Lung Transplantation

5

5.1 Epidemiological, Clinical and Surgical Considerations

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CONTENTS

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5.1.1 Introduction

The first human lung transplantation (LuTX) was performed by Dr James Hardy (Hardy et al. 1963) in June 1960 at the University of Mississippi in a patient with unresectable lung cancer and obstructive pneumonitis. The patient received immunosuppression with azathioprine (Aza) and irradiation, but he died due to renal failure after 17 days.

Surgeons in the United States, Canada and Europe performed about 40 human lung transplantations between Hardy's operation and the end of 1980. But success was limited by anastomotic healing problems immediately after the operation, technical complications, infections and the inability to differentiate infection from rejection. Improvement of bronchial anastomotic healing was achieved by

introducing ciclosporin (CsA) and reducing the dose of corticosteroids.

In 1983 the Toronto Lung Transplant Group (1986) performed the first single-lung transplantations for patients with end-stage chronic obstructive pulmonary disease and advanced pulmonary fibrosis. Their technique was later expanded to bilateral sequential single-lung transplantation for patients with bronchiectasis and cystic fibrosis.

More recently, use of living donors for lobar allografts has been demonstrated to be a useful alternative for selected patients who require isolated lung transplantation.

5.1.1.1 Survival, Indications and Contraindications

Despite the wide acceptance of LuTX as a treatment option for patients with end-stage lung disease, the long-term outcome of this procedure is inferior compared with the results of other solid organ transplants. However, at experienced transplant centres 1-year survival rates have increased recently, achieving more than 85% in selected patients. Survival rates depend on recipient age, underlying disease, physical status at the time of transplantation, comorbidities and other factors (Fig. 5.1.1) (Hertz et al. 2002).

To date more then 15,000 lung transplantations have been performed worldwide, indications have been expanded (Fig. 5.1.2; Table 5.1.1) and more patients are being accepted as recipients despite being older or having comorbidities.

The main indications (Glanville and Estenne 2003) are chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), primary (PPH) and secondary pulmonary (SPH) hypertension and cystic fibrosis (CF), but also rare diseases (Saleem et al. 2005) such as lymphangi-

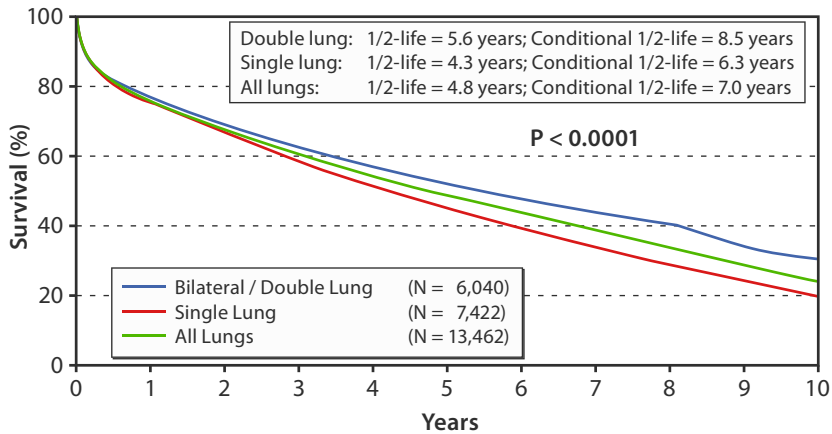

Fig. 5.1.1. Adult lung transplantation: survival

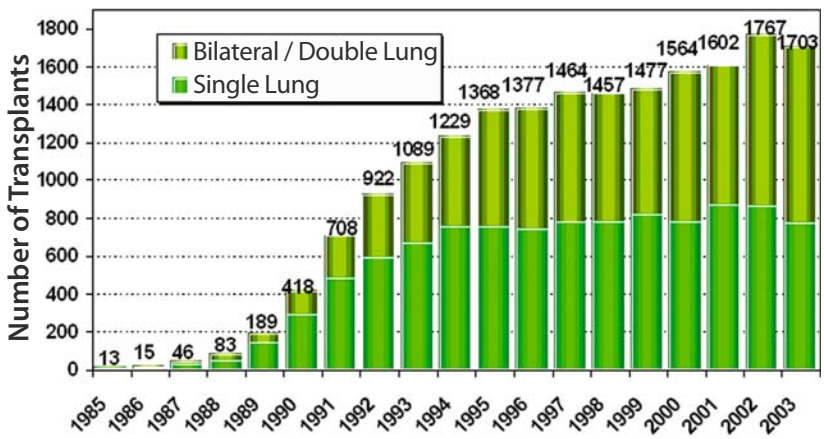

Fig. 5.1.2. Number of lung transplants reported by year and procedure type

Table 5.1.1. Indications for lung transplantation

Lung emphysema/COPD
Cystic fibrosis
Idiopathic pulmonary fibrosis
Alpha-1-antitrypsin deficiency
Primary pulmonary hypertension
Re-transplantation
Secondary pulmonary hypertension
Lymphangioleiomyomatosis
Langerhans' cell histiocytosis
Sarcoidosis

oleiomyomatosis (LAM), Langerhans' histiocytosis, alveolar cell carcinoma and sarcoidosis have gained more acceptance as indications for transplantation.

Absolute (Boe et al. 2003) contraindications to LuTX include serious dysfunction of the kidney and liver, active extrapulmonary infection, current tobacco use or other substance abuse (e.g. alcohol, narcotics), progressive neuromuscular disease and active malignancy within the past 5 years.

Relative contraindications include medical conditions of the recipients that are felt to potentially impact on the long-term outcome and should be optimally treated and well controlled prior to surgery [diabetes mellitus, systemic hypertension and peptic ulcer disease, osteoporosis, age, body mass index (BMI) < 18 or $> 25–30$ kg/m^2, steroid dose > 20 mg/day].

5.1.1.2 Immunosuppression

The majority (Knoop et al. 2003) of lung transplant recipients receive a triple-drug maintenance regimen including calcineurin inhibitors [CsA or tacrolimus (Tac)], cell-cycle inhibitors [mycophenolate mofetil (MMF), sirolimus, everolimus] and steroids (Fig. 5.1.3). Equal proportions receive CsA and Tac. There is also a trend to prescribe MMF instead of Aza. Steroid withdrawal is uncommon even 5 years after transplantation. The use of induction therapy with poly- or monoclonal antibodies is discussed controversially and differs between transplant centres.

A high-dose intravenous steroid pulse is the standard treatment for uncomplicated acute rejection. A switch from CsA to Tac is the first treatment step of refractory acute rejection followed by high-dose steroids or antilymphocyte agents, total lymphoid irradiation or extracorporeal photopheresis.

The treatment of chronic rejection is challenging and includes different strategies such as modification of the maintenance regimen, augmentation of the immunosuppressive medication, addition of inhaled immunosuppressant or other immunomodulatory treatments.

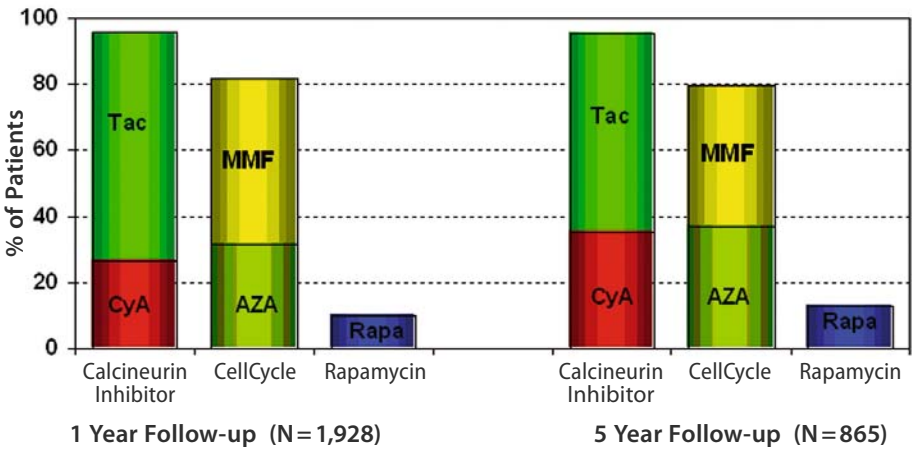

Fig. 5.1.3. Adult lung recipients. Maintenance immunosuppression at time of follow-up for follow-ups between January 2001 and June 2004

5.1.1.3 Transplant Procedures

Single-lung transplantation is the most common form of transplantation used in patients with COPD and IPF. Due to organ scarcity other TX techniques, such as lobar and split lung transplantation, are used and allow the use of living donors especially in younger patients.

