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EDITED BY
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Christopher P. Conlon
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Lung transplantation

P. Hopkins and A.J. Fisher

ESSENTIALS

Lung transplantation offers the only therapeutic option for many patients with end-stage pulmonary and cardiopulmonary diseases, but donors are scarce and the major challenge facing lung transplantation (as with all solid organ transplants) is the shortage of donor organs.

Recipient selection—emphysema/chronic obstructive pulmonary disease, cystic fibrosis, idiopathic pulmonary fibrosis, and pulmonary vascular disease are the main disease groups referred for lung transplantation. Most suitable patients are listed for transplantation when their 2-year survival is estimated to be less than 50% without transplantation.

Donor selection—almost all organs come from cadaveric donors who have sustained brainstem death, but an increasing proportion come after withdrawal of life support leads to donation after circulatory death (DCD) in those who have sustained irreversible cardiac or neurological injury. Ideal donors have satisfactory lung function and are free of systemic infection and disease. Donor/recipient matching is on the basis of ABO blood group, and size.

Transplant procedure—three types of transplant are performed: (1) single lung transplantation; (2) bilateral sequential single or double lung transplantation (required for septic lung diseases and preferred for patients with chronic obstructive pulmonary disease); and (3) heart–lung transplantation (required for Eisenmenger's syndrome or those with complex congenital heart disease).

Immediate post-transplantation management—important issues are early extubation, fluid (crystalloid) restriction and diuresis, early mobilization, ensuring adequate nutrition, and prevention of infection (with antibacterial, antifungal, antipneumocystis, and anticytomegalovirus prophylaxis).

Immunosuppression—most centres employ a combination of an induction regimen based on either an antithymocyte globulin or interleukin-2 receptor blocker, followed by triple therapy with a calcineurin inhibitor (cyclosporin or tacrolimus), a cell cycle inhibitor (azathioprine or mycophenolate), and a corticosteroid (usually prednisolone).

Longer-term management—the incidence of acute rejection and infection are highest in the first 3 months. Acute rejection is diagnosed via transbronchial biopsy and defined by perivascular lymphocytic infiltrates of varying severity, graded from minimal (grade 1) to severe (grade 4): it is usually treated with intravenous methylprednisolone. Chronic rejection is defined histologically by airway fibrosis with/without accompanying vascular sclerosis (obliterative bronchiolitis), and is the

main cause of death in long-term survivors of lung transplantation, with complicating infection the most common terminal event. Solid organ and lymphoid malignancies affect up to 4% of recipients.

Prognosis—Long term survival beyond 10 years is increasingly common yet development of chronic lung allograft dysfunction is likely to be a major limitation to normal life. The complications of very long term immunosuppression use contribute to overall prognosis as much as graft function.

Introduction

For many patients with end-stage lung disease, the only prospect for long term survival and improved quality of life is through a successful lung transplant. The first lung transplant was performed in 1963 and the first successful heart–lung transplant in 1981. Since then, over 55 000 pulmonary transplants have been reported to the registry of the International Society for Heart and Lung Transplantation (ISHLT) from 345 participating institutions. This number, however, falls considerably short of the number of patients with advanced lung disease who might benefit from lung transplantation, and the major challenge facing lung transplantation (as with all solid organ transplants) is the critical shortage of donor organs.

Increasing pressure on transplant waiting lists has translated into much more liberal donor acceptance criteria, including the use of donors after circulatory death (DCD donors), with donors over the age of 60 now becoming common. Despite this apparent reduction in donor quality, survival following lung transplantation in the modern era (2009–2016 ISHLT Registry) has improved to the point where a first-time lung or heart–lung transplant recipient has a 12-month survival of 86%, and a 57% chance of surviving for 5 years with a median survival 6.5 years.

Infection remains the most significant problem encountered by the lung transplant recipient at any time. The lung allograft is unique within solid organ transplants in that it is in direct contact with the external environment, and recipients have poor cough reflexes and impaired mucociliary clearance. These factors continuously expose the allograft to potential infections and allergens, which predispose to many of the problems encountered both early and late after transplantation.

Obliterative bronchiolitis (OB) remains the most significant long-term challenge faced by lung transplant recipients and lung

transplant physicians, with most deaths after the first year attributable to this complication. However, the impact of OB is lessening, and recipients are enjoying improved quality of life for many years.

The transplant process

The transplant process comprises an amalgamation of six separate steps:

- recipient selection
- donor selection
- donor/recipient matching
- the transplant (surgical) procedure
- immediate post-transplantation care
- longer-term monitoring

Each of these steps is critical, and a compromise in any one of these areas can spell disaster for the overall outcome.

Lung transplantation is unique among solid organ transplants in that several transplant options are available (single lung, bilateral lung, and combined heart–lung) with the choice of procedure determined primarily by the recipient's underlying disease process.

Recipient selection

Type of pulmonary disease

Most pulmonary diseases can be considered for transplantation, with emphysema/chronic obstructive pulmonary disease (COPD, including α_1 -antitrypsin deficiency), cystic fibrosis, idiopathic pulmonary fibrosis, and pulmonary vascular disease (idiopathic pulmonary arterial hypertension (iPAH) and Eisenmenger's syndrome) being the main disease groups referred for lung transplantation. The ISHLT Registry, from January 1995 to June 2017, recorded that 30.6% of lung transplants were performed for emphysema, 25.7% for idiopathic pulmonary fibrosis, 15.4% cystic fibrosis, 4.9% α_1 -antitrypsin deficiency, and 4.4% pulmonary vascular disease.

Disease (or the major impact of any disease process) should be confined to the thorax, although in carefully selected patients some systemic diseases with predominantly pulmonary manifestations (scleroderma, sarcoidosis, and others) can be transplanted successfully. There are also limited opportunities (largely dictated by donor organ availability and allocation policies) for combined organ transplantation, such as lung–liver transplantation in patients with cystic fibrosis.

Prognosis at time of listing

Most patients are listed for transplantation when their 2-year survival is estimated to be less than 50% without a transplant. The prognosis of patients with cystic fibrosis, idiopathic pulmonary arterial hypertension, and idiopathic pulmonary fibrosis can be estimated within this sort of time frame. In patients with Eisenmenger's syndrome and emphysema, however, survival on the waiting list is less predictable, and in some cases can be as good if not better than following a transplant. There is continued debate as to whether transplantation in this setting should be performed primarily for quality-of-life issues. **Box 18.16.1** summarizes the specific disease referral recommendations, based on guidelines published by the ISHLT.

Box 18.16.1 Disease-specific indications for lung transplantation (based on ISHLT guidelines 2014)

Patients with the following characteristics should be considered for referral for transplant assessment.

