyxoviral infections who were treated with inhaled ribavirin died or did not return to baseline lung function [91].

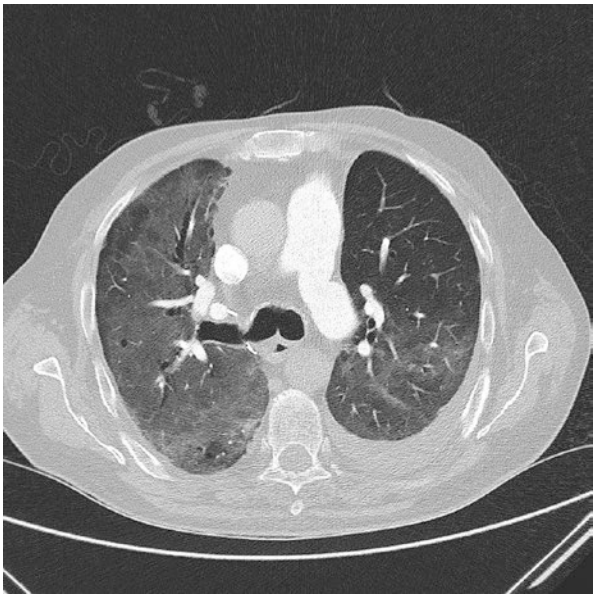


Fig. 15.11 CT scan of a patient with severe PIV infection. Courtesy of Professor Allan Glanville

Infection Control

Droplet and standard precautions.

15.2.4.12 Human Metapneumovirus (hMPV)

hMPV was first described as recently as 2001 and has been increasingly recognised as a seasonal (predominantly late winter) respiratory pathogen causing both upper and lower respiratory tract infection. About 100% of school aged children have antibodies to this virus indicating the widespread nature of hMPV [92].

HMPV is closely related to RSV and in lung transplant recipients is thought to result in graft dysfunction. However there was mainly anecdotal data to support this until a recent review by Dosanjh [93] who conducted a literature search to identify cases of both hMPV and allograft rejection within 6 months of the initial infection. 1007 lung transplantation recipients, with a total of 2883 samples, were identified. Of these, 57 had hMPV without co-infection with other agents. The results of the study indicated that 35% of acute hMPV infections without co-infection were associated with acute cellular rejection within 3 months and 9.4% of the cases subsequently developed chronic allograft dysfunction/bronchiolitis obliterans syndrome suggesting that hMPV is an important pathogen in the lung transplant setting.

Treatment

Ribavirin has been shown to have activity against hMPV in vitro [94] and in animal models of infection [95]. However no human studies in hMPV infection have been performed and the use of ribavirin remains controversial. Case reports have supported ribavirin therapy with concomitant intravenous immunoglobulins (IVIG) for improving symptoms.

Infection Control

Droplet and standard precautions.

15.2.4.13 Coronavirus/Rhinovirus

Coronavirus and rhinovirus are the most frequent cause of the 'common cold' in the general population. However in immunocompromised patients these viruses can cause pneumonia which may be fatal, particularly in bone marrow transplant recipients [96]. Persistent rhinovirus infection associated with graft dysfunction has been described in lung transplant recipients [97].

Treatment

There are no specific treatment options available. Decreasing immunosuppression may have a role but there is little data to support this.

Infection Control

Droplet and standard precautions.

15.2.4.14 Adenovirus

Adenoviruses consist of a large group of DNA viruses with over 50 types known to cause a variety of illnesses including gastroenteritis, encephalitis, hepatitis, haemorrhagic cystitis, upper and lower respiratory infections and conjunctivitis. In immunosuppressed patients adenovirus infection can develop at any time after transplantation and is associated with significant morbidity and mortality rates up to 75% [98]. Adenovirus infection has been reported to be associated with organ rejection following cardiac and renal transplantation. Bridges et al. reported 4 of 9 patients with adenovirus infection alone developed bronchiolitis obliterans syndrome and graft failure [99].

Treatment

There are no randomised studies of treatment. Anecdotal case reports suggest cidofovir may have a role but results are mixed.

Infection Control

Droplet and standard precautions.

References

1. Christie JD, Edwards LB, Kucheryavaya AY, et al. The registry of the International Society for Heart and Lung Transplantation: twenty-seventh official adult lung and heart-lung transplant report—2010. J Heart Lung Transplant. 2010;29:1104–18.
2. Lipuma JJ. The changing microbial epidemiology in cystic fibrosis. Clin Microbiol Rev. 2010;23(2):299–323.
3. Shields RK, Clancy CJ, Minces LR, et al. *Staphylococcus aureus* infections in the early period after lung transplantation: epidemiology, risk factors, and outcomes. J Heart Lung Transplant. 2012;31:1199–206.
4. Hoen AG, Li J, Moulton LA, et al. Associations between gut microbial colonization early life and respiratory outcome in cystic fibrosis. J Paediatr. 2015;167:138–47.
5. Florescu DF, Kalil AC, Qiu F, et al. What is the impact of hypogammaglobulinemia on the rate of infections and survival in solid organ transplantation? A meta-analysis. Am J Transplant. 2013;13:2601–10.
6. Drevinek P, Mahenthiralingam E. *Burkholderia cenocepacia* in cystic fibrosis: epidemiology and molecular mechanisms of virulence. Clin Microbiol Infect. 2010;16(7):821–30.
7. Zhou J, Chen Y, Tabibi S, et al. Antimicrobial susceptibility and synergy studies of Burkholderia cepacia complex isolated from patients with cystic fibrosis. Antimicrob Agents Chemother. 2007;51(3):1085–8.
8. Torre-Cisneros J, Doblas A, Aguado JM, et al. Tuberculosis after solid-organ transplant: incidence, risk factors, and clinical characteristics in the RESITRA (Spanish Network of Infection in Transplantation) cohort. Clin Infect Dis. 2009;48:1657.
9. Singh N, Paterson DL. Mycobacterium tuberculosis infection in solid-organ transplant recipients: impact and implications for management. Clin Infect Dis. 1998;27:1266.
10. Subramanian AK, Morris MI, AST Infectious Diseases Community of Practice. Mycobacterium tuberculosis infections in solid organ transplantation. Am J Transplant. 2013;13(Suppl 4):68.
11. Bumbacea D, Arend SM, Eyuboglu F, et al. The risk of tuberculosis in transplant candidates and recipients: a TBNET consensus statement. Eur Respir J. 2012;40:990.
12. Meije Y, Piersimoni C, Torre-Cisneros J, et al. Mycobacterial infections in solid organ transplant recipients. Clin Microbiol Infect. 2014;20(Suppl 7):89.
13. Aguado JM, Torre-Cisneros J, Fortun J, et al. Tuberculosis in solid-organ transplant recipients: consensus statement of the group for the study of infection in transplant recipients (GESITRA) of the Spanish Society of Infectious Diseases and Clinical Microbiology. Clin Infect Dis. 2009;48:1276.
14. Lewinsohn DM, Leonard MK, LoBue PA, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention clinical practice guidelines: diagnosis of tuberculosis in adults and children. Clin Infect Dis. 2017;64:e1.