Double-lung TX is mandatory for all infectious lung diseases, for example cystic fibrosis, chronic infected obstructive lung diseases and in most cases of severe pulmonary hypertension.

Bilateral LuTX is performed as two subsequent single LuTXs, replacing one side after the other through a transverse thoracosternotomy or through minithoracotomies.

Combined (Boe et al. 2003) heart-lung transplantation is indicated in cases of end-stage lung disease with irreversible heart failure and in patients suffering from complex Eisenmenger's syndrome.

5.1.2 Pretransplant Evaluation and Imaging

5.1.2.1 Recipient Evaluation

Different imaging techniques play an important role in evaluating patients for lung transplantation, predicting transplant risk and searching for comorbidities.

The following radiological investigations are performed routinely in lung transplant candidates:

- Chest CT and radiograph
- Thoracoabdominal CT scan
- Abdominal ultrasound
- Ventilation/perfusion scan especially for single LuTX
- Sinus CT (in cystic fibrosis).

Radiology, together with pathology, is necessary to establish the accurate diagnosis of the candidate's lung disease. In combination with functional diagnostic methods, imaging methods are important for calculating the loss of functional lung tissue, finding the optimal time of referral and finally helping to decide the appropriate surgical technique in each distinct case.

For patients with emphysema (Slone et al. 1998), imaging studies have been useful for selecting patients for surgical interventions, such as bullectomy and lung volume reduction surgery (LVRS), both methods being used as bridging techniques to LuTX.

5.1.2.2 Donor Evaluation

Typically a donor is an intubated ventilated patient; brain death diagnosis should be initiated and the transplant team be sent information about the patient's history and cause of death. A recent chest radiograph is performed to evaluate infectious or posttraumatic lesions and to compare donor and recipient size and measured or calculated lung volume.

Basic criteria for consideration for lung donation now comprise an organ donor with a lack of significant pulmonary disease, although donors with mild asthma may be accepted, and a chest radiograph demonstrating one clear lung field. A multiorgan donor with pneumonia or severe contusion to one lung may be a satisfactory single-lung donor.

Pneumonia, trauma, pneumothorax, hematothorax, effusions and solid tumours are radiographically visible.

Aspiration, atelectasis and pneumonia are common in potential donors, and therefore endotracheal suctioning, percussion, turning for postural drainage and occasional manual lung inflation are critically important. Mucopurulent secretions are frequent in donors with a normal chest radiograph and do not preclude lung donation.

The current definition of brainstem death is based on coma, absent brainstem reflexes and apnoea, with the criteria for organ donation listed in Table 5.1.2.

Table 5.1.2. Minimum donor criteria for organ donation. From Boe et al. (2003)

Patient meets criteria for brainstem death
Absence of malignancy with metastatic potential
Absence of sepsis or communicable disease

5.1.3 Imaging During the First 3 Months After Transplantation

5.1.3.1 Normal Appearance

5.1.3.1.1 At the ICU

After arrival at the intensive care unit (ICU) patients are always monitored by arterial and Swan–Ganz catheter measurements. Arterial blood-gas, cardiac output and urine production are measured and the position of the endotracheal tube has to be checked.

Sometimes extracorporeal membrane oxygenation (ECMO) or cardiopulmonary bypass is required, especially in patients with pulmonary hypertension, to protect the pulmonary circulation and the left ventricle from volume overload. After single-lung TX double-lumen tracheal tubes are sometimes used to ventilate both lungs separately for some hours to avoid hyperinflation of the native emphysematous lung.

Chest tubes are obligatory for the first few days: two tubes are placed on each transplanted side. The quantity and quality of the fluid have to be monitored and postoperative bleeding has to be detected by measuring the haemoglobin value of the pleural fluid.

The first thoracic radiograph, which is performed immediately after arrival at the ICU, gives important information (see Table 5.1.3). It provides evidence relating to the presence of oedema or atelectasis, pneumothorax, lung expansion and size, and position of the diaphragm and mediastinum. If some form of lung shadowing is recognized, a differential diagnosis has to be made and the resulting therapeutic interventions have to be initiated (see Sect. 5.1.4).

Table 5.1.3. Interpretation of chest radiograph shadowing post lung transplant

	Time after transplantation (h)	
	< 24	> 24
Diffuse	Overhydration Reperfusion injury	Overhydration Rejection Late reperfusion injury
Localised	Surgical residua Localized graft injury Haemorrhage pleural fluid accumulation	Pneumonia Pleural fluid accumulation
Lobar	Vascular problem Obstructing clot	Vascular problem Sputum plug Pneumonia

5.1.4 Complications

5.1.4.1 Complications of the First 24 H

5.1.4.1.1 Size Mismatch

Size mismatch of donor lung and recipient hemithorax can cause mechanical and infectious problems. Therefore, a careful pretransplant evaluation of donor lung size is essential to reduce postoperative problems. If the implanted lung is too large, atelectasis can occur with subsequent severe infection problems. Possible solutions to overcome this problem include intraoperative size reduction or use of single lobes.

A mismatch of 25%–30% is acceptable but size mismatch less than 10% would be ideal (Massard et al. 1993).

Chest radiograph, thoracic CT and lung function with body plethysmography are important to assess the size of donor and recipient lungs, one of the most important criteria for defining the matching donor.

5.1.4.1.2 Pneumothorax

See Sect. 5.1.4.2 for complication after 24 h.

5.1.4.1.3 Reperfusion Oedema/Reimplantation Response (RIR)

The reimplantation response is a type of noncardiogenic pulmonary oedema resulting from the unavoidable trauma associated with transplantation (Montefusco and Veith 1986). The aetiology is unknown but considered to be secondary to a com-

bination of surgical trauma, ischaemic damage to capillaries, denervation, and interruption of lymphatic drainage, surfactant deficiency and different coagulation factor disturbances (Collins 2000).

Some degree of reperfusion oedema is present in almost all lung transplant recipients.

Management of this problem includes exclusion of other differential diagnoses (particularly pulmonary venous obstruction) and supportive therapy in terms of oxygen, NO and the avoidance of fluid overloading. However, running the patient dry in these early days can lead to significant short- and long-term renal impairment.

Radiographically, a diffuse alveolar pattern of infiltration or reticulonodular change is identified in the perihilar and basilar regions of the transplanted lung. Abnormalities are first detected on the chest radiograph at 24–48 h postoperatively. The changes reach a peak before day 4 and begin to resolve by day 5. In the majority of cases, complete resolution should be achieved by day 14. The differential diagnosis of this alveolar and interstitial infiltration also includes acute rejection and pneumonic infiltration. Localized densities can occur for a variety of reasons.

Histologically diffuse alveolar damage (DAD) or BOOP-like reactions (BOOP is bronchiolitis obliterans organizing pneumonia) are described. Any change in the chest X-ray beginning after day 5 should be assumed to be due to some other cause such as infection or rejection.

Use of CT scan seems of no diagnostic benefit; X-ray investigation together with the clinical picture, histology and time course should fix a diagnosis of RIR.

5.1.4.2 Early Complications (< 1–2 Months)

5.1.4.2.1 Pneumothorax, Transient Air Leak and Pleural Effusions

All patients experience pleural effusion ipsilateral to the transplanted lung in the postoperative period that requires drainage with thoracostomy tubes. In the initial phase after lung transplantation, pleural drainage is haemorrhagic in most patients but tends to self-limit and becomes progressively less haemorrhagic until becoming serous after 7 days (Judson et al. 1996).

Postoperative pleural complications occur in up to 22%. The most frequent complications are pneumothorax and empyema (Herridge et al. 1995). During post-transplant follow-up, the majority of surviving patients have residual pleural alterations detectable with CT. These alterations do not seem to worsen the progress of these patients, although they may be an inconvenience should re-transplantation be required.

Haemothorax and persistent air leak are associated with increased postoperative mortality. Chest CT shows pleural alterations in most patients 12 months after transplantation (Ferrer et al. 2003).

5.1.4.2.2 Phrenic Nerve Injury (PNI)

Injury of the phrenic nerve can be caused from stretching or direct instrumentation of the nerve and occurs after double-lung transplantation in up to 40% in different degrees. Paralysis of the diaphragm results in prolonged ventilation time and longer ICU time (Sheridan et al. 1995; Ferdinande et al. 2004).

Radiologic signs of PNI are atelectasis of the lower lobe or raised diaphragm.