Obstructive lung disease

- BODE index of 5–6
- FEV_1 <25% predicted
- Diffusing capacity of the lung for carbon monoxide (D_{LCO}) <20%
- Homogenous emphysema unsuitable for lung volume reduction surgery
- Respiratory failure with pO_2 <60 mm Hg or 8 kPa and/or pCO_2 >50 mm Hg or 6.6 kPa
- Cor pulmonale

Cystic fibrosis

The following parameters are associated with 20% 2-year survival on the waiting list, and ideally patients will be referred for assessment before reaching them:

- FEV_1 <30% predicted
- Severe reduction in exercise capacity— \leq 400 m on a 6-min walk or equivalent
- Development of pulmonary hypertension

In addition, early referral should be considered for:

- Adolescent females with rapidly declining lung function
- Patients with increasingly frequent and difficult infective exacerbations
- Patients with recurrent severe haemoptysis or pneumothorax
- Patients with multiple antibiotic resistant organisms

Idiopathic pulmonary arterial hypertension

- WHO functional class III or IV
- Requirement for increasing doses of prostacyclin

The following parameters are associated with a median survival of only 12 months and/or an overall survival of less than 20% at 3 years and are also indications for referral:

- Mean right atrial pressure >15 mm Hg
- Mixed venous oxygen saturation <60%
- Cardiac index <2.0 litres/min per m^2
- 6-min walk test <350 m

Eisenmenger's syndrome

- Severely compromised quality of life
- Refractory right heart failure
- Frequent presyncopal or syncopal events
- Poorly controlled arrhythmia

Eisenmenger's syndrome patients with complex lesions and/or repairs tend to require or benefit from transplantation in their third decade: those with 'simple' lesions such as ventricular septal defects (VSD) and patent ductus arteriosus (PDA) tend to come to transplantation later, in their fourth decade.

Idiopathic pulmonary fibrosis

These patients often deteriorate rapidly, with no effective treatment and up to a 30% death rate on the waiting list after only 12 months. Early referral is therefore warranted in the following circumstances:

- Radiology or histopathology evidence of usual interstitial pneumonia (UIP) or fibrotic nonspecific interstitial pneumonia (NSIP) regardless of function
- Forced vital capacity (FVC) <80% predicted
- Transfer factor (D_LCO) <40% predicted
- Ambulatory oxygen requirement
- Dyspnoea or exercise limitation due to lung disease

Contraindications to transplantation

Lung transplantation is a complex undertaking, associated with significant mortality and the potential for significant morbidity, and patients with a bigger burden of disease (including age) simply do not fare as well after a lung transplant as younger and (in relative terms) fitter patients. Most contraindications are relative and are considered in the context of the patient's overall status and expected outcome. Patients are generally considered up to 65 years of age, but many units have expanded age criteria so that 13.5% of all lung transplants worldwide are now in recipients 65 years of age or over. The compromise with older recipients is inferior 12 month and longer-term survival given the burden of immunosuppression and indices of frailty in older people.

Major contraindications include patients with untreatable psychiatric conditions, or social issues associated with an inability to cooperate or comply with a complex medical regime; substance addiction including cigarette smoking within 6 months; active or incurable extrapulmonary infection; pulmonary infection with pan- or multiresistant pathogens; significant chest wall or spinal deformity; and significant extrathoracic organ dysfunction. Relative contraindications include severe osteoporosis, frailty, and active replicating viral infection with hepatitis B or C. Successful lung transplantation has been reported in individuals with HIV infection provided their CD4 count is more than 200, undetectable viral load, and no AIDS-defining illness.

Disease recurrence

Some diseases for which lung transplantation is applicable can recur after transplantation, including sarcoidosis and some hard metal pneumoconioses, pulmonary lymphangioleiomyomatosis, histiocytosis, α -1 antitrypsin deficiency, and desquamative interstitial pneumonitis. As a general rule, recurrence of these conditions

does not significantly affect the transplant outcome, but on occasions they do cause diagnostic dilemmas. Cystic fibrosis does not directly affect lung allografts (which do not carry the CFTR genetic abnormality), and idiopathic pulmonary arterial hypertension has not been documented to recur after transplantation

Donor selection

Types of donor

Most lung allografts are procured from cadaveric donors who have sustained brainstem death, typically from spontaneous intracranial haemorrhage, ischaemic stroke, or traumatic head injury. Nonetheless, up to 30% of all lung transplants (depending on region) are performed from DCD donors. DCD donors have suffered catastrophic neurological or cardiac injury and have no prospect of recovery, with withdrawal of life-supporting measures undertaken in a controlled environment such as the Intensive Care Unit or operating theatre setting. Following cessation of cardiac activity and declaration of death, the deceased donor is transferred to theatre for organ procurement.

Marginal lung donors (defined as at least one of age >60 years, smoking >20 pack years, abnormal chest radiograph, or pO_2 less than 300 mm Hg on 100% oxygen) may be accepted for donation and are a source in 45% of all lung transplants. The development of *ex-vivo* lung perfusion (EVLP), enabling human lungs to be placed on an external circuit after organ retrieval, has demonstrated ability to expand the donor pool further (see Fig. 18.16.1). Perfusion with fluid with a high albumin content reduces interstitial and alveolar oedema, the key consequences of neurogenic pulmonary oedema in the donor, and thereby facilitates improved gas exchange. Other manoeuvres including ventilation and toilet bronchoscopy may be performed while the lungs are placed on the EVLP circuit to address areas of atelectasis, consolidation, and retention of secretions.

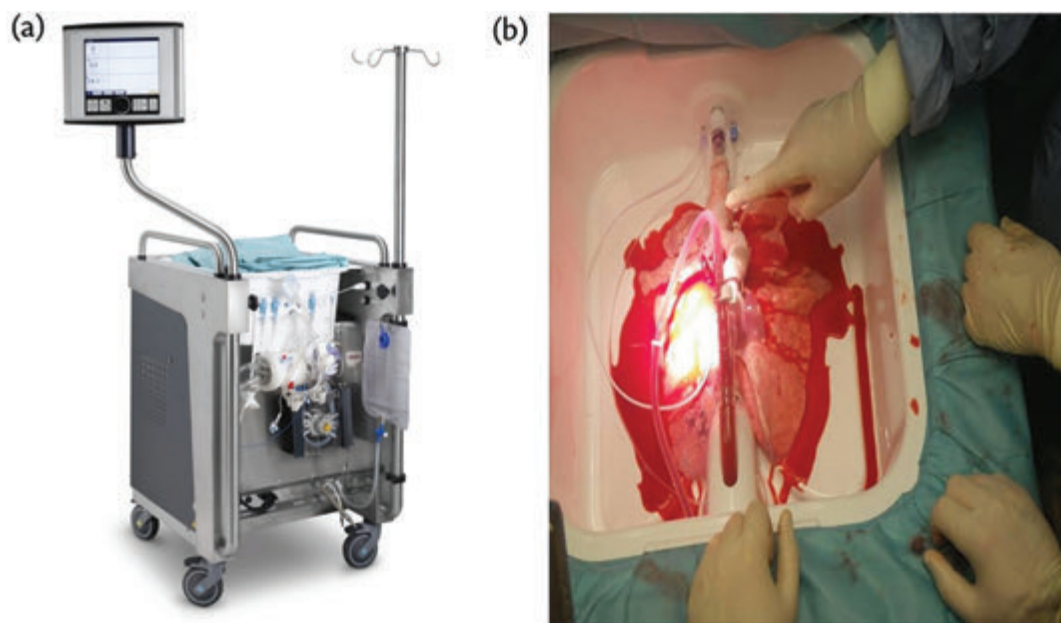


Fig. 18.16.1 (a) *Ex vivo* lung perfusion (EVLP) machine incorporating an oxygenator, rotator pump, ventilation connections, leukocyte filter, and fluid chamber. (b) A human lung placed on the EVLP circuit being perfused with Steen solution.

(a) Reproduced with permission from Vivoline Medical.

A small number of living related lung transplants are performed internationally each year, predominately by adult parents donating a lower lobe to their child with cystic fibrosis.

Other criteria

The following details refer primarily to donors sustaining brainstem death, but the principles applying to the selection of a lung allograft from any type of donor are the same.