15. Rodrigues C, Mehta A, Jha U, Bharucha M, Dastur FD, Udwadia TE. Nosocomial Mycobacterium chelonae infection in laparoscopic surgery. Infect Control Hosp Epidemiol. 2001;22:474.
16. Bryant JM, Grogono DM, Greaves D, Foweraker J, Roddick I, Inns T, et al. Whole-genome sequencing to identify transmission of Mycobacterium abscessus between patients with cystic fibrosis: a retrospective cohort study. Lancet. 2013;381:1551.
17. Malouf MA, Glanville AR. The spectrum of mycobacterial infection after lung transplantation. Am J Respir Crit Care Med. 1999;160:1611.
18. Piersimoni C. Nontuberculous mycobacteria infection in solid organ transplant recipients. Eur J Clin Microbiol Infect Dis. 2012;31:297.
19. Lee Y, Song JW, Chae EJ, et al. CT findings of pulmonary non-tuberculous mycobacterial infection in non-AIDS immunocompromised patients: a case-controlled comparison with immunocompetent patients. Br J Radiol. 2013;86:20120209.
20. Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med. 2007;175:367.
21. Chopra S, Matsuyama K, Hutson C, Madrid P. Identification of antimicrobial activity among FDA-approved drugs for combating Mycobacterium abscessus and Mycobacterium chelonae. J Antimicrob Chemother. 2011;66:1533.
22. Lyu J, Jang HJ, Song JW, Choi CM, Oh YM, Lee SD, et al. Outcomes in patients with Mycobacterium abscessus pulmonary disease treated with long-term injectable drugs. Respir Med. 2011;105:781.
23. Taylor JL, Palmer SM. Mycobacterium abscessus chest wall and pulmonary infection in a cystic fibrosis lung transplant recipient. J Heart Lung Transplant. 2006;25:985–8.
24. Lobo LJ, Chang LC, Esther CR, Gilligan PH, Tulu Z, Noone PG. Lung transplant outcomes in cystic fibrosis patients with pre-operative Mycobacterium abscessus respiratory infections. Clin Transpl. 2013;27:523.
25. Robinson PD, Harris KA, Aurora P, Hartley JC, Tsang V, Spencer H. Paediatric lung transplant outcomes vary with Mycobacterium abscessus complex species. Eur Respir J. 2013;41:1230.
26. Bryant JM, Grogono DM, Rodriguez-Rincon D, et al. Emergence and spread of a human-transmissible multi-drug resistant nontuberculous mycobacterium. Science. 2016;354:751.
27. Tortoli E, Kohl TA, Trovato A, et al. Mycobacterium abscessus in patients with cystic fibrosis: low impact of inter-human transmission in Italy. Eur Respir J. 2017;50:1602525.
28. Hasworth CS, Banks J, Capstick T, et al. British Thoracic Society guidelines for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD). Thorax. 2017;72:969.
29. Wlaker J, Moore G, Collins S, et al. Microbiological problems and biofilms associated with Mycobacterium chimera in heater-cooler units used for cardiopulmonary bypass. J Hosp Infect. 2017;96:209.
30. Peleg AY, Husain S, Qureshi ZA, et al. Risk factors, clinical characteristics, and outcome of Nocardia infection in organ transplant recipients: a matched case-control study. Clin Infect Dis. 2007;44:1307.
31. Grim SA, Pham T, Thielke J, et al. Infectious complications associated with the use of rituximab for ABO-incompatible and positive cross-match renal transplant recipients. Clin Transpl. 2007;21:628.
32. Corales R, Chua J, Mawhorter S, et al. Significant post-transplant hypogammaglobulinemia in six heart transplant recipients: an emerging clinical phenomenon? Transpl Infect Dis. 2000;2:133.
33. Peleg AY, Husain S, Kwak EJ, et al. Opportunistic infections in 547 organ transplant recipients receiving alemtuzumab, a humanized monoclonal CD-52 antibody. Clin Infect Dis. 2007;44:2014.
34. Kanne JP, Yandow DR, Mohammed TL. CT findings of pulmonary nocardiosis. Am J Roentgenol. 2011;197:W266.