Sheridan et al. (1995) evaluated 27 lung transplant recipients and found 8 with phrenic nerve injury, an incidence of 30%. An increased hospital stay was noted in these patients. In most cases, the event occurred in patients with bilateral LuTX and had little impact on lung function.

5.1.4.2.3 Reimplantation Response (RIR)

See Sect. 5.1.4.1.3.

5.1.4.2.4 Acute Rejection (AR)

Acute rejection (AR) of the lung manifests pathologically as infiltration of mainly lymphocytes in the perivascular and peribronchial/peribronchiolar regions. It is graded according to the intensity of the infiltrating cells and to the extent of lung parenchyma involvement. Air space oedema and mononuclear cells are also present features.

Acute rejection of the lung is graded according to the International Society for Heart Lung Transplantation (ISHLT) Working Formulation (Yousem

et al. 1996). Acute rejection consists of five grades ranging from A0 (no rejection) to A1–A4 (minimal to severe AR).

A diagnosis of AR should only be made when other possible causes of abnormal function or radiological shadowing are excluded histologically, microbiologically and clinically. Common differential diagnoses are infections and in the early postoperative period acute lung injury or reperfusion injury (Zenati et al. 1990). Usually AR develops during the first 6 months after transplantation, but any decrease in lung function or infiltrate on chest X-ray should be suspected as AR even years after transplantation.

In addition, AR tends to arise after the 5th postoperative day, in contrast to the reimplantation response that tends to become manifest within the first 48 h.

The clinical diagnosis of acute lung rejection includes the presence of fever, infiltrates on the chest radiograph, decreased oxygen uptake, exclusion of infection (by bronchial lavage, BAL) and a rapid improvement of symptoms after an IV steroid bolus but in some cases no clinical or radiological signs develop and AR is only diagnosed histologically. Almost all lung transplant patients experience at least one episode of AR.

Although the chest X-ray is relatively insensitive and nonspecific in the diagnosis of acute pulmonary rejection, it may be the first hint that rejection is occurring. Chest X-ray may be normal in 50%, others may show peribronchial thickening, areas of increased opacity, pleural effusions or consolidations (Ward and Muller 2000).

A radiographic response to treatment may confirm the suspicion of rejection. In most cases rejection is confirmed by transbronchial biopsy.

Findings on CT scan and HRCT are nonspecific and have a low positive predictive value. Herber et al. (2001) reported ten patients with proven AR, ground glass opacities, bronchial wall thickening, septal thickening, dilatation of the bronchus, pleural effusions and centrilobular densities with a specificity of 30%–50%.

5.1.4.3 Infection

Infection is a frequent cause of mortality and morbidity in lung transplant recipients. Direct communication of the transplanted lung with the atmosphere and impaired mucociliary action in an immunocompromised patient predispose them to bacterial, viral and fungal infections. Within the first postoperative month, bacteria and fungi are common causes of infection, while viral infections are common in the 2nd and 3rd months (Tables 5.1.4, 5.1.5). Transplanted infections of the donor or persisting microorganisms of the recipient, especially after single-lung transplant are sources of early postoperative infections. Although bacteria are responsible for the majority of infections following lung transplantation, fungal infections are associated with the highest mortality (Alexander and Tapson 2001).

Collins and co-workers (2000) identified 39 patients with 45 pneumonias. Of these 45 pneumonias, the most common single infectious organisms were *Cytomegalovirus* in 15 pneumonias, *Pseudomonas* in 7 pneumonias, and *Aspergillus* in 8 pneumonias. The most common CT findings of pneumonia were consolidation in 82%, ground glass opacification in 76%, septal thickening in 73%, pleural effusion in 73%, multiple nodules in 56%, and single nodules in 4% of pneumonias. There were no significant differences in the prevalence of findings among bacterial, viral and fungal pneumonias (Ward and Muller 2000).

Radiographic findings are often nonspecific and usually do not distinguish pneumonia from rejection, unless findings are present in the native lung. CT is useful for early detection of pneumonia and is helpful in directing bronchoscopy or transbronchial biopsy, and is very useful in following response to therapy.

5.1.4.3.1 Bacterial Infection

Bacterial pneumonia accounts for the majority of infections, generally occurring in the first 2 months. *Pseudomonas* and *Klebsiella* are the most common pathogens. The radiologic features of infection are generally nonspecific and sometimes subtle but CT, and in particular HRCT, is very helpful when making the diagnosis, showing consolidation, ground glass opacification and nodularity. The nodularity may have a tree-in-bud pattern (Collins et al. 2000). Diagnosis should be confirmed by bacteriology taken from bronchoalveolar lavage; transbronchial biopsy should be performed to distinguish pneumonia from AR, diffuse alveolar damage (DAD) or BOOP.

Table 5.1.4. Timeline of complications following lung transplantation that may require intensive care unit treatment (from Lau et al. 2004). (*BOS* Bronchiolitis obliterans syndrome, *CMV* cytomegalovirus, *GI* gastrointestinal)

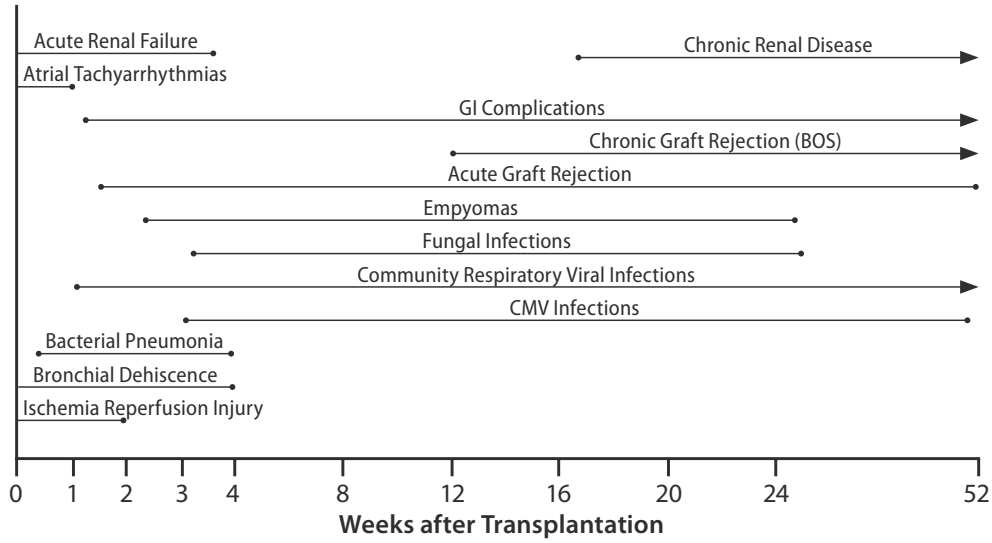

Table 5.1.5. Relevant infections after lung transplantation grouped according to type and frequency. (*CMV* Cytomegalovirus, *EBV* Epstein–Barr virus, *HIV* human immunodeficiency virus, *HHV* human herpes virus, *HSV* herpes simplex virus, *RSV* respiratory syncytial virus, *VZV* varicella zoster virus)

Group	Frequent	Infrequent
Bacterial	Bacterial bronchitis and/or pneumonia *Pseudomonas aeruginosa* Enterobacteriaceae *Staphylococcus aureus* *Enterococcus* *Haemophilus influenzae* Paranasal sinusitis Gastroenteritis	Atypical pneumonias Tuberculosis Nontuberculous mycobacteriosis Nocardiosis Anaerobic infections (actinomyces, etc.)
Viral	Herpes virus infections CMV EBV HSV VZV Viral respiratory tract infection Rhinovirus Parainfluenza virus Influenza virus RSV Adenovirus Viral gastroenteritis	HIV infection JC virus infection Polyoma BK virus infection HHV6? HHV7? Hepatitis B and C
Fungal	*Aspergillus fumigatus/niger/flavus* *Candida* species	Mucormycosis *Cryptococcal* infection *Penicillium* infection
Protozoa		*P. carinii* pneumonia Toxoplasmosis

5.1.4.3.2 Fungal Infection

Fungal (Kubak 2002) infections are a significant cause of postoperative morbidity and mortality in lung transplant recipients. The lung recipient remains continuously open to the environment and to the myriad of fungal spores and pathogens.

Early fungal infections are related to surgical complications or derived from the implanted lung; fungal infections after months 1–6 reflect opportunistic, relapsed, or residual infections. Late fungal infections are usually associated with treatments for chronic rejection or bronchial airway mechanical abnormalities.