All donors should be free of systemic infection or disease. The donor lung is assessed on the basis of function (gas exchange and compliance) and appearance (macroscopic, bronchoscopic, and radiographic). In heart–lung transplantation, cardiac function is assessed via haemodynamic performance based on systemic arterial and venous pressures, urine output, and via Swann–Ganz catheterization. The donor lung is assessed on the basis of function. If indicated (and available), coronary angiography and/or echocardiography may be performed, but these investigations are not routinely available at every donor hospital.

Lung donors are generally under 60 years of age, although because of the critical shortage of donor organs there is an increasing trend to accept organs from donors significantly older than this. Older donors are more prone to early graft dysfunction, and this is particularly the case in combination with longer organ ischaemic times. Unlike the situation in heart transplantation, there are limited options for improving donor lung function in the donor prior to retrieval. Nonetheless, it is important to optimize function by employing ventilator strategies that minimize barotrauma, promote alveolar recruitment, perform active airway clearance to prevent accumulation of secretions and basal collapse, and use cautious fluid resuscitation of the donor to avoid pulmonary oedema.

A potential donor lung will generally be considered acceptable if, just before retrieval, the arterial oxygen level is at least 300 mm Hg (35 kPa) on 100% inspired O₂, airways are free of purulent secretions, and a chest radiograph is free of consolidation. However, suitability is always considered in the light of donor age, projected ischaemic time, and condition of the potential recipient. EVLP can be used to further assess marginal lungs not meeting traditional criteria for acceptance at time of retrieval.

Donor/recipient matching

Matching the donor organ with a suitable recipient is done simply on the basis of ABO blood group, with the same principles of ABO matching applying in solid organ transplantation as in blood transfusion practice, and size based on predicted total lung capacity calculated from donor sex and height. Perfect size matching is rarely achieved because recipients will have either a restricted or hyperinflated chest cavity reflecting their underlying disease process (e.g. pulmonary fibrosis and emphysema, respectively). Size-matching algorithms are largely based on the experience of the lung transplant team, who need to take into account measured and predicted total lung capacity (TLC) of the recipient, predicted TLC of the donor, CXR measurements from apex to diaphragm, and the type of transplant being performed (single or bilateral lung transplant). As a general rule, oversizing should be avoided as the resultant lung compression and atelectasis predisposes to postoperative infection. By contrast, undersizing creates the opportunity for development of hyperinflation physiology of the lung allograft.

The transplant (surgical) procedure

Management of the donor, donor lung preservation, and surgical retrieval of donor lungs are outside the scope of this chapter (but for information, see ‘Further reading’).

Surgical options

There are three basic options available when replacing diseased lung tissue—single lung transplantation, bilateral sequential single lung (or double lung) transplantation, and heart–lung transplantation. The choice of procedure is determined by the recipient’s underlying disease process, by the expected outcome of the procedure in terms of survival and functional result, and on occasions by surgical preference. The commonest disease indications for bilateral lung transplantation have been COPD/emphysema (26.4%), cystic fibrosis (22.3%), and interstitial lung disease (25.7%) and for single lung transplantation, COPD/emphysema (39.4%) and interstitial lung disease (37.1%). However, it is now recognized that bilateral sequential single lung transplantation is superior to single lung transplantation in terms of both long-term survival and functional status for recipients with emphysema/COPD. Thus, for patients with emphysema/COPD (including α_1 -antitrypsin deficiency), bilateral lung replacement is now the preferred transplant option. Individuals with severe hyperinflation (TLC >150% predicted) are best served with a bilateral procedure to reduce the risk of native lung hyperinflation causing compression of the transplanted single lung. When this does occur, patients may require surgical lung volume reduction of the native lung with attendant risks of prolonged air leak and infection.

Septic lung diseases such as cystic fibrosis and bronchiectasis require the replacement of both lungs (either bilateral lung transplantation or heart–lung transplantation). Diseases such as Eisenmenger’s syndrome that involve both the heart and lungs mandate combined heart–lung replacement. Some centres/surgeons also prefer heart–lung transplantation for idiopathic pulmonary arterial hypertension, which avoids issues in the immediate post-transplantation period with a severely dysfunctional right ventricle.

Single lung transplantation can be applied to most other diseases but is most effectively used in patients with pulmonary fibrosis (Fig. 18.16.2). In this situation, the underlying restrictive lung disease allows hyperinflation of the allograft, and as a consequence these recipients will often achieve near-normal spirometry despite only receiving a single lung. Older patients with emphysema can also benefit from single lung transplantation because longer-term functional requirements in this group are not as demanding as those in younger individuals. Additional benefits of single lung replacement include less blood loss, reduced cardiopulmonary bypass time, and decreased phrenic nerve injury.

Bilateral lung transplantation is performed as two sequential single lung transplantations and can be done via a sternotomy, a bilateral thoracotomy, or a ‘clamshell’ incision which involves a bilateral thoracotomy with transection of the lower sternum (Fig. 18.16.3). Heart–lung transplantation mandates cardiopulmonary bypass and is performed via a sternotomy or clamshell approach. Bilateral sequential single lung transplantation can be performed with or without cardiopulmonary bypass or with extracorporeal lung support (ECLS) depending on the underlying disease (e.g. severe pulmonary hypertension almost always requires cardiopulmonary bypass), and surgical/anaesthetic preference.



Fig. 18.16.2 Chest radiograph of a patient with a left single lung transplant for pulmonary fibrosis. Note the relative hyperinflation of the allograft compared to the native lung.

Surgical principles

Successful outcome from any form of lung transplantation requires observation of key surgical principles. Careful and unhurried dissection minimizes intra- and postoperative bleeding, and avoids damage to mediastinal (phrenic, vagus, and recurrent laryngeal) nerves. Careful implantation reduces the chances of vascular or airway anastomotic complications after transplantation. For example, trimming the donor main bronchus flush with the upper lobe take off and preserving the recipient airway enhances the bronchial

circulation and promotes better airway healing. Technical complications, are responsible for 11.8% of the early deaths reported in the latest ISHLT Registry.

Implantation and reperfusion should ideally be achieved within 6–8 hours, because shorter ischaemic times are generally associated with better immediate and short-term results, particularly when older donors are utilized, as there is less propensity for development of ischaemia/reperfusion injury (see next). Likewise, controlled reperfusion of the allograft(s) using low pressures over a prolonged (≥ 10 min) period is also associated with reduced risk of severe reperfusion injury and therefore improved early allograft function and outcome.

Immediate post-transplantation care

The first 24–48 h after reperfusion of the allograft(s) are critical for minimizing early complications and setting the scene for a good long-term result.

Ischaemia/reperfusion injury

Immediate postoperative care is aimed specifically at reducing the impact of the ischaemia/reperfusion injury that is sustained by all lung allografts to some degree, and is the underlying cause of primary lung allograft dysfunction, reported in the ISHLT Registry to be the most common cause (24.0%) of death within 30 days of transplantation.