35. Clark NM, Reid GE, AST Infectious Diseases Community of Practice. Nocardia infections in solid organ transplantation. Am J Transplant. 2013;13(Suppl 4):83.
36. Brown-Elliott BA, Brown JM, Conville PS, et al. Clinical and laboratory features of the Nocardia spp. based on current molecular taxonomy. Clin Microbiol Rev. 2006;19:259.
37. Moylett EH, Pacheco SE, Brown-Elliott BA, et al. Clinical experience with linezolid for the treatment of Nocardia infection. Clin Infect Dis. 2003;36:313.
38. Welsh O, Salinas-Carmona MC, Brown-Elliott BA, et al. Disseminated actinomycetoma due to Nocardia wallacei. Int J Dermatol. 2018. https://doi.org/10.1111/ijd.13909. [Epub ahead of print].
39. Pappas PG, Alexander BD, Andes DR, et al. Invasive fungal infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). Clin Infect Dis. 2010;50:1101.
40. Vazquez R, Vazquez-Guillamet MC, Suarez J, et al. Invasive mold infections in lung and heart-lung transplant recipients: Stanford University experience. Transpl Infect Dis. 2015;17:259.
41. Weigt SS, Elashoff RM, Huang C, et al. *Aspergillus* colonization of the lung allograft is a risk factor for bronchiolitis obliterans syndrome. Am J Transplant. 2009;9:1903.
42. Gordon SM, Avery RK. Aspergillosis in lung transplantation: incidence, risk factors and prophylactic strategies. Transpl Infect Dis. 2001;3:161.
43. Sutton DA, Sanche SE, Revankar SG, et al. In vitro amphotericin B resistance in clinical isolates of *Aspergillus terreus*, with a head to head comparison to voriconazole. J Clin Microbiol. 1999;37:2343.
44. Husain S, Mooney ML, Danziger-Isakov L, et al. A 2010 working formulation for the standardization of definitions of infections in cardiothoracic transplant recipients. J Heart Lung Transplant. 2011;30:361.
45. Husain S, Sole A, Alexander BD, et al. The 2014 International Society for Heart and Lung Transplantation guidelines for the management of fungal infections in mechanical circulatory support and cardiothoracic organ transplant recipients. J Heart Lung Transplant. 2016;35:261.
46. Neoh CF, Snell GI, Levvey B, Morrissey CO, et al. Antifungal prophylaxis in lung transplantation. Int J Antimicrob Agents. 2014;44:194.
47. Singh N, Husain S. *Aspergillus* infections after lung transplantation: clinical differences in type of transplant and implications for management. J Heart Lung Transplant. 2003;22:258.
48. Chong PP, Kennedy CC, Hathcock MA, et al. Epidemiology of invasive fungal infections in lung transplant recipients on long-term azole antifungal prophylaxis. Clin Transpl. 2015;29:311.
49. Mehrad B, Paciocco G, Martinez FJ, et al. Spectrum of *Aspergillus* infection in lung transplant recipients: case series and review of the literature. Chest. 2001;119:169.
50. Palmer SM, Perfect JR, Howell DN, et al. Candidal anastomotic infection in lung transplant recipients: successful treatment with a combination of systemic and inhaled antifungal agents. J Heart Lung Transplant. 1998;17:1029.
51. Hadjiliadis D, Howell DN, Davis RD, et al. Anastomotic infections in lung transplant recipients. Ann Transplant. 2000;5:13.
52. Morgan J, Wannemuehler KA, Marr KA, et al. Incidence of invasive aspergillosis following hematopoietic stem cell and solid organ transplantation: interim results of a prospective multicentre surveillance program. Med Mycol. 2005;43(Suppl 1):S49.
53. Patterson TF, Thompson GR 3rd, Denning DW, et al. Practice guidelines for the diagnosis and management of invasive aspergillosis. 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;63:e1.
54. Palmer SM, Alexander BD, Sander LL, et al. Significance of blood stream infection after lung transplantation: an analysis in 176 consecutive patients. Transplantation. 2000;69:2360.
55. Koo S, Kubiak DW, Issa NC, et al. A targeted peritransplant antifungal strategy for the prevention of invasive fungal disease after lung transplantation: a sequential cohort analysis. Transplantation. 2012;94:281.

56. Horn DL, Neofytos D, Anaisse EJ, et al. Epidemiology and outcomes of candidemia in 2019 patients: data from the prospective antifungal therapy alliance registry. Clin Infect Dis. 2009;48:1695.
57. Rakvit A, Meyerrose G, Vidal AM, et al. Cellulitis caused by *Cryptococcus neoformans* in a lung transplant recipient. J Heart Lung Transplant. 2005;24:642.58.
58. Singh N, Lotholary O, Alexander BD, et al. Immune reconstitution syndrome-like illness associated with *Cryptococcus neoformans* infection in organ transplant recipients. Clin Infect Dis. 2005;40:1756.
59. Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of america. Clin Infect Dis. 2010;50:291.
60. Manchikalapati P, Canon CL, Jhala N, Eloubeidi MA. Gastrointestinal zygomycosis complicating heart and lung transplantation in a patient with Eisenmenger's syndrome. Dig Dis Sci. 2005;50:1181.
61. Singh N, Aguado JM, Bonatti H, et al. Zygomycosis in solid organ transplant recipients: a prospective matched case-control study to assess risk for disease and outcome. J Infect Dis. 2009;200:1002.
62. Katragkou A, Dotis J, Kotsiou M, et al. Scedosporium apiospermum infection after near-drowning. Mycoses. 2007;50:412.
63. Johnson LS, Shields RK, Clancy CJ. Epidemiology, clinical manifestations, and outcomes of Scedosporium infections among solid organ transplant recipients. Transpl Infect Dis. 2014;16:578.
64. Hage CA, Ribes JA, Wengenack NL. A multicenter evaluation of tests for diagnosis of histoplasmosis. Clin Infect Dis. 2011;53:448.
65. Miller R, Assi M, AST Infectious Diseases Community of Practice. Endemic fungi in solid organ transplantation. Am J Transplant. 2013;13(Suppl 4):250.
66. Wheat LJ, Freifeld AG, Kleiman MB, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. Clin Infect Dis. 2007;45:807.
67. Edman JC, Kovacs JA, Masur H, et al. Ribosomal RNA sequence shows Pneumocystis carinii to be a member of the fungi. Nature. 1988;334(6182):519.
68. Gigliotti F. Pneumocystis carinii: has the name really been changed? Clin Infect Dis. 2005;41:1752.
69. Cushion MT, Stringer JR. Has the name really been changed? It has for most researchers. Clin Infect Dis. 2005;41:1756.
70. Sepkowitz KA. Opportunistic infections in patients with and patients without acquired immunodeficiency syndrome. Clin Infect Dis. 2002;34:1098.
71. Rodriguez M, Fishman JA. Prevention of infection due to Pneumocystis spp. in human immunodeficiency virus-negative immunocompromised patients. Clin Microbiol Rev. 2004;17:770.
72. Radisic M, Lattes R, Chapman JF, et al. Risk factors for Pneumocystis carinii pneumonia in kidney transplant recipients: a case-control study. Transpl Infect Dis. 2003;5:84.
73. Karageorgopoulos DE, Qu JM, Korbila IP, et al. Accuracy of β-D-glucan for the diagnosis of Pneumocystis jirovecii pneumonia: a meta-analysis. Clin Microbiol Infect. 2013;19:39.
74. de Boer MG, Bruijnesteijn van Coppenraet LE, et al. An outbreak of Pneumocystis jiroveci pneumonia with 1 predominant genotype among renal transplant recipients: interhuman transmission or a common environmental source? Clin Infect Dis. 2007;44:1143.
75. Siegel JD, Rhinehart E, Jackson M, et al. 2007 guideline for isolation precautions: preventing transmission of infectious agents in healthcare settings. 2007. http://www.cdc.gov/ncidod/dhqp/pdf/isolation2007.pdf. Accessed 25 Feb 2018.
76. Malkin J, Morand P, Malvy D. Seroprevalence of HSV-1 and HSV-2 in the general French population. Sex Transm Dis. 2002;78:201–3.