Most frequent fungal infections in lung transplant recipients are related to *Aspergillus* species, followed by *Candida* and *Cryptococcus*. Infection with *Aspergillus* species can present in different forms, such as tracheobronchitis, bronchopneumonia, bronchocentric granulomatosis, angioinvasive disease, allergic bronchopulmonary aspergillosis, acute eosinophilic pneumonia, mycetoma and empyema. The identification of high-risk patients (preoperatively and postoperatively) is essential in implementing prophylactic or pre-emptive management.

The most frequent CT pattern in patients with invasive fungal infection is a combination of nodules, consolidation and ground glass opacities. The angioinvasive type of aspergillosis often has a typical CT appearance of a mass with surrounding ground glass opacity or halo sign. These masses or nodules may be multiple and some may go on to cavitate.

5.1.4.3.3 Viral Infection

Cytomegalovirus (CMV) pneumonia was the second commonest infection in transplant recipients with a very high mortality, occurring in up to 50% of patients in some series. It may be difficult to distinguish CMV infection from AR since the clinical signs and symptoms are usually similar; however, the timing of symptoms may provide a clue to the diagnosis as being CMV infection, which rarely occurs within the first 2 weeks after transplantation.

The chest radiograph in patients with CMV pneumonia may be normal or show ground glass opacities or reticulonodular opacities. HRCT is more sensitive and may help to guide the appropriate site for biopsy. The HRCT features of CMV infection include ground glass opacities, nodules which may tend to coalesce and consolidations.

When only ground glass opacification is seen on CT, *Pneumocystis carinii* pneumonia and AR should also be considered in the differential diagnosis.

5.1.4.3.4 Tuberculosis

Infections may be caused by reactivation of a primary infection in the recipient, reactivation of a lesion from the donor lung, or as a primary infection. The (Morales et al. 2005) increase in the number of solid organ transplants has resulted in an increased incidence of opportunistic infections, including infection by typical and atypical mycobacteria, with the risk of developing tuberculosis. Pretransplant chemoprophylaxis with isoniazid has become increasingly common in an attempt to prevent the disease. The source of infection in tuberculosis (TB) may be difficult to identify. There are few reports on TB in lung transplantation (Baldi et al. 1997; Miller et al. 1995).

The incidence of infections with tuberculosis ranges from 6.5% to 10%. In a series from Spain Morales and co-workers (2005) found a rate of 2.6% with a high mortality of 42.8% due to failing or not successfully completed treatment.

Malouf and Glanville (1999) found an incidence of 9% (23 patients of 261) with mycobacterial infections, 19 cases with pulmonary (*M. avium complex* $n=13$, *M. tuber* $n=2$, *M. abscessus* $n=2$, *M. asiaticum* $n=1$ and *M. kansasii* $n=1$) and 6 with extrapulmonary infections. Most episodes were treated and graft function improved in most cases. They concluded that mycobacterial infections, particularly due to nontuberculous mycobacteria, are relatively common after lung transplantation and may be an unrecognized cause of graft dysfunction.

Schulman et al. (1997) published two cases of pulmonary tuberculosis, both 3 months after bilateral lung transplantation, and found radiographically a narrowing of the middle lobe bronchus of the right lung caused by an endobronchial granulomatous mass (n=1) and a focal cluster of small nodules in the upper lobe of the left lung and small bilateral pleural effusions (n=1).

5.1.4.3.5 Bronchial Problems/Anastomotic Problems

The most common airway problems are anastomotic dehiscence and bronchial stenosis due to strictures. The reason is mostly a lack of perfusion of the bronchial tree, as the donor airways depend on a retrograde pulmonary-to-bronchial arterial circulation until revascularization of the bronchus wall occurs. Ischaemia is greater on the right main bronchus than on the left, therefore anastomotic healing is better on the left and early stenotic problems or dehiscence occur on the right anastomosis more frequently than on the left side. In the early years of transplantation the en bloc technique was mainly performed with a high incidence of tracheal dehiscence, which prompted the development of bilateral lung transplantation.

To reduce the risk of ischaemic airway problems the steroid dose was lowered in the early postoperative period and surgical tricks such as omental wrap or different sutures types were tried.

Airway dehiscence can be suspected when a pneumothorax with a persistent air leak occurs some days after the operation or anastomotic wound healing problems are detected via bronchoscopy.

Radiographically dehiscence can be detected by the presence of extrapulmonary peribronchial air on chest X-ray or CT. Using thin-section CT, small amounts of extraluminal air can be found and can lead to early interventions such as endobronchial stenting before infectious problems occur.

Delayed bronchial problems such as stenosis can be suspected when atelectasis occurs weeks or months after transplantation. Diagnosis of stenosis has to be confirmed by bronchoscopy and CT. Reasons for late bronchial stenotic problems are chronic infectious problems due to ischaemia and strictures due to shrinking bronchial walls.

5.1.5 Long-Term Follow-Up

5.1.5.1 Normal Appearance

In double-lung recipients the chest X-ray can appear without any pathology. If a size reduction has to be performed intraoperatively stapler devices can be seen. A raised diaphragm could give a hint of phrenic nerve injury. Pleural thickening is mostly seen on the lower parts of the lungs.

In single-lung recipients hyperinflation of the native lung in COPD patients can be observed. In contrast in IPF recipients the transplanted lung can impose hyperinflated.

5.1.5.2 Long-Term Complications

5.1.5.2.1 Chronic Rejection/BO(S)

Chronic rejection (bronchiolitis obliterans, BO) is the single most important cause of chronic allograft dysfunction and of late mortality after lung transplantation. It is an inflammatory disorder of the small airways leading to obstruction and destruction of pulmonary bronchioles and severe obstructive airway disease. This condition is difficult to prove using biopsy specimens, because BO may be patchy in distribution; therefore, a clinical term, bronchiolitis obliterans syndrome (BOS), has been in use for >10 years to describe the progressive decrease of pulmonary function (Verleden 2005). Following the ISHLT grading system BOS is graded BOS grade 0, 0p, 1, 2 and 3, depending on the decrease of forced expiratory volume in 1 s (FEV_1) compared to the best reproducible value reached after transplantation.

The recent incidence of chronic lung dysfunction due to BO is about 60% at 5 years post transplantation and this is one of the main indications for retransplantation.

Immune-mediated injury has been recognized as the leading cause of BOS, but recently nonimmune mechanisms, such as gastro-oesophageal reflux, have been recognized as potential cofactors. The results of various treatment options have generally been frustrating, therefore early diagnosis is needed to prevent or reverse progression of disease.

Bronchiolitis obliterans usually begins later than 3 months following transplant and manifests as dyspnoea, obstruction of the airways, recurrent lower tract infections and a rapid progression over months with a clinical course similar to that of COPD.

Several potential early markers such as lung function, BAL analysis, analysis of exhaled gases, breath condensate and CT are known and routinely

used to assess the time course of changes and to predict the decrease in lung function and the risk for BOS.

The radiographic features of BO are: peribronchial and interstitial opacities, bronchial dilatation, decreased vascular markings with areas of hyperinflation (best detected on expiratory CT), peripheral patchy consolidation and multiple pulmonary nodules 0.5–1.5 cm in diameter. The presence of air trapping on expiratory HRCT is a good indicator of the bronchiolar obliteration. In patients with BOS, areas with obstructed airways cannot empty and remain more radiolucent, while in areas that have normal airways the density increases during the expiratory phase. In a study by Bankier et al. (2001) five of six patients with initial false-positive findings (with significant air trapping but an $FEV_1 > 80\%$ of baseline) later developed BOS, which suggests that expiratory CT may contribute to the early detection of the condition. Conversely, air trapping has a very high negative predictive value, i.e. a low score of air trapping in a patient with declining lung function makes the diagnosis of BOS very unlikely. Quantification of air trapping using expiratory HR showed a good correlation between BOS grade and percentage of expiratory trapping, with a cut-off level of more than 32% as an early indicator for BO (Bankier et al. 2001).

5.1.5.2.2 Infections

See Sect. 5.1.4.3.

5.1.5.2.3 Post-Transplant Lymphoproliferative Disease (PTLD)

PTLD is a typical complication with an incidence of about 1%–3% and an onset 8–12 months post-transplantation. It is associated with EBV infection and induced through T-cell suppression due to CsA, Tac or MMF. Most cases are B-cell lymphoma with a significantly higher incidence after lung transplantation compared to other organs. PTLD can involve multiple organ systems, commonly lymph nodes cervical, GI tract, particularly distal small bowel, proximal colon or multicentric, or the lungs as a solitary mass, multiple nodules or as hilar lymph adenopathy.