The pathophysiology of this process involves injury to and consequent dysfunction of the pulmonary vascular endothelium, resulting in a breakdown of the normal alveolar–capillary endothelial barrier, the endothelial injury itself being perpetuated by ventilator-induced barotrauma and infection. This manifests as leakage of fluid into alveoli (pulmonary oedema) and impaired gas exchange and is essentially a form of acute lung injury, which in its severest form results in diffuse alveolar damage with all its consequences. Severe pulmonary oedema can be precipitated by injudicious fluid management, even in cases where the initial injury is only mild. Severe



Fig. 18.16.3 Chest radiographs taken before (left panel) and after (right panel) bilateral sequential single lung transplant in a patient with cystic fibrosis.

injury inevitably results in prolonged mechanical ventilatory support with the increased risk of infection and barotrauma, thus perpetuating the injury and potentially leading to irreversible damage to the allograft. Any bleeding requiring significant fluid resuscitation inevitably results in severe pulmonary oedema, the requirement for increased ventilatory support, which again will be associated with the aforementioned problems; hence all efforts should be made to ensure haemostasis at the conclusion of the transplant procedure.

With careful management, most cases of severe primary graft dysfunction will resolve over a few days. There is no specific treatment, although there are reports of the effective use of exogenous surfactant therapy instilled into distal airways via a fibre-optic bronchoscope. Nitric oxide can improve gas exchange and thus reduce ventilation pressures, but as yet has not been shown to alter outcomes. In the most severe cases, temporary support with extracorporeal lung support (ECLS) may be required while waiting for allograft recovery.

In addition to severe primary graft dysfunction, the other major cause of postoperative morbidity and mortality is infection, predominantly bacterial sepsis, which accounts for 19.1% of reported 30-day mortality.

Key issues in early postoperative management

Early extubation

Extubation is possible within 12 h of the procedure in most patients, and in many cases much earlier than this, which permits active coughing and clearance of secretions, the institution of enteral nutrition, and the early commencement of rehabilitation.

Fluid restriction and diuresis

This minimizes the development of pulmonary oedema, thus optimizing gas exchange and enabling early extubation. Colloid solutions are used for haemodynamic requirements, with vigorous diuresis achieved by regular administration of a loop diuretic (furosemide). Diuresis (removal of water) should not be discontinued simply because colloid is required to maintain filling pressures, and total input of oral fluids and intravenous crystalloid (combined) should be rigorously restricted to 1500 ml/24 h (or thereabouts) in association with vigorous diuresis for at least the first 48 h. Achieving a central venous pressure target of 4–6 mm Hg is critical early post-transplant.

Early mobilization

Patients with end-stage lung disease are usually debilitated and it is important they are mobilized and commence rehabilitation as early as possible. This prevents complications such as basal atelectasis and deep venous thrombosis, improves appetite, and promotes sleep. Most patients are able to sit out of bed within 24 h and can participate in a gymnasium programme by day 3. Adequate analgesia is imperative for effective rehabilitation at this early stage, with epidural anaesthesia very effective for pain control following thoracotomy or clamshell incisions. With a sternotomy approach, patient-controlled analgesia is normally sufficient.

Nutrition

Patients with end-stage lung disease are usually nutritionally compromised and an adequate calorie intake is necessary to overcome the severe catabolism stimulated by surgery. Enteral feeding can

usually be started within 24 h (either orally or via a nasogastric tube), but parenteral nutrition may be considered if the gut is not functioning as a result of gastroparesis or postoperative ileus.

A new issue that has been increasingly recognized as a potential cause of early allograft dysfunction is gastro-oesophageal reflux. This can be a particular problem in patients with cystic fibrosis, and can be exacerbated by mediastinal nerve injury (usually reversible) sustained during the transplant procedure. Such neural injury may contribute to the development of oesophageal dysmotility and gastroparesis. The problem is discussed in more detail next.

Prevention of infection

Bacterial infection remains one of the commonest problems encountered in the perioperative period and responsible for many deaths during the first 30 days. It is a significant factor in the exacerbation of ischaemia/reperfusion injury and acute lung injury, and is the final common pathway of death in most cases affected by this problem. The organisms encountered can be either donor or recipient derived, hence antibiotic prophylaxis (started immediately before transplantation) is tailored according to the recipient's known or likely microbiology, but can be modified once donor culture results are available.

Antibiotics are commonly administered until the patient is mobile, all drains have been removed, and respiratory secretions are clear. Antibiotics are chosen to cover *Pseudomonas aeruginosa* and *Staphylococcus aureus* in cystic fibrosis and other septic lung diseases, and patients with these conditions will usually have well-documented microbiology, antibiotic sensitivity, and drug allergy data available to aid in the choice of antibiotic. In other patients, community-acquired respiratory pathogens (pneumococcus, haemophilus, and others) and *Staphylococcus aureus* are targeted. Many units administer a broad-spectrum antibiotic such as vancomycin to cover the transplantation procedure and peri-transplant period until methicillin-resistant *Staphylococcus aureus* (MRSA) cultures are confirmed negative. However, despite the availability of effective antibiotics it should be stressed again that the most effective strategy for prevention of bacterial infection after transplantation is early extubation and mobilization.

Oropharyngeal candidiasis is common after transplantation and is effectively controlled with topical nystatin or amphotericin: routine systemic prophylaxis against candida is not generally necessary.

Aspergillus is the commonest cause of invasive fungal disease in the early postoperative period, and in both single and bilateral lung transplantation, any airway ischaemia renders patients at particular risk of developing this infection and its associated complications. They are at increased risk if exposed to high aspergillus loads, such as can occur in the setting of hospital building work (Figs. 18.16.4 and 18.16.5). Nebulized amphotericin prophylaxis given for the first month after transplantation is effective in reducing aspergillus-related problems. Added prophylaxis with azole preparations is dependent on local policy and experience. Documented aspergillus infection is treated with either liposomal amphotericin B or voriconazole, with an echinocandin (caspofungin or anidulafungin) or posaconazole used if these agents are ineffective or not tolerated. Widespread invasive disease may require combination therapy. Systemic azole therapy interacts with calcineurin inhibitors and an appropriate dose reduction is required to avoid drug toxicity.

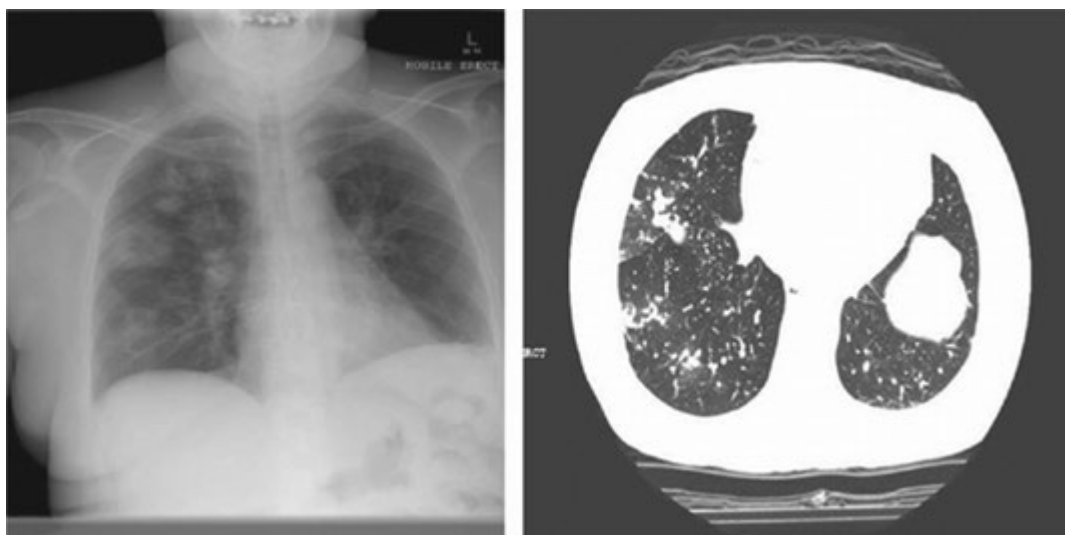


Fig. 18.16.4 Chest radiograph and CT showing invasive aspergillosis after bilateral lung transplant.