77. Vyse A, Gay N, Slomka M. The burden of infection with HSV-1 and HSV-2 in England and Wales: implications for the changing epidemiology of genital herpes. Sex Transm Dis. 2000;76:183–7.
78. Avery RK, Michaels RM. Update on immunisations in solid organ transplant recipients: what clinicians need to know. Am J Transplant. 2008;8(1):9–14.
79. Kalil AC, Levitsky J, Lyden E, et al. Meta-analysis: the efficacy of strategies to prevent organ disease by cytomegalovirus in solid organ transplant recipients. Ann Intern Med. 2005;143(12):870–80.
80. Cervera C, Marcos MA, Linares L, et al. A prospective survey of human herpes virus 6 infection in solid organ transplant recipients. Transplantation. 2006;82(7):979–82.
81. Lehto JT, Halme M, Tukiainen P, et al. Human herpesvirus-6 and -7 after lung and heart-lung transplantation. J Heart Lung Transplant. 2007;26(1):41–7.
82. Breese Hall C. Human herpesvirus 8. In: Long S, Pickering L, Prober C, editors. Principles and practice of paediatric infectious diseases. 3rd ed. Philadelphia: Churchill Livingstone; 2008.
83. Beral V, Peterman TA, Berkelman RL, Jaffe HW. Kaposi's sarcoma among persons with AIDS: a sexually transmitted infection? Lancet. 1990;335(8682):123–8.
84. Kumar D, Erdman D, Keshavjee S, et al. Clinical impact of community-acquired respiratory viruses on bronchiolitis obliterans after lung transplant. Am J Transplant. 2005;5:2031.
85. Bridevaux PO, Aubert JD, Soccal PM, et al. Incidence and outcomes of respiratory viral infections in lung transplant recipients: a prospective study. Thorax. 2014;69(1):32.
86. Palmer SM Jr, Henshaw NG, Howell DN, et al. Community respiratory viral infection in adult lung transplant recipients. Chest. 1998;113(4):944.
87. Hopkins P, McNeil K, Kermeen F, et al. Human metapneumovirus in lung transplant recipients and comparison to respiratory syncytial virus. Am J Respir Crit Care Med. 2008;178(8):878.
88. Vilchez RA, McCurry K, Dauber J, et al. Influenza virus in solid organ transplant recipients. Am J Transplant. 2012;293:287–91.
89. Hayney MS, Welter DL, Francois M, et al. Influenza vaccine responses in lung transplant recipients. Prog Transplant. 2004;14(4):346–51.
90. Zambon M, Bull T, Sadler CJ, et al. Molecular epidemiology of two outbreaks of parainfluenza 3 in a bone marrow transplant unit. J Clin Microbiol. 1998;36:2289.
91. McCurdy LH, Milstone A, Dummer S. Clinical features and outcomes of paramyxoviral infection in lung transplant recipients treated with ribavirin. J Heart Lung Transplant. 2003;22:745.
92. Principi N, Esposito S. Pediatric human metapneumovirus infection: epidemiology, prevention and therapy. J Clin Virol. 2014;59:141–7.
93. Dosanjh A. Respiratory metapneumoviral infection without co-infection in association with acute and chronic lung allograft dysfunction. J Inflamm Res. 2015;8:79–82.
94. Wyde PR, Chetty SN, Jewell AM, et al. Comparison of the inhibition of human metapneumovirus and respiratory syncytial virus by ribavirin and immune serum globulin in vitro. Antivir Res. 2003;60(1):51–9.
95. Hamelin ME, Prince GA, Boivin G. Effect of ribavirin and glucocorticoid treatment in a mouse model of human metapneumovirus infection. Antimicrob Agents Chemother. 2006;50(2):774–7.
96. Gutman JA, Peck AJ, Kuypers J, et al. Rhinovirus as a cause of fatal lower respiratory tract infection in adult stem cell transplant patients: a report of two cases. Bone Marrow Transplant. 2007;40:809.
97. Kaiser L, Aubert JD, Pache JC, et al. Chronic rhinoviral infection in lung transplant recipients. Am J Respir Crit Care Med. 2006;174:1392.
98. Symeonidis N, Jakubowski A, Pierre-Louis S, et al. Invasive adenoviral infection in T-cell depleted hematopoietic stem cell transplantation: high mortality in the era of cidofovir. Transpl Infect Dis. 2007;9:108.
99. Bridges ND, Spray TL, Collins MH, et al. Adenovirus infection in the lung results in graft failure after lung transplantation. J Thorac Cardiovasc Surg. 1998;116:617–23.