Reduction of immunosuppressive medication, chemotherapy and B-cell antibodies are all therapeutic options.

Diagnosis is suspected on radiography and CT scan, but is confirmed by open lung biopsy or transbronchial biopsy.

5.1.5.2.4 Malignancies

An increased risk of developing certain malignancies is a recognized complication of organ transplantation. The patterns and incidence of malignancy in transplant recipients differ from those in the general population and are substantially influenced by the specific type of allograft and immunosuppressive therapy received (Penn 1993). The Registry of the International Society for Heart and Lung Transplantation has reported the incidence of malignancy at 1-year follow-up after lung transplantation to be 4.3%, with 50.7% due to lymphoproliferative disorders, and at 5-year follow-up to be 7.7%, with 17.8% due to lymphoproliferative disorders and 50.7% due to skin malignancies (Hosenpud et al. 2000).

Bronchogenic carcinoma develops in the native lung of transplant recipients with emphysema and pulmonary fibrosis at frequencies of 2% and 4%, respectively. The carcinomas most commonly manifest as a pulmonary nodule or mass on chest radiographs, with more nodules seen on CT scans (Collins et al. 2002). This rate is similar to that in other high-risk populations (e.g. elderly smokers with emphysema or other chronic lung disease). The majority of cancers are associated with a poor prognosis. The most common imaging manifestations are a solitary pulmonary nodule or mass.

5.1.5.2.5 Complications of the Native Lung

McAdams and co-workers (2001) published a series of 111 single-lung recipients and complications occurred in 17 (15%) recipients, most commonly due to infections or lung cancer, and this caused serious morbidity or mortality in 12 (71%) of the 17 patients affected. Infectious complications typically manifested as lobar or segmental opacities on chest radiographs or CT scans. Lung cancer manifested as a solitary, circumscribed nodule, multiple nodules, or a hilar mass.

Hyperinflation of the native lung is a specific problem of recipients of a single lung for COPD. Due to the progression of the underlying disease the obstruction increases and subsequent air trapping re-

sults in hyperinflation of the old lung and compression of the transplanted lung, producing increasing dyspnoea during exercise. Lung volume reduction surgery is the only therapeutic option, and perhaps endobronchial volume reduction is a future option in such cases.

5.1.5.2.6 Recurrence of the Underlying Disease

Recurrence of the primary disease in the transplanted lung has been reported for several diseases, for example sarcoidosis, pulmonary Langerhans' cell histiocytosis, giant cell interstitial pneumonia, LAM and bronchioloalveolar carcinoma.

Sarcoidosis is the most commonly reported recurrent disease. Milman et al. (2005) reported a recurrence rate of 50% in seven lung-transplanted patients without clinical significance.

Dauriat et al. (2006) described a recurrence rate of histiocytosis X (HX) of about 20% in 39 transplant recipients. The present authors transplanted 12 patients with histiocytosis X: 3 of them developed a recurrence during the first 3 years postoperatively, 1 received a re-transplantation and HX relapsed again 12 months after the redo surgery.

Boehler (2001) has reported that 1 in 34 patients transplanted for LAM developed recurrence of underlying disease.

There is controversy regarding whether bronchioloalveolar carcinoma should be accepted as an indication for LuTX. A recurrence of the disease within the donor lungs was noted in four of seven lung-transplanted patients by Garver et al. (1999). At the University of Birmingham Zorn et al. (2003) transplanted nine patients with bronchioloalveolar carcinoma and just two of them were free from recurrence.

In all cases of suspected recurrence of the primary lung disease standard radiography together with changes in lung function can give a hint of relapse, but a CT scan and transbronchial biopsy are necessary to confirm the diagnosis.

5.1.5.2.7 Bronchial or Tracheal Stenosis

See Sect. 5.1.4.3.5

5.1.5.2.8 Pulmonary Nodules

Schulman and co-workers (2000) assessed clinical and radiographic findings of pulmonary nodules and masses after lung and heart-lung transplantation. In total, 159 patients were followed by serial chest radiographs for a median of 27 months. Single or multiple lung nodules or masses were noted at chest radiography in 15 (9.4%) of 159 patients. Imaging findings and causes of these nodules and masses were reviewed retrospectively.

Infection was found in 10 (6%) of 159 patients. Specific pathogens (11 pathogens in 10 patients) were *Aspergillus* ($n=4$), *Mycobacteria* ($n=4$), and other bacteria ($n=3$). Noninfectious causes were found in 5 (3%) of the patients and included B-cell lymphoma ($n=2$), bronchogenic carcinoma ($n=2$), and pulmonary infarcts ($n=1$). Nodules and masses appeared a median of 11 months after transplantation (range: 0.2–36 months). Five patients (33%) had single lesions; the other ten (67%) patients had multiple lesions (range 2–50). *Aspergillus* lesions were most commonly located in the upper lobes, were cavitary in three of four patients, and all were fatal. Nodules and masses arose in the transplanted lung in 12 (80%) of the patients, and in the native lung in 3 (20%) of the patients (2 bronchogenic carcinoma, 1 *M. tuberculosis* simulating bronchogenic carcinoma).

Nodules and masses detected by chest radiography are not uncommon (9.4%) after lung and heart-lung transplantation. Infectious are more common than noninfectious causes of post-transplant nodules and masses. Specific clinical and imaging characteristics may provide clues to the aetiology (Schulman et al. 2000).

5.1.5.2.9 New Entities and Rarities

5.1.5.2.9.1 Fibrosis of the Upper Lobe

Konen et al. (2003) published HRCT findings in seven lung transplant recipients who developed a progressive lung fibrosis, predominantly in the upper lobes with relative sparing of the basal segments. This radiographic feature may represent a specific and rare type of rejection in lung transplant recipients. Clinical, laboratory, microbiological and

pathological studies did not reveal any specific findings that could explain a common mechanism in this group of patients.

5.1.5.2.9.2 Sirolimus-Induced Pneumonitis

Interstitial pneumonitis (Garrean et al. 2005) is an ill-defined side-effect of sirolimus, a new immunosuppressant drug recently introduced for patients after solid organ transplantation. Lymphocytic alveolitis and radiologic BOOP are the key findings in sirolimus-associated pneumonitis. Sirolimus withdrawal was associated with recovery within 6 months. Published first as occurring in patients after kidney transplantation, one case report describes a stable heart-lung transplant recipient who developed a pulmonary infiltrate that reversed after ceasing sirolimus therapy (McWilliams et al. 2003).

5.1.6 Imaging of Interventional Complications

5.1.6.1 Transbronchial Biopsies (TBB)

Scheduled bronchoscopies are performed routinely during the first year after transplantation at most transplant centres. Inspection of the anastomotic sutures, control of anastomotic wound healing, BAL with microbiologic cultures and transbronchial biopsies are taken to document lung tissue quality and to diagnose acute or chronic lung rejection, invasive infections and eventually to perform interventional procedures such as dilatation or stenting of bronchial stenosis.

One of the most common radiological findings after TBB is pneumothorax (incidence between 0.1%–3%), which is easily recognized on a chest radiograph. Postbioptic haemorrhage can present as small nodules or ground glass opacifications. They are most often seen in the periphery of the lung and may contain a small cavity. Clearing is generally seen over a 2-week period. The same picture can be seen after BAL taken mostly from the middle lobe or the lingula, when about 100 ml of saline is instilled but not completely removed.

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5.2 Imaging of Lung Transplantation

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5.2.1 Introduction

Between the performance of the first successful lung transplantation in 1988 (Hosenpud et al. 2000) and June 2004, there have been 3154 heart-lung and 19,296 lung transplantations recorded in the Registry of the International Society for Heart and Lung Transplantation (Trulock et al. 2005). The procedure has gained widespread acceptance as a therapeutic option for a diverse array of lung diseases. However, complications are frequent and result in constraints on long-term preservation of graft function and patient survival.