Viral infections (specifically herpesviruses) tend to occur later in the recovery period, but prophylaxis must be administered from the early stages to be effective. Ganciclovir is very effective in reducing both the incidence and severity of cytomegalovirus (CMV)-related illness. There is no consensus on the optimal prophylaxis regimen. Some units have opted for a combination of intravenous for the first week followed by oral therapy with valganciclovir for 3–6 months. The oral formulation of ganciclovir (valganciclovir) is well absorbed

and achieves equivalent blood concentrations to intravenous therapy. CMV mismatched transplant recipients (donor CMV positive, recipient CMV negative) are at the highest risk of developing CMV disease and will require a period of prophylaxis, often followed by a period of monitoring of CMV viral load by polymerase chain reaction. Herpes simplex virus, which most commonly causes mucocutaneous infection and occasionally lower airway infection, is also effectively covered by ganciclovir.

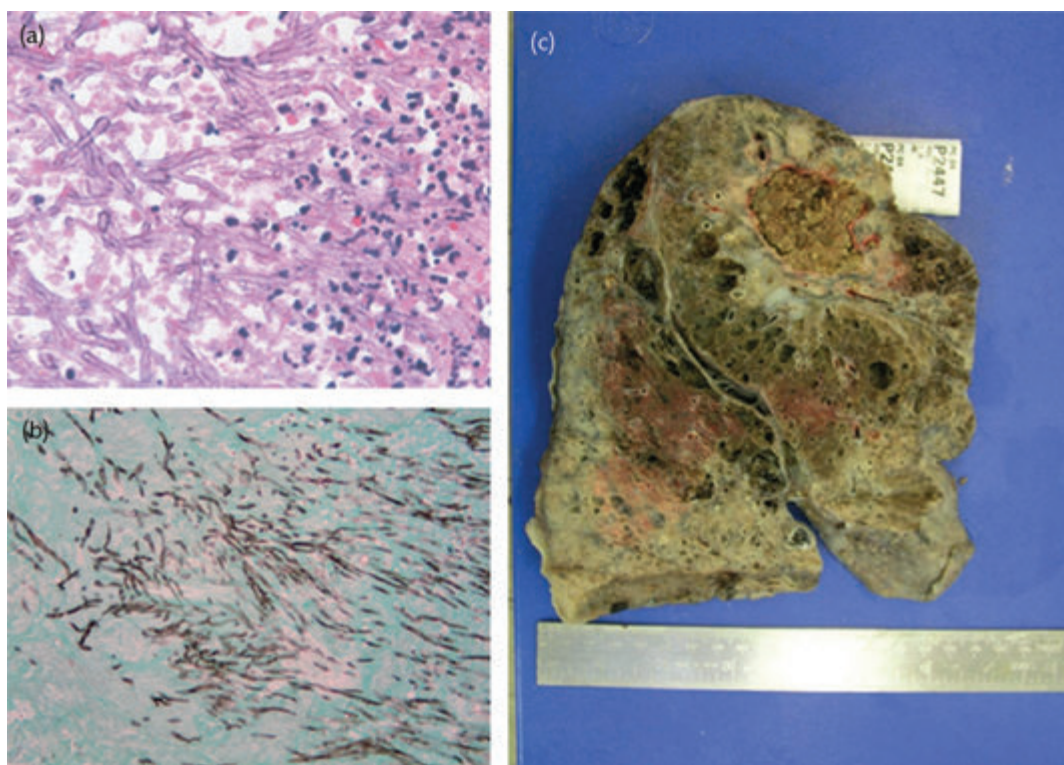


Fig. 18.16.5 (a) Hyphae of aspergillus seen in sputum. (b) Hyphae of aspergillus seen within a heart valve in a case of aspergillus endocarditis after bilateral sequential single lung transplant. (c) Aspergilloma in the upper lobe of an explanted lung.

Co-trimoxazole prophylaxis is effective in preventing both pneumocystis infection and toxoplasma reactivation. Standard therapy is 480 mg daily or 960 mg three times a week. Therapy is usually continued for a minimum of 12 months but in some units is given lifelong. Nebulized pentamidine or oral dapsone are effective alternatives for those who cannot tolerate co-trimoxazole.

Immunosuppression

Three phases of immunosuppression are used in lung transplantation—induction, consolidation, and maintenance. Although the details of the exact combinations and doses of agents used vary from unit to unit, the principles are similar.

Most regimens employ a combination of three agents: a calcineurin inhibitor (CNI—cyclosporin or tacrolimus); a lymphocyte proliferation inhibitor (azathioprine or mycophenolate); and a corticosteroid (usually prednisolone). Induction therapy, given either immediately before or after transplantation, is used variably in lung transplantation according to individual unit protocols and/or individual patient requirements. There is no consistent or conclusive evidence that induction with any agent is associated with better or worse outcomes compared with no induction therapy, but data from the ISHLT Registry shows a small favourable impact of induction therapy on long-term survival (conditional on 14-day survival) in lung transplant recipients. There are, however, other benefits of using an induction regimen, such as the ability to introduce CNI therapy more slowly in patients with renal dysfunction, and a reduction in the number of episodes of acute rejection.

Induction agents

Induction agents commonly used are antithymocyte/antilymphocyte globulin (ATG/ALG) and interleukin-2 receptor (IL-2R) antagonists. ATG and ALG are polyclonal immunoglobulin preparations derived from animals (typically rabbit or horse) and directed at CD3 positive cell including T-lymphocytes. Use of one of these agents for 3–7 days is associated with profound depletion of circulating T cells, as well as nonspecific immunomodulatory effects which also appear to affect B-cell functions. Use of these agents can be associated with an increased incidence of side effects, the most important being infection and malignancy, but these are much reduced with shorter (3-day) and less intense courses such that the risk of infection at 1 year and malignancy at 10 years is no different from a cohort who received no induction therapy.

Monoclonal antibodies directed at IL-2R are increasingly being used for induction in lung transplantation, with evidence for this practice being extrapolated from other solid organs, particularly kidney, or taken from small clinical series. IL-2 is an important signalling molecule leading to the proliferation of activated T cells, hence blocking this signal is very effective at reducing T-cell alloreactivity. The safety and side effect profile of these agents (either daclizumab or basiliximab) appears to be excellent.

Calcineurin inhibitors

Calcineurin inhibitors (CNIs) are the cornerstone of immunosuppressive regimens in all solid organ transplants: they work by preventing IL-2 production by T cells. Cyclosporin and tacrolimus are the two agents used from this class of drugs. Although they have similar immunosuppressive efficacy, there are several important differences in side effect profiles which dictate use of one or other

agent in individual patients. Cyclosporin causes upregulation of TGF β production and as such contributes to the growth of tissue in general. This can result in cosmetic issues with hirsutism and gum hypertrophy, and overgrowth of nasal polyps, particularly in patients with cystic fibrosis. For this reason, tacrolimus is often substituted for cyclosporin at the onset of bronchiolitis obliterans syndrome in an attempt to reduce airway scarring (see next). Tacrolimus is also diabetogenic, whereas cyclosporin is not. Both agents list nephrotoxicity, hypertension, and dyslipidaemia among their extensive side effect profiles.