Chapter 16
How to Measure Success

Rebecca Pearson

16.1 Introduction

Patients with end stage lung disease are well known to have a poor quality of life and despite advances in medical therapy, continue to have a high mortality rate [1, 2]. Lung transplantation can now offer these patients the potential for extended survival and improved health-related quality of life. Survival outcomes and health-related quality of life data can be assessed to measure success post transplant. Factors which affect quality of life can also be measured including rates of re-employment, functional status and social participation post lung transplantation.

16.2 Survival Outcomes

The International Society for Heart and Lung Transplantation (ISHLT) publishes an annual report regarding the outcomes of lung and heart-lung transplant recipients, worldwide. Between January 1990 and June 2015, a total of 53,396 patients underwent lung transplantation, with a median survival of 6.0 years and recipients who survived the first 12 months, had a median survival of 8.1 years [3]. Survival rates post bilateral lung transplantation are higher than single lung transplantation with 1 year survival at 82% and 78%, 59% and 48% at 5 years and 41% and 23% at 10 years, respectively. These survival rates are inferior to those of other solid organ transplants. For example, 1 year and 5 year survival for deceased donor kidney transplants in the United States are 94% and 72%, respectively [4]. The Australia and New Zealand Organ Donation Registry Annual

R. Pearson
Lung Transplant Unit, St. Vincent's Hospital, Darlinghurst, NSW, Australia

A. R. Glanville (ed.), *Essentials in Lung Transplantation*,
https://doi.org/10.1007/978-3-319-90933-2_16

report for 2016 published the 1 year and 5 year survival post lung transplantation as 89.5% and 70.8%, respectively [5]. This compares to the 1 year and 5 year survival for kidney transplants from deceased donors in Australia at 95% and 82% respectively.

The development of bronchiolitis obliterans syndrome is one of the primary reasons for decreased survival post lung transplantation and heavy immunosuppression contributes to significant morbidity including systemic hypertension, renal dysfunction and diabetes [6].

Patients undergoing lung re-transplantation have a lower median survival of 2.9 years compared with primary lung transplantation, and survival rates are 40% at 5 years and 21% at 10 years. Heart-lung transplant recipients have lower short-term survival rate in the first year, however, of those patients who survive the first year, the mortality risk is lower and median survival increases to 10.3 years [3].

Survival outcomes also vary according to the patient's primary diagnosis with the highest median survival of 9.2 years for those diagnosed with cystic fibrosis, 6.7 years for alpha-1 antitrypsin deficiency, 6.0 years for interstitial lung disease other than idiopathic pulmonary fibrosis, 5.8 years for COPD and 4.9 years for idiopathic pulmonary fibrosis [3].

There is a significant decline in survival during the first year post transplant as this period is associated with increased morbidity and mortality risk. Infection (including CMV and non-CMV) and graft failure (reported as obliterative bronchiolitis/bronchiolitis obliterans syndrome, acute rejection and "graft failure") remain the major causes of death in the first year and account for 36.8% and 22.7% of deaths respectively [3]. The decline in the survival rate at 5 years is also predominantly associated with the development of obliterative bronchiolitis/bronchiolitis obliterans syndrome or "graft failure" (25% and 16% respectively) and infection accounts for 17.3% of deaths. Malignancy (lymphoma and non-lymphoma) rates increase over time and account for 10% of deaths after 5 years [3].

Overall, the survival rates post lung transplantation have continued to improve over time. During the 1990–1998 era, 1 year survival was 72% worldwide compared to the most recent era of 2009-June 2015 with a 1 year survival rate of 84% [3]. The improvement in surgical techniques and post-operative care is thought to contribute to this trend in the first year period. The 5 year survival has increased from 46% during the 1990–1998 era and to 57% during the 2009-June 2015 era.

Several studies have sought to compare survival post-transplant with survival on the waiting list. Of those patients diagnosed with pulmonary fibrosis, there is a proven improved survival benefit post transplantation however for conditions such as COPD, the benefit is less clear [7]. Researchers have developed prognostic models to compare wait list and post-transplant survival for those patients with COPD. Thabut et al. determined 45% of COPD patients who underwent bilateral lung transplantation would have an increased survival benefit of 1 year [8]. Another recent study stated only COPD patients with a BODE index of greater than 7 would have a survival benefit compared to those on the waiting list [9].

16.3 Quality of Life

Quality of life measurement is an integral component of the assessment of success post lung transplantation. The international guidelines for patient selection to undergo lung transplantation indicates quality of life benefits should be considered in addition to the potential survival benefit to assist decision-making for patients and physicians [10]. As previously discussed, in some respiratory conditions the survival benefit of transplantation remains uncertain therefore improved quality of life may be the only expected benefit [2].

Quality of life is defined by the World Health Organisation as "an individual's perception of their position in life, in the context of culture and value systems in which they live and in relation to their goals, expectations and standards and concerns". It is a general term influenced by multiple factors including financial status, housing, employment, social support and health [11]. Health related quality of life (HRQL) is a more specific measure with a focus on the health and the aspects of quality of life related to the patient's disease [12]. HRQL measures the effect of the patient's condition and management on their daily life and includes areas of physical, psychological and social functioning [2].

See Fig. 16.1.

Health status is a broad term that encompasses both quality of life and the functional status of the patient [12]. Functional status or performance describes a patient's ability to function day to day on a physical, emotional and social level and is a component of functional capacity which refers to the patient's maximum potential to perform various daily activities [12, 13]. Functional status can be assessed using tools such as the Karnofsky performance status (KPS) which measures the patient's level of self-care with various levels of assistance. Scores range from 0 to 100 as the level of independence increases [14].

See Table 16.1.