5.2.1.1 Indications and Contraindications

Lung transplantation is indicated for patients with end-stage lung disease who demonstrate declining function despite of optimal therapy (Trulock et al. 2005). Candidates for lung transplantation should have a chronic disease that is refractory to other medical or surgical therapies, and for which survival is limited to usually less than 2–3 years (Trulock et al. 2005). During the period from January 1995 to June 2004 the most frequent indications for lung transplantation were chronic obstructive pulmonary disease (COPD, 38%), idiopathic pulmonary fibrosis (IPF, 17%), cystic fibrosis (CF, 17%) and 1-anti-trypsin deficiency emphysema (9%) (Trulock et al. 2005) (Fig. 5.2.1). Critically ill patients in desperate clinical situations such as significant cardiac, renal, or hepatic impairment are rarely appropriate candidates for transplantation (Maurer et al. 1998). Further contraindications include uncontrolled infection, uncured malignancies as well as active cigarette smoking and/or other drug/alcohol dependency (Collins

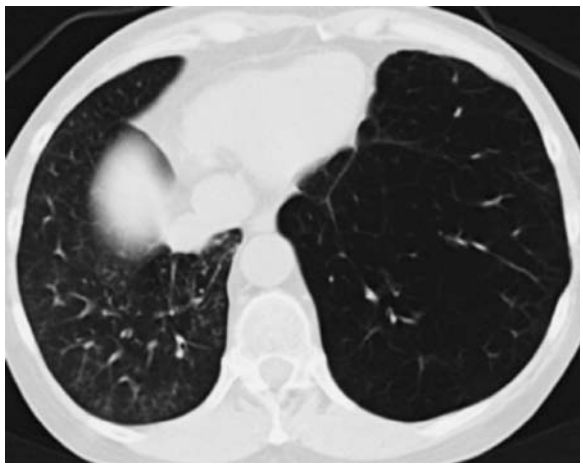


Fig. 5.2.1. Transverse CT section in a single right-lung transplant recipient. Native emphysematous lung (*left*) is overinflated, while the transplanted lung shows normal density

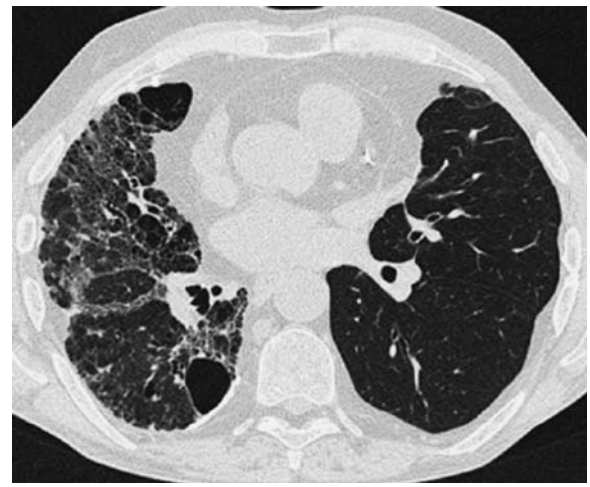


Fig. 5.2.2. Transverse CT section in a single-lung transplant recipient. Native fibrotic lung (*right*) shows increased density, whereas the density of the transplanted left lung is normal

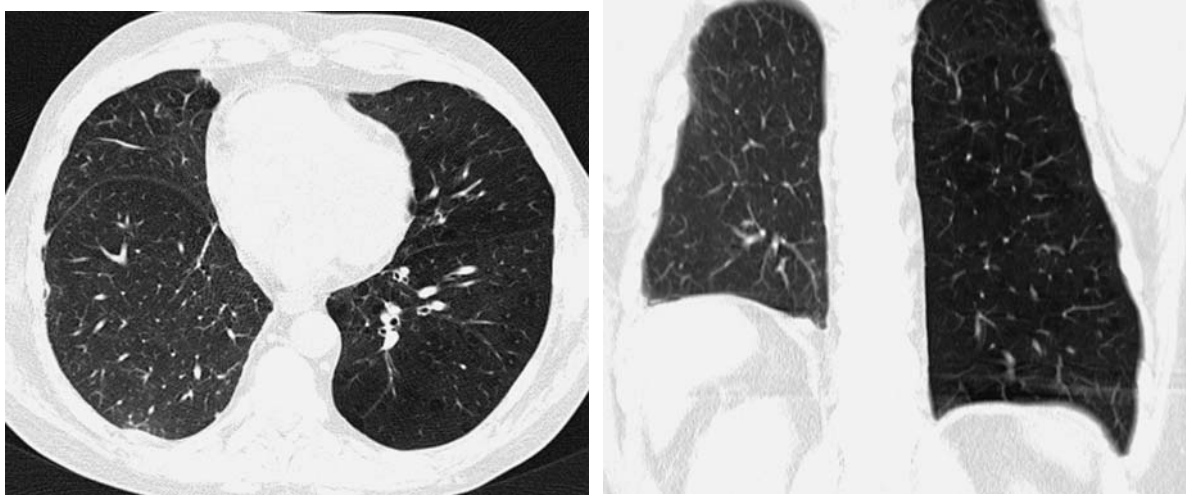
2002). Important considerations are also irresolvable psychosocial problems or noncompliance with medical management (Collins 2002).

5.2.1.2 Transplant Allocation

Prioritization on the waiting list according to the recipient's primary disease is considered the fairest allocation of donor lungs, since obvious waiting-list mortality differences depending on the primary disease exist (Glanville and Estenne 2003). For example, patients with IPF (Fig. 5.2.2), who have disproportionately high mortality rates while on the waiting list, are currently assigned a bonus of 90 days by the United Network for Organ Sharing of the USA upon registration on the active list (Glanville and Estenne 2003).

5.2.1.3 Surgical Procedures

The number of combined heart-lung transplantations has been rapidly declining, while the recently more common double-lung procedure has been surpassing in number the earlier dominating single-lung procedure since 2002 (Trulock et al. 2005) (Fig. 5.2.3). The decrease in donor organ pool by performing double-lung procedures is unsatisfactory considering the long waiting time of more than 18 months to receive lung transplantation (Trulock et al. 2005). This trend is, however, most likely motivated by better overall survival results, by better lung function and fewer occurring complications after double-lung transplantation (Trulock et al. 2005). To date, the procedure of choice is single or bilateral lung transplantation, with the limited number of donor organs determining the surgical approach in individual situations. The formerly common heart-lung transplantation under cardiopulmonary bypass is now rarely performed. Bilateral transplantation is usually performed sequentially with two single-lung transplants. If the rarely employed extracorporeal support is necessitated, it is instituted through the femoral approach. The surgical approach has been modified and the original clamshell incision has been replaced by two small anterior thoracotomies (Venuta et al. 2005). Donor shortage has led to the development of living lobar transplantation. In living lobar transplantation, one donor provides a right lower lobe, the other donor a left lower lobe to a single bilateral lobar recipient (Fig. 5.2.4). One transplant center describes an overall significant morbidity of 4.6% and no donor mortality in living donor transplantation (Starnes et al. 2004). The shortage of donor lungs suitable for children and small adults has led to the development of the "split-lung" technique. In this procedure, the left lung is separated into two lobes. The left lower lobe is used for left lung transplant and the left upper lobe for



a b

Fig. 5.2.3. a Transverse CT section in a single-lung transplant recipient. Transplanted lung and native lung show marked differences in size and density. **b** Coronal multiplanar reconstructed CT section in a different single-lung transplant recipient as **a**. Transplanted lung and native lung show marked differences in size and density

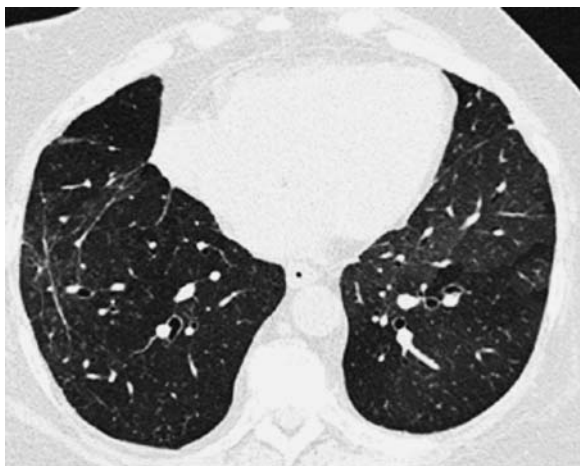


Fig. 5.2.4. Transverse CT scan in double-lung transplant recipient with two sequentially performed single-lung transplants. Lungs of different donors in the same patient show different sizes and densities

right lung transplant. The rotation of the left upper lobe into the right pleural space requires anastomizing the membranous portion of the bronchus to the cartilaginous ring on each of the donor and recipient side. This technique allows bilateral lung transplantation to be performed in a small-size recipient with excellent short- and long-term outcome (Artemiou et al. 1999; Couetil et al. 1997).