Cell cycle inhibitors

These agents act to directly suppress lymphocyte proliferation at the bone marrow level. Azathioprine is a purine analogue, converted to 6-mercaptopurine in the liver. It inhibits the early stages of purine metabolism, as well as blocking several enzyme systems, leading to a reduction in the synthesis of nucleic acids. Its major side effects are bone marrow suppression and gastrointestinal (including liver) toxicity. Approximately 1 in 300 patients have a deficiency of thiopurine methyltransferase, the main enzyme in azathioprine metabolism. Such individuals are at heightened risk of adverse events with azathioprine and doses need to be reduced.

Mycophenolate mofetil (MMF) is an inhibitor of inosine-5'-monophosphate dehydrogenase (IMPDH) and works in a similar fashion to azathioprine, interfering with *de novo* DNA synthesis. Major side effects are gastrointestinal toxicity and bone marrow suppression. Mycophenolate may have additional clinical benefits in transplantation as it has a potent anti-B-cell effect, including inhibition of the Epstein–Barr (EBV)-driven B-cell replication responsible for post-transplantation lymphoproliferative disorders. Furthermore, in heart transplantation the use of MMF in standard immunosuppressive regimens has been shown to be associated with a significantly lower risk of developing malignancy in general.

Corticosteroids

Corticosteroids have several effects on the immune system, disrupting a variety of signalling and transcription pathways. This results in a nonspecific anti-inflammatory response, with a predominantly lympholytic action when used in high doses. Prednisolone is most commonly used in small oral doses in combination with a CNI and a cell cycle inhibitor as part of a triple immunosuppression maintenance regimen, or in high doses as intravenous methylprednisolone as part of the transplant induction regimen or for treatment of episodes of acute rejection or nonspecific allograft dysfunction, including organizing pneumonia.

mTOR inhibitors

Other immunosuppressive agents in clinical use include the mTOR (mammalian Target Of Rapamycin) inhibitors sirolimus and everolimus. These drugs are structurally similar to tacrolimus but work downstream of CNIs, interfering with the T-cell response to IL-2 signalling by preventing the progression of the T cell from the G1 to the S phase of the cell cycle. They also have a powerful antiproliferative action and hence are generally not used immediately after transplantation because of their adverse effect on wound healing, including airway anastomotic healing. Other major side effects include oral ulceration, skin rash, haematological (thrombocytopaenia, anaemia) disturbances, and dyslipidaemia.

In lung transplantation mTOR inhibitors have mainly been used in bronchiolitis obliterans syndrome because of their antiproliferative profile, and also as CNi-sparing agents in cases of significant renal impairment. However, caution should be exercised if these agents are used for the latter indication: some (but not all) trials in kidney and heart transplantation, and anecdotal reports in lung transplantation, have highlighted an unacceptably high rate of acute rejection when mTOR inhibitors have been used without any adjunctive CNi therapy.

Longer-term monitoring

The incidence of acute rejection and infection is highest in the first 3 months. Acute rejection episodes are uncommon after 6 months unless immunosuppression strategies are changed (either intentionally or through noncompliance), but infection remains an ever-present threat.

Baseline lung function is usually established by 6–9 months after transplantation, this level being used to define subsequent development of chronic lung allograft dysfunction in the form of bronchiolitis obliterans syndrome, discussed in detail next, which is the greatest threat to long-term survival and quality of life faced by lung transplant recipients.

The thrust of long-term management is to maintain allograft function and to minimize the side effects of immunosuppression. As a general principle, immunosuppression should be gradually reduced, but dose adjustments of all agents must be tailored to individual requirements, balancing the need to prevent acute rejection against minimization of adverse effects.

As time from the transplant increases, outpatient visits to the transplant centre occur less frequently. Monitoring of symptoms, chest radiography, and spirometry are the basis of lung allograft surveillance. Small handheld spirometers are used in some centres and enable daily home monitoring of lung function, with a 10% or greater fall in the forced expiratory volume in 1 second (FEV₁) prompting review and investigation of the cause.

Bronchoscopy and transbronchial biopsy are performed in the event of new onset allograft dysfunction. Acute rejection and infection cannot be distinguished clinically and may occur simultaneously, hence histopathological confirmation of the cause(s) of dysfunction is highly desirable. Some units perform regular surveillance transbronchial biopsies but there is no evidence that this improves long-term outcome compared to symptom-driven biopsies.

Specific complications

Many of the complications experienced by lung transplant recipients are common to all forms of solid organ transplantation and relate to immunosuppressive drug side effects, including the increased risk of infection. The following discussion focuses on issues specific to lung transplantation.

Rejection

As in all solid organ transplantation, the lung allograft is at risk of both acute and so-called 'chronic' rejection. These are defined not by their timing of occurrence after transplantation but by their histopathology and/or clinical presentation. Acute rejection can occur

at any time after transplantation and is directly related to the efficacy of the immunosuppression strategy used. Chronic rejection can occur early (in the first year after transplantation), but is more commonly seen after 2–3 years. The two processes can coexist. Histopathological criteria for the diagnosis and grading of rejection have been published by the ISHLT.

Hyperacute rejection

This is a very rare cause of primary graft failure in lung transplantation. It is caused by preformed anti-HLA antibodies in the recipient, which activate complement, leading to rapid destruction of the allograft. Plasma exchange, intravenous immunoglobulin, and specific anti-B-cell therapies such as intravenous cyclophosphamide and rituximab are used in this scenario.

Acute rejection

There are two types of acute allograft rejection: cellular and humeral (antibody-mediated). Acute cellular rejection is diagnosed via transbronchial biopsy and defined by perivascular or airway wall lymphocytic infiltrates of varying severity. Perivascular infiltrates are graded from minimal (grade A1) to severe (grade A4) and airway wall infiltration, also termed lymphocytic bronchiolitis, from mild to moderate (grade B1R) to severe (grade B2R). It is conventionally treated with high-dose intravenous methylprednisolone followed by an oral taper back to the maintenance dose, which is effective in most cases. Steroid resistant acute rejection is usually treated with adjunctive ATG, and if moderate to severe acute rejection occurs on two or more occasions it is now usual practice to change the background immunosuppression by either substituting tacrolimus for ciclosporin, or mycophenolate for azathioprine (or both), and/or adding an mTOR inhibitor.

Another emerging category of acute rejection is acute humeral rejection, also known as antibody-mediated rejection, involving the formation of donor specific antibodies generally against HLA antigens. It is defined by the presence of allograft dysfunction, detection of circulating donor specific antibodies, and complement deposition with C4d staining on transbronchial lung biopsy. Treatment consists of B-cell depletion using rituximab and antibody removal with plasmapheresis followed by intravenous immunoglobulin therapy.

Chronic lung allograft dysfunction

In lung transplantation, the term 'chronic rejection' is something of a misnomer, as both alloimmune and nonalloimmune processes may result in fibrotic obliteration of the airway lumen or fibrotic remodelling of the lung parenchyma. The term 'chronic lung allograft dysfunction', or CLAD, is therefore preferred.

There are now two main phenotypes of CLAD recognized (see Fig. 18.16.6). The commonest is bronchiolitis obliterans syndrome (BOS), which is a physiological entity defined by airflow obstruction on spirometry and histologically by airway fibrosis with or without accompanying vascular sclerosis. The other phenotype is restrictive allograft syndrome (RAS) which is characterized by a restrictive defect on spirometry and extensive parenchymal fibrosis, particularly in the upper lobes.