Genoa et al. found lung transplantation resulted in improved functional status as measured by the mean KPS [15]. At 12 months post lung transplantation, all groups of transplant recipients had a higher mean KPS compared to their scores at transplantation (ages ranged from 18 to 64 years). Of note however, the average KPS post transplantation was 2.1 points higher for the younger cohort and 2.6 points higher for bilateral as opposed to single transplantation. A higher KPS, and transplantation at a large volume centre were also factors associated with a better KPS at 1 year post transplantation. Average KPS decreased by 3.2 points per year after the first 12 months post transplantation. This effect was noted to be similar in both the younger and older patient cohorts.

There are several tools used to assess HRQL (see Table 16.2). These methods can be classified as either generic or disease specific, such as the St George's Respiratory Questionnaire (SGRQ). The SGRQ contains questions relevant to lung disease with questions or 'items' to assess symptoms such as breathlessness, cough, sputum, activity level and social and emotional impact on daily life [12]. In addition to disease specific tools, researchers may also use utility measures, which assess patient's

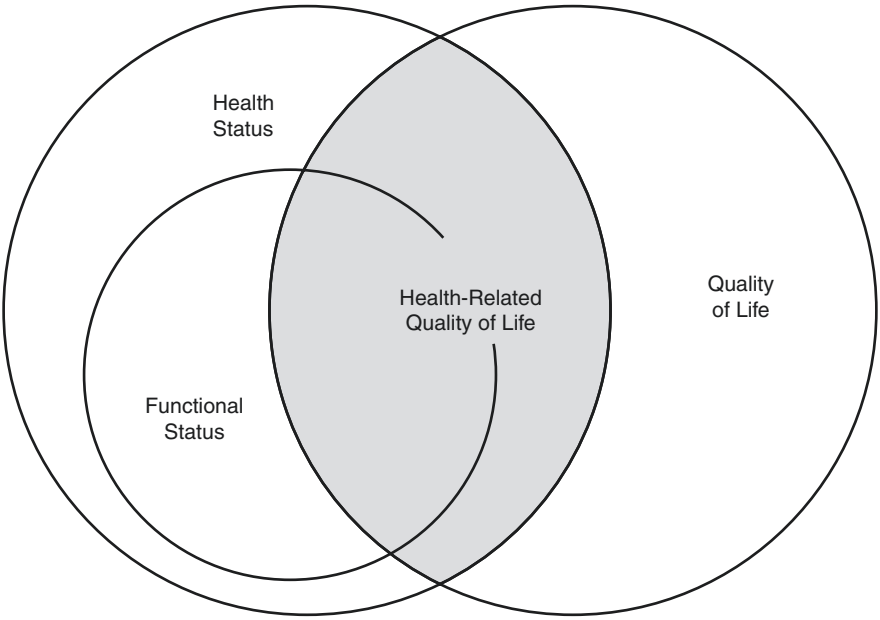


Fig. 16.1 Model of overlapping areas of terms to describe patient-assessed health outcomes. Reprinted with permission of the American Thoracic Society. Copyright © 2017 American Thoracic Society. Curtis JR, Martin DP, Martin T. Patient-assessed health outcomes in chronic lung disease. What they are, how do they help us and where do we go from here? Am J Respir Crit Care Med 1997;156:1032–1039. The *American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society [12]

values or preferences [2]. Utilities are scored on a scale of 0.00–1.00 where 1.00 is the most healthy state and death has a score of 0 [2]. Utility measures give an assessment of the quality of life benefit provided by an intervention and combined with survival data allow researchers to estimate quality-adjusted life years (QALYs). QALYs can be used to compare different interventions and their cost effectiveness. Hence QALY measurement can assist in decisions regarding allocation of resources to a particular intervention [12].

See Table 16.2.

There are several studies to date which illustrate an improvement in HRQL post lung transplantation. However, it is important to note there are limitations to these studies due to small sample sizes, use of non-utility measurements (which do not account for patient death) and cross sectional study designs.

A recent large prospective study of 326 patients, found a significant improvement in HRQL post transplantation using both generic and disease specific instruments. They found a 17.7 improvement in the generic 36 Item Short Form Survey (SF-36) physical score and an average improvement of 47 points in the SGQR [16]. This improvement in the SGQR was noted to be more than 10 times the minimally clinical important difference (MCID). For most of the measures of HRQL they

Table 16.1 Karnofsky performance status

	Index	Specific criteria
Able to carry on normal activity; no special care needed	100	Normal, no complaints, no evidence of disease
	90	Able to carry on normal activity, minor signs or symptoms of disease
	80	Normal activity with effort, some signs or symptoms of disease
Unable to work, able to live at home and care for most personal needs, varying amount of assistance needed	70	Cares for self, unable to carry on normal activity or to do work
	60	Requires occasional assistance from others but able to care for most needs
	50	Requires considerable assistance from others and frequent medical care
Unable to care for self, requires institutional or hospital care or equivalent, disease may be rapidly progressing	40	Disabled, requires special care and assistance
	30	Severely disabled, hospitalization indicated, death not imminent
	20	Very sick, hospitalization necessary, active supportive treatment necessary
	10	Moribund
	0	Dead

Adapted from Mor V, Laliberte L, Morris JN, Wiemann M. The Karnofsky performance scale – an examination of its reliability and validity in the research setting. Cancer 1984;53:2002–2007;with permission

Table 16.2 Tools used to measure quality of life [6, 16]

Type	Instrument	Acronym	Score range	Minimal important difference
Generic	The 36-item short form survey	SF-36	0–100	5 units
	The 12-item short form survey	SF-12	0–100	5 units
	EuroQol health utility and health-related quality of life questionnaire	EQ-5D	−0.59 to 1.00	0.07 units
	Health status visual Analog scale	VAS	0–100	9 units
Specific	St George's respiratory questionnaire	SGRQ	0–100	4 units for obstructive disease 7 units for interstitial lung disease

found no significant difference between age groups however HRQL did vary for recipient primary diagnosis. For example, patients who underwent lung transplantation for cystic fibrosis had greater improvement in SGRQ and SF-36 compared to patients with interstitial lung disease. The study also determined the mean number of QALYs for the first 5 years post transplantation and concluded patient age and diagnosis had a minimal effect on the variability of QALYs.