5.2.1.4 Survival and Morbidity

Survival rates have been improving consistently since the beginnings of lung transplantations. To date, the 1-year survival rate of lung transplantation is approximately 76%, as opposed to 70% in 2000, and the 5-year survival rate of lung transplantation is 49%, as opposed to 45% in 2000 (Trulock et al. 2005). Repeated hospitalization after lung transplantation is further declining, but is still affecting a substantial percentage of patients (Trulock et al. 2005). The most common morbidities among the 1- and 5-year survivors are hypertension, renal dysfunction, hyperlipidemia, diabetes and bronchiolitis obliterans (BO). Infection and BO, presumed to reflect chronic allograft rejection, are the leading causes of mortality. Complications of lung transplantation can be divided in perioperative and postoperative complications, of which the leading causes relate to surgical technique, primary graft failure, infection, acute and chronic rejection and malignancy as well as recurrence of the primary disease (Trulock et al. 2005).

5.2.2 Preoperative Imaging

5.2.2.1 Preoperative Planning

Evaluation of both the donor and the recipient prior to transplantation is needed, to match donor and recipient lung size and, in cases of single-lung transplantation, to select which side of the recipient's lung ought to be removed (Winton 1992). Postero-anterior and lateral chest radiographs are effective in estimating the donor lung situation in terms of obvious disease or/and injury as well as size matching between donor lung and recipient thorax. Size matching is approximated by comparing the height from the lung apex to the diaphragm at the midclavicular line and the width at the level of the dome of the diaphragms of the donor and recipient's lung; a 10%–20% difference in size is acceptable (Winton 1992). In the so-called split-lung technique, the donor lung is downsized by peripheral nonanatomic segmental resections and transplanted in recipients with smaller thorax size (Wisser et al. 1996).

5.2.2.2 Preoperative Screening

Other than obvious disease, it is important to not only exclude clinically occult disease preoperatively in the recipient patient, but also to perform routine chest radiographical check-ups while on the waiting list to exclude occult disease such as small interval malignancies. Routine CT of the thorax is also recommended in recipients while on the waiting list to differentiate potential opacities seen in routine interval radiographs as well as for the preoperative assessment for lung transplantation. Rarely noninvasive evaluation with positron emission tomography using [^{18}F]fluorodeoxyglucose (FDG) is performed in cases where there are suspicious nodules shown at CT examination (Kazerooni et al. 1995).

Right and left heart catheterizations, quantitative ventilation–perfusion scanning as well as multiple-gated acquisition radionuclide ventriculography are also obtained if clinically relevant (Kazerooni et al. 1995).

5.2.3 Postoperative Complications

After overcoming the surgical procedure, a new pool of complications must be dealt with by the patients undergoing lung transplantation. One challenge facing the medical team involved is determining the correct differential diagnosis and consequently assessing the complication with the right treatment strategy. The similarity of the clinical presentations and radiological features of acute complications such as infection, early graft dysfunction and acute lung transplant rejection complicates the diagnosis. Another reason for the diagnostic difficulty is the timely occurrence overlap between "normal" postoperative complications such as mild, transient pulmonary edema, post-biopsy nodules (Fig. 5.2.5), or postoperative atelectasis (Fig. 5.2.6), or chest wall defects (Fig. 5.2.7), and the potentially serious complications related to transplantation such as severe reperfusion edema and adult respiratory distress syndrome (ARDS) (Fig. 5.2.8). The time of occurrence of post transplantation complications is one of the key factors in helping to narrow the differential diagnosis, when "normal" postoperative features are ruled out and the patient presents with nonspecific clinical signs of postoperative complications such as low-grade fever, dyspnea, cough and impaired oxygenation.

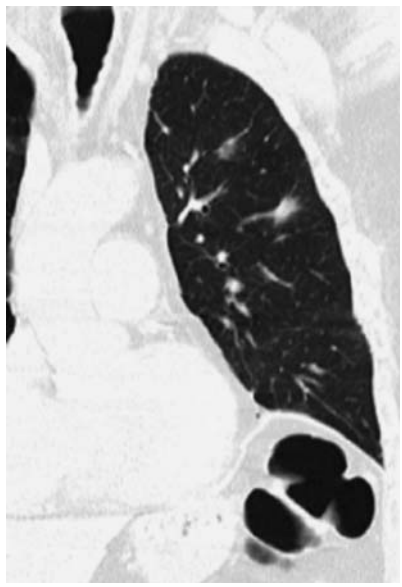


Fig. 5.2.5. Coronal multiplanar reconstructed CT section of left lung. CT section shows a postbiopsy nodule

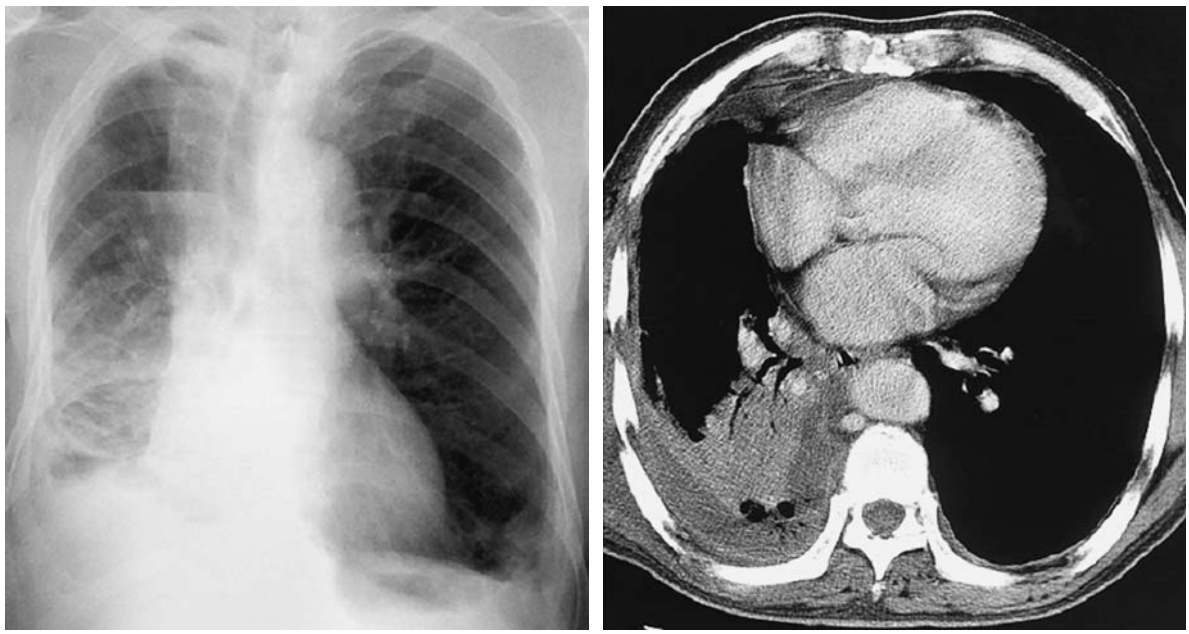


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Fig. 5.2.6. a Chest radiograph and **b** in a double-lung transplant recipient. Both modalities show postoperative atelectasis

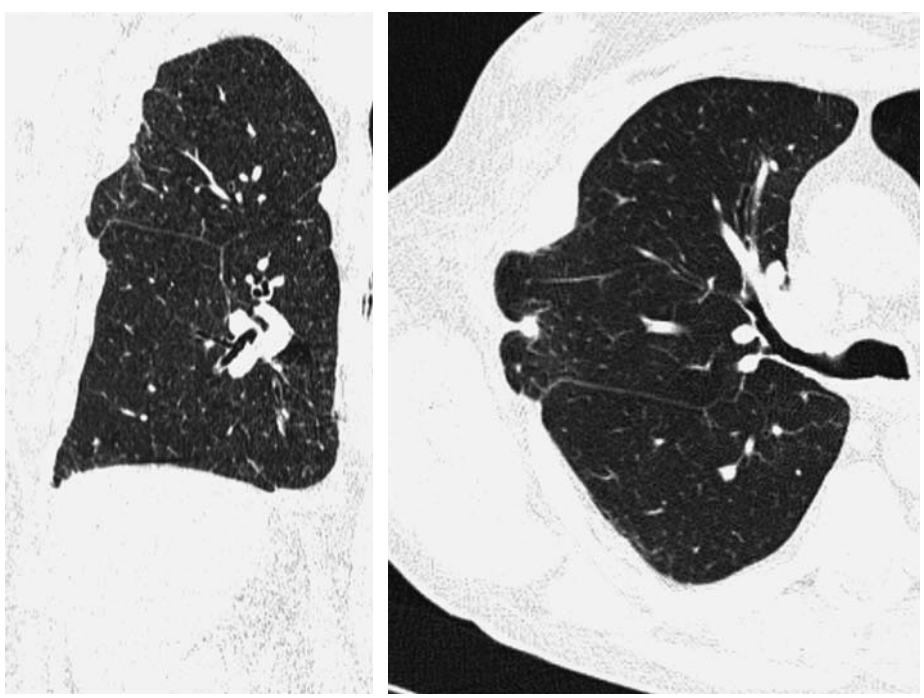

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Fig. 5.2.7. a Transverse CT section through right lung. CT section shows postoperative chest wall defect. **b** Coronal multiplanar reconstructed CT section through right lung. CT section shows postoperative chest wall defect