The fibroproliferative scarring characteristic of obliterative bronchiolitis leads to either total or subtotal obliteration of the affected airway lumen. This translates clinically into progressive airflow obstruction of varying severity, which can be easily measured using

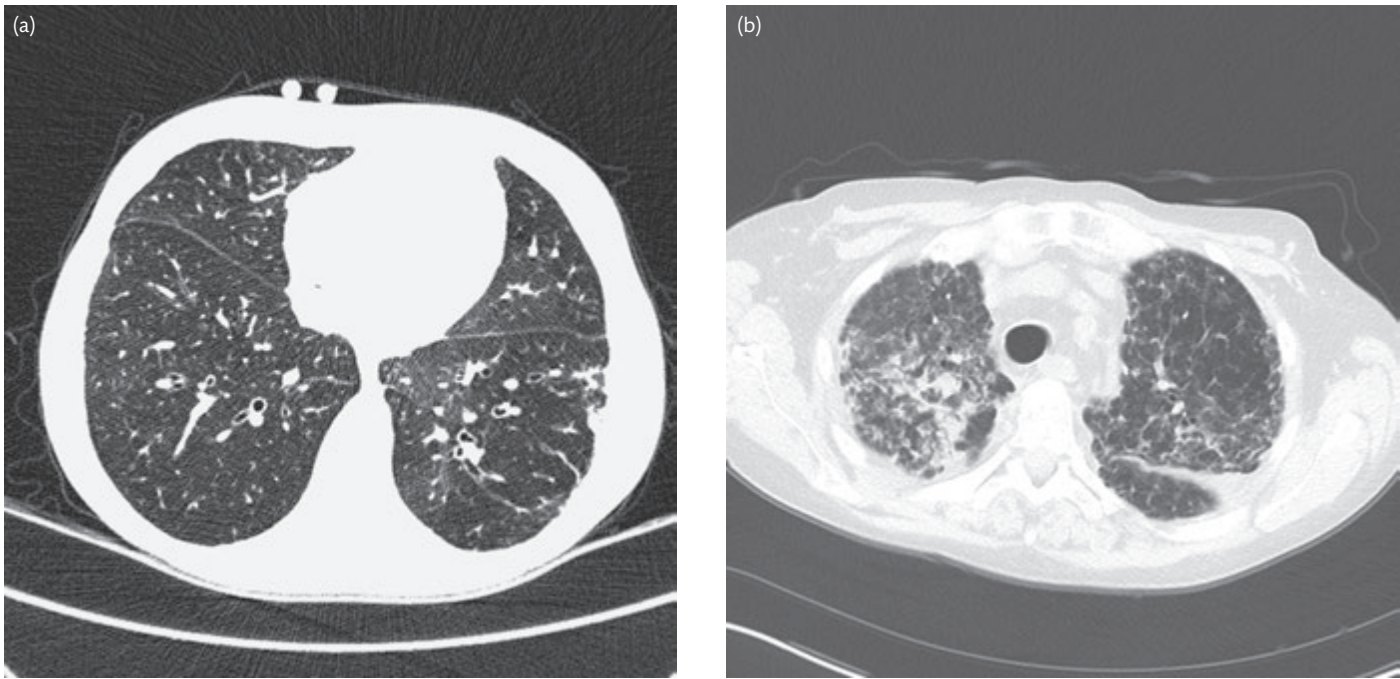


Fig. 18.16.6 Representative high-resolution computer tomography (HRCT) images of lung transplant recipients with chronic lung allograft dysfunction. (a) HRCT chest section through the lower lobe in a patient with bronchiolitis obliterans syndrome. Findings include mild bronchiectasis, focal mucous plugging peripherally, peribronchial thickening, and mosaic attenuation indicative of airways disease. (b) HRCT chest section through the upper lobe in a patient with restrictive allograft syndrome. Findings include patchy consolidation, relative volume loss in the right upper lobe and subtle interstitial thickening. Subsequent lung biopsy confirmed organizing pneumonia, diffuse alveolar damage, and interstitial fibrosis with accompanying cellular infiltrate.

spirometry, providing a useful noninvasive marker of the both the presence and severity of the condition. Bronchiolitis obliterans syndrome is defined and graded by a fall in FEV₁, as measured from baseline, defined as the average of the two best FEV₁ measurements achieved after transplantation, taken at least 1 month apart (Table 18.16.1). Reversible causes of a fall in lung function should be excluded before a diagnosis of BOS is made. It has been confirmed in a number of large series that bronchiolitis obliterans syndrome accurately reflects the presence and severity of obliterative bronchiolitis, and it is widely used in clinical practice for this purpose.

The number of severe acute rejection episodes remains the strongest risk factor for the development of obliterative bronchiolitis. However several nonalloimmune factors are increasingly recognized as independent risk factors including gastro-oesophageal reflux disease, infection with community respiratory viruses, *Pseudomonas aeruginosa*, or *Aspergillus* species. Obliterative bronchiolitis is the main cause of death in long-term survivors of lung

transplantation, with complicating infection precipitating respiratory failure being the most common terminal event.

The rate of progression of CLAD is variable. In some cases of BOS, the disease arrests spontaneously and patients can live for many years with significant airflow obstruction. In many cases the condition slowly progresses, and increases morbidity and contributes to early mortality. In a subgroup of patients, BOS may progress very rapidly and lead to early onset respiratory failure and death despite all attempts to intervene. The prognosis in patients who develop the RAS form of CLAD is now recognized to be worse than that in most cases of BOS.

Although CLAD is often given a label of ‘chronic rejection’, augmented immunosuppression is rarely effective and substantially increases the risk of infection. Most experienced centres change immunosuppression early in the disease process, focusing on antiproliferative strategies, with the substitution of ciclosporin with tacrolimus and the use of mycophenolate and mTOR inhibitors. It is common practice to reduce immunosuppression levels in an attempt to minimize the impact of infections. Other immunomodulatory therapies used to treat BOS include total lymphoid irradiation or extracorporeal photopheresis (ECP), which have both been shown in single centre experiences to slow or even halt disease progression. Selected patients may be considered for retransplantation.

The biggest advance in the treatment of potential BOS has come from the use of low-dose azithromycin to modulate airway inflammation. It is now accepted that approximately 30–40% of patients who develop clinical features of BOS will show a response to azithromycin by either stabilizing or partially/fully reversing their fall in lung function. Two randomized controlled trials have confirmed the beneficial effects of azithromycin given either early after transplant to reduce the

Table 18.16.1 Classification of bronchiolitis obliterans syndrome

Baseline	Average of two best FEV ₁ measurements achieved post-transplantation, taken at least 1 month apart
Bronchiolitis obliterans syndrome	
Grade 0	FEV ₁ >80% baseline
Grade 1	FEV ₁ 66–79% baseline
Grade 2	FEV ₁ 51–65% baseline
Grade 3	FEV ₁ <50% baseline

incidence of BOS and also given after BOS diagnosis to improve lung function. Unfortunately, some of those who initially responded to azithromycin will subsequently develop progressive BOS again.

Malignancy

Solid organ and lymphoid malignancies occur at an increased frequency in lung transplantation, affecting up to 4% of recipients. Post-transplant lymphoproliferative disease (PTLD) is frequently related to EBV-driven B-cell proliferation and to the intensity of immunosuppression, and in a small number of cases to primary EBV infection in EBV-naïve recipients. In lung transplantation most cases of lymphoproliferative disorder are focused in the allograft, with most occurring in the first 12–18 months after transplantation. Patients are usually treated with dramatically reduced background immunosuppression, which involves reducing calcineurin inhibitor levels to 30–50% of previous maintenance levels, stopping the cell cycle inhibitor, and reducing prednisolone. Careful monitoring for acute rejection is required once levels of immunosuppression have been substantially reduced.