Similar improvements in generic HRQL scores were found by Singer et al., who assessed 211 patients transplanted in the United States during the Lung Allocation Score (LAS) era [17]. The study concluded lung transplant delivers clinically significant improvements in HRQL, generally 3–4 times the MCID in the recent LAS era. These improvements were seen within the first 6 months post-surgery and persisted for up to 3 years.

A recent systematic review of HRQL and psychological outcomes post lung transplantation identified 63 articles for final review, 39 of which assessed HRQL [18]. Again, the review found lung transplantation provides significant improvements in HRQL in the first 3–5 years.

The development of bronchiolitis obliterans syndrome has been shown to negatively affect HRQL and appears to be a primary cause of a decline in HRQL measures [19].

16.4 Return to Work

Given the significant financial costs of health care associated with lung transplantation, it is becoming increasingly relevant to measure the societal gains of this life saving intervention. Quality of life measures are generally subjective however studies have assessed other indicators including return to work and social participation to provide objective measures for success post transplantation.

Research has shown patients with chronic disease significantly benefit from participation in society, as through participation, patients are given the opportunity to connect with members of the community and find purpose in life [20]. Returning to work and social participation such as volunteer work, are therefore vital to the patient's recovery and are associated with improved quality of life [21]. These factors significantly influence the patient's journey and improve potential for success post transplantation.

There have been several studies which have assessed return to work in organ transplant recipients however there are some limitations in this area. The definition of 'employment' is varied and some studies have not compared their results to national population employment rates [22]. In addition, cross sectional studies do not take into account the time elapsed after transplant for each recipient, as the data is collated from patients with a range of periods post transplantation.

One of the first studies to address rates of return to work in the United States found the overall employment rate was 22% post transplantation and 37% for those medically able to work [23]. Factors influencing return to work included employment pre-transplantation, a self-report of being physically able to work, increased post- transplant forced vital capacity and a 6-min walk test greater than 550 m.

A German cross sectional study published in 2015, found the return to employment rate to be 37% from a questionnaire completed by 476 lung transplant recipients [24]. Thirty five percent of patients returned to the same job they had left prior to transplant. Those patients who had returned to work, reported higher quality of

life scores than those who were unemployed however this association does not imply causation. Sixty five percent of those working however, reported employment had improved their quality of life. Most of the patients employed were involved in part-time work and took an average of 10 sick days from their work annually. This was comparable to the national average of 8.4 days per year. Again, factors that influenced the return to work included educational level, employment 6 months before transplantation and physical performance ability.

Similar findings were reflected in a cross sectional study from Italy with a return to work rate of 39% (combined rate of heart and lung transplant recipients) and a Canadian cross sectional study with a rate of 37% [25, 26]. Cicutto et al. again showed those who had returned to paid employment were more likely to be younger and have a tertiary education.

Baere et al. assessed 388 patients post heart, lung, liver and kidney transplant and of those, 170 patients had received a lung transplant [20]. The study defined employment as a formal, paid job at the time of completing the questionnaire. They found 26.6% were retired, 31% were employed and 43% were not working. Of those 43%, the reasons for not working included, current student status (n = 2), medically unable to work (n = 94), early retirement (n = 22) and searching for employment (n = 4). The rates of employment post-transplant for kidney, heart, liver and lung were 58.6%, 43.6%, 37.5% and 28.1% respectively. Patients returned to work at a median of 6 months post-transplant and became less likely to return, later that 1 year after transplant. They also found the rates of employment in the lung transplant cohort were below the national rate of 62%. Variables that influenced return to work included younger age at time of transplant, male sex, marriage status, employment 1 year prior to transplantation and having a positive perception of one's ability to work.

With regard to social participation, the study found 17.4% worked as volunteers and 80% had taken up again their activities for leisure. There were no differences across all organ groups and the rates of volunteer work were comparable with the general population.

See Fig. 16.2.

This study did not assess morbidity and exercise capacity post transplantation and were therefore unable to confirm reasons for the varied employment rates between the different organ groups. It is possible patients post lung transplant have higher rates of comorbidities that present barriers to re-employment.

Finally, a recent Australian study assessed 100 patients post-transplant and of those patients who had not retired, 44.2% were employed post transplantation [27]. Participation in paid work was associated with young age, primary diagnosis of cystic fibrosis and low scores for depression. Employment in managerial roles and completion of high school education were found to be independent predictors of returning to paid employment.

These studies have highlighted the potential for improvement in the rates of return to employment. There are areas where transplant physicians and social workers can play a significant role in supporting re-employment. Patients should be encouraged to continue working in the lead up to transplantation and advocacy for

Fig. 16.2 Lung transplant patient 5 years post transplantation

patients from the medical profession and education for employers is required to facilitate transplant recipients return to work [28].

16.5 Conclusion

In addition to survival outcome data, it is appropriate to assess quality of life measures, functional status and social participation to determine the success of lung transplantation.

Quality of life measures are particularly relevant given the survival benefit of transplantation in some respiratory conditions is unclear. Rates of re-employment and social participation must also be considered to determine the benefits of this procedure, not only for the individual but for society in general. Continued research

in these areas are indicated, given that survival outcomes and health status post lung transplantation should continue to improve with the advancement of medical therapies in this challenging field.