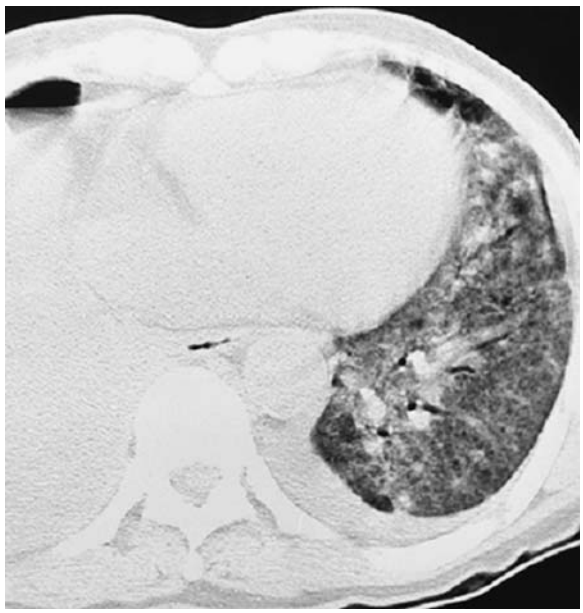


Fig. 5.2.8. Transverse CT section shows ground glass opacities and reticulations in an ARDS-affected lung

5.2.3.1 Complications in the Acute Phase

Complications in the acute phase occur in a time window between the first few hours and 3 months after transplantation. Usually patients are extubated within 24–48 h of transplantation. The intubation time can be prolonged and a tracheostomy may be necessitated if a complication such as early graft dysfunction or infection arises.

The most common causes of death in the initial hospitalization period or within the first 60 days right after patients are discharged are cardiac-related and primary graft failure (Meyers et al. 1999). Other common causes include parenchyma bleeding, ARDS, sepsis, bacterial pneumonia, and pulmonary embolism and neurological injury (Meyers et al. 1999). Anastomotic dehiscence, a previously common postoperative complication, is now very rare because of improved surgical techniques (Date et al. 1995). Treatment usually consists of overstenting the anastomotic dehiscence via bronchoscopy (Fig. 5.2.9) (Susanto et al. 1998).

5.2.3.1.1 Early Graft Dysfunction

Early graft dysfunction (EGD) is defined as a clinical scenario that includes radiographic abnormalities, poor oxygenation, and, if biopsies are performed, a histological pattern of diffuse alveolar damage or organizing pneumonia (Paradis et al. 1992). In the first 3 days and decreasing thereafter, up to 98% of patients present with a form of EGD in their first radiographic routine check-ups (Anderson et al. 1995; Kundu et al. 1998). Causes for EGD may include ischemia–reperfusion injury, implantation response, acute lung injury and hyperacute rejection (Paradis et al. 1992). The most common contributing factor of EGD is the reperfusion edema that reflects the increased capillary permeability and occurs to some degree in all transplanted lungs (Kaplan et al. 1992). The cause of reperfusion edema is multifactorial, including interruption of lymphatic drainage in the donor lung, preexisting donor lung injury, surfactant deficiency, abnormalities of coagulant factors, and ischemic damage to pulmonary capillaries (Kaplan et al. 1992).

The chest radiographic findings of reperfusion injury are nonspecific and are similar to those in patients who have left ventricular failure, fluid overload and acute rejection (Anderson et al. 1995). The findings range from a subtle perihilar haze to patchy or confluent airspace consolidation (Anderson et al. 1995). Also, peribronchial and perivascular thickening and a pattern of reticular interstitial lung opacities are seen in most patients. Up to 98% of patients present with these radiological findings in the first postoperative chest radiograph (Anderson et al. 1995; Kundu et al. 1998). Simultaneously, patients who had mild interstitial abnormalities on the initial chest radiograph usually present with normal findings by day 10 (Davis and Pasque 1995). There is poor correlation between the severity of radiographic findings and the alveolar-arterial oxygen gradient (Davis and Pasque 1995). Although most patients experience radiographic changes from reperfusion edema, only 5%–10% of patients with radiologically apparent moderate or severe early graft dysfunction develop early graft failure (Davis and Pasque 1995). Overall, the early postoperative radiological findings are poorly predictive when it comes to ruling out early graft failure. They are, however, diagnostically relevant when assessing infections, which are also frequent complications in the acute postoperative phase (Trulock 1997).

5.2.3.1.2 Infection in the Acute Postoperative Phase

Infection is the most common cause of morbidity and mortality in the acute and subacute phase af-

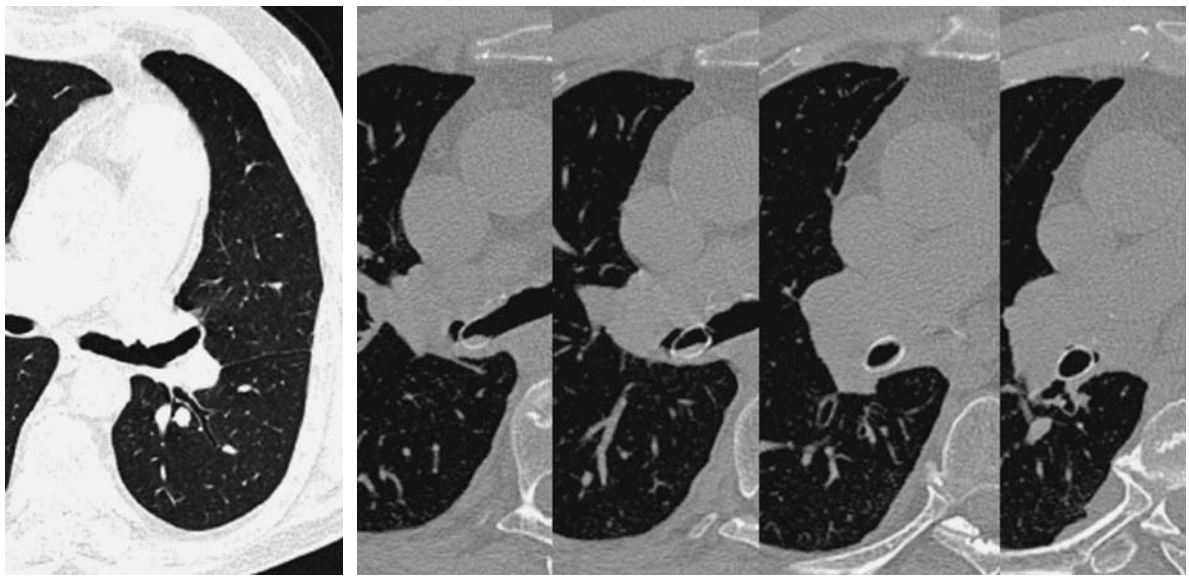


Fig. 5.2.9a,b. Transverse CT scan in double-lung transplant recipient shows irregularities of the bronchial anastomosis (**a**) and a stent bridging this irregularity (**b**)

ter lung transplantation and the second most common cause of late death after lung transplantation (Williams and Snell 1997). Because in the lung transplant patient population respiratory infection may progress rapidly to respiratory failure and death, correct and quick diagnosis is crucial. The rate of infection among lung transplant recipients is significantly higher than in recipients of other solid-organ transplants. This is most likely due to the exposure of the allograft to the external environment (Kramer et al. 1993a). Other reasons for the high incidence of respiratory infection include impaired mucociliary clearance because of diffuse ischemic injury to the bronchial mucosa, blunted cough due to postoperative pain, altered phagocytosis in alveolar macrophages and poor lymphatic drainage.

The lung allograft can become infected by passive transfer of organisms with the donor organ and by persistent recipient's organisms in the proximal airways, the sinuses, or the remaining native lung. Infection can also occur by de novo acquisition following transplantation, especially due to augmented