If the PTLD does not show regression with reduce immunosuppression or if the disease is threatening organ function, rituximab is administered for B-cell dominant tumours and CHOP-based chemotherapy is indicated for those who do not respond, or if histology demonstrates high-grade lymphoma. There are no evidence-based data to support these recommendations, which are based on clinical experience only. The prognosis of these disorders is surprisingly good, especially if confined to a single organ system and if disease responds to a reduction in immunosuppression, but patients diagnosed with advanced disease invariably have a poor outcome.

Occasionally, despite thorough donor screening, a lung malignancy will be transplanted into the recipient. Inevitably this will lead to the development of clinically significant disease, although surprisingly this may not occur for many years.

Airway complications

The bronchial anastomosis is devoid of its normal bronchial arterial supply and therefore prone to the development of problems

relating to ischaemia and subsequent scarring (Fig. 18.16.7). These range from asymptomatic narrowing (often related to size mismatching of the donor and recipient airway) to severe stenosis requiring intervention, and occasionally to dehiscence and death. Areas of ischaemic airway are at increased risk of infection, particularly with fungi, and care is needed to ensure organisms such as *Aspergillus* species do not worsen the viability of the anastomosis.

Most units experience an airway complication rate of between 5 and 10%. Bronchial artery revascularization procedures are time-consuming, technically demanding, and not widely performed. Bronchial stenoses are effectively treated with airway dilatation and stenting, which is optimally performed after the early inflammation related to ischaemia and infection has resolved (Fig. 18.16.8).

Heart–lung transplantation is rarely associated with airway complications as the tracheal anastomosis has a collateral blood supply derived from the coronary arteries and is generally not ischaemic.

Gastro-oesophageal reflux

Gastro-oesophageal reflux disease (GORD) is common in lung transplant recipients. There is a high prevalence of GORD in patients with severe chronic lung disease before transplant but the risk of intraoperative vagal nerve injury and the side effects of post-transplant medication can cause sphincter dysfunction and delayed gastric emptying, which significantly exacerbate the problem. It can be strongly suspected if transbronchial biopsy of the allograft reveals food matter or highly positive Oil Red O staining, and should be considered if there are recurrent acute episodes of allograft dysfunction, particularly if associated with organizing pneumonia. The condition is asymptomatic in upwards of 60% of lung transplant recipients because of the widespread use of proton pump inhibitors. It is a particular problem in the patient with cystic fibrosis. There are no standardized approaches to screening for GORD after lung transplant. Some centres refer all patients for routine 24 h pH monitoring and oesophageal manometry at 3 months post-transplant, whereas others will refer

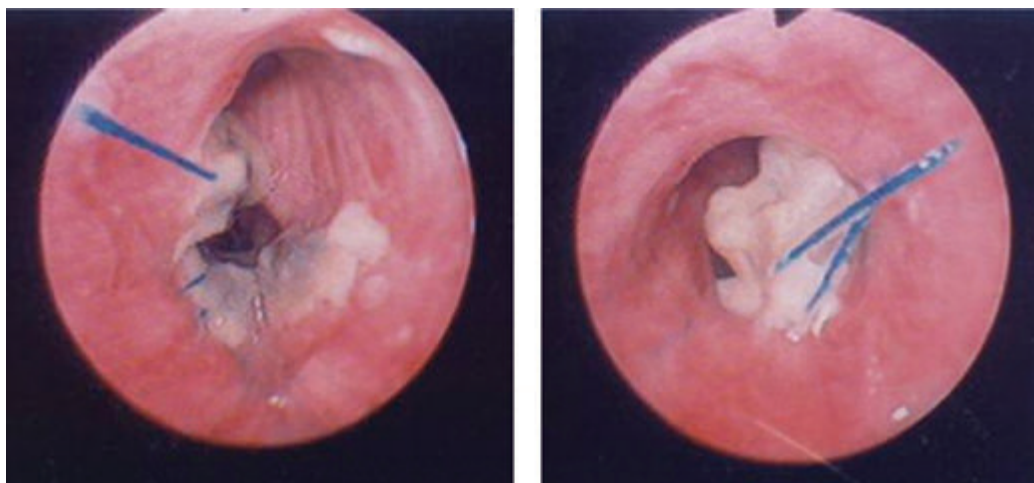


Fig. 18.16.7 Appearance at 2 weeks of bronchial anastomosis with mucosal slough secondary to ischaemia: this airway would be expected to heal well.

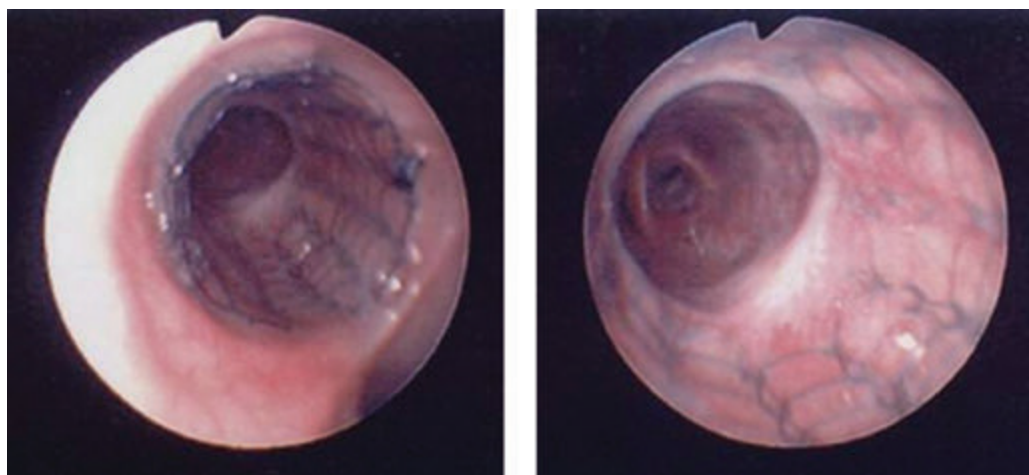


Fig. 18.16.8 An expanding metal 'ultraflex' stent in a bilateral sequential single lung transplant recipient.

symptomatic patients or those with unexplained allograft dysfunction. Laparoscopic fundoplication is the treatment of choice if significant reflux is demonstrated.

Outcome

Many studies have shown that lung transplantation confers significant survival and quality-of-life-benefits. Survival figures of 90% at 1 year, 70% at 5 years, and 50% at 10 years are now achievable for all types of lung transplant and underlying disease categories.

The main contributor to mortality in the first 12 months is infection (predominantly bacterial). Acute rejection rarely causes death directly. CLAD is the main factor determining long-term survival in most lung transplant recipients. Coronary artery vasculopathy affecting the cardiac allograft in a heart–lung transplant occurs predominantly in the setting of CLAD, and it is the airway disease that dominates the clinical picture long term in all forms of lung transplantation.

Survival is usually associated with markedly improved lung function that translates into improved functional capacity. As long as lung function is maintained (implying an absence of bronchiolitis obliterans syndrome), quality and quantity of life are maintained. Many patients are able to return to work and live a near-normal life.

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