References

1. Eskander A, Waddell TK, Faughnan ME, Chowdhury N, Singer LG. BODE index and quality of life in advanced chronic obstructive pulmonary disease before and after lung transplantation. J Heart Lung Transplant. 2011;30:1334–41.
2. Yusen R. Survival and quality of life of patients undergoing lung transplant. Clin Chest Med. 2011;32:253–64.
3. Chambers DC, Yusen RD, Cherikh WS, Goldfarb SB, Kucheryavaya AY, Khusch K, Levvey BJ, Lund LH, Meiser B, Rossano JW, Stehlik J. The registry of the International Society for Heart and Lung Transplantation: thirty-fourth adult lung and heart-lung transplantation report-2017;focus theme: allograft ischaemic time. J Heart Lung Transplant. 2017;36:1047–59.
4. Hart A, Smith JM, Skeans MA, et al. Annual report of the U.S organ procurement and transplantation network and the scientific registry of transplant recipients: kidney. Am J Transplant. 2016;16(Suppl 2):11–46.
5. ANZOD Registry. 2016 annual report. Chap. 13: Transplant outcome. Australia and New Zealand dialysis and transplant registry. Adelaide. 2016. http://www.anzdata.org.au.
6. Yusen R. Technology and outcomes assessment in lung transplantation. Proc Am Thorac Soc. 2009;6:128–36.
7. Kotloff RM, Thabut G. Lung transplantation. Am J Respir Crit Care Med. 2011;184:159–71.
8. Thabut G, Mal H. Outcomes of lung transplantation. J Thorac Dis. 2017;9:2684–91.
9. Lahzami S, Bridevaux PO, Soccal PM, Wellinger J, Robert JH, Ris HB, Aubert JD. Survival impact of lung transplantation for COPD. Eur Respir J. 2010;36:74–80.
10. Orens JB, Estenne M, Arcasoy S, Conte JV, Corris P, Egan JJ, Egan T, Keshavjee S, Knoop C, Kotloff R, Martinez FJ, Nathan S, Palmer S, Patterson A, Singer L, Snell G, Studer S, Vachiery JL, Glanville AR. International guidelines for the selection of lung transplant candidates: 2006 update—a consensus report from the pulmonary scientific council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2006;25:745–55.
11. World Health Organization. WHOQOL. Measuring quality of life. http://www.who.int/mental_health/media/68.pdf.
12. Curtis JR, Martin DP, Martin T. Patient-assessed health outcomes in chronic lung disease. What they are, how do they help us and where do we go from here? Am J Respir Crit Care Med. 1997;156:1032–9.
13. Leidy NK. Using functional status to assess treatment outcomes. Chest. 1994;106:1645–6.
14. Mor V, Laliberte L, Morris JN, Wiemann M. The Karnofsky performance scale – an examination of its reliability and validity in the research setting. Cancer. 1984;53:2002–7.
15. Genoa L, Whitson HE, Zaas D, Sanders LL, Schmader KE. Functional status after lung transplantation in older adults in the post-allocation score era. Am J Transplant. 2013;13:157–66.
16. Singer LG, Chowdhury NA, Faughnan ME, Granton J, Keshavjee S, Marras TK, Tullis E, Waddell TK, Tomlinson G. Effects of recipient age and diagnosis on health-related quality-of-life benefit of lung transplantation. Am J Respir Crit Care Med. 2015;192:965–73.
17. Singer LG, Katz PP, Soong A, Shrestha P, Huang D, Ho J, Mindo M, Greenland JR, Hays SR, Golden J, Kukreja J, Kleinhenz ME, Shah RJ, Blanc PD. Effect of lung transplantation on health-related quality of life in the era of lung allocation score: a U.S prospective cohort study. Am J Transplant. 2017;17:1334–45.
18. Seiler A, Klaghofer R, Ture M, Komossa K, Martin-Soelch C, Jenewein J. A systematic review of health-related quality of life and psychological outcomes after lung transplantation. J Heart Lung Transplant. 2016;35:195–202.

19. Kunsebeck HW, Kugler C, Fischer S, Simon AR, Gottlieb J, Welte T, Haverich A, Strueber M. Quality of life and bronchiolitis obliterans syndrome in patients after lung transplantation. Prog Transplant. 2007;17:136–41.
20. Law M. Participation in the occupations of everyday life, 2002 distinguished scholar lecture. Am J Occup Ther. 2002;56:640–9.
21. Hathaway DK, Winsett RP, Johnson C, Tolley EA, Hartwig M, Milstead J, Wicks MN, Gaber AO. Post kidney transplant quality of life prediction models. Clin Transpl. 1998;12:168–74.
22. De Baere C, Delva D, Kloeck A, Remans K, Vanrenterghem Y, Verleden G, Vanhaecke J, Nevens F, Dobbels F. Return to work and social participation: does type of organ transplantation matter? Transplantation. 2010;89:1009–15.
23. Paris W, Diercks M, Bright J, Zamora M, Kesten S, Scavuzzo M, Paradis I. Return to work after lung transplantation. J Heart Lung Transplant. 1998;17:430–6.
24. Suhling H, Knuth C, Haverich A, Lingner H, Welte T, Gottlieb J. Employment after lung transplantation – a single-center cross-sectional study. Dtsch Arztebl Int. 2015;112:213–9.
25. Petrucci L, Ricotti S, Michelini I, Vitulo P, Oggionni T, Cascina A, D'Armini AM, Goggi C, Campana C, Vigano M, Dalla-Toffola E, Tinelli C, Klersy C. Return to work after thoracic organ transplantation in a clinically-stable population. Eur J Heart Fail. 2007;9:1112–9.
26. Cicutto L, Braidy C, Moloney S, Hutcheon M, Holness DL, Downey GP. Factors affecting attainment of paid employment after lung transplantation. J Heart Lung Transplant. 2004;23:481–6.
27. Cumming K, O'Brien L, Harris J. Predictors of employment participation following lung transplant. Aust Occup Ther J. 2016;63:347–51.
28. Carter JM, Winsett RP, Rager D, Hathaway DK. A center-based approach to a transplant program. Prog Transplant. 2000;10:204–8.

Index

A. R. Glanville (ed.), *Essentials in Lung Transplantation*,
https://doi.org/10.1007/978-3-319-90933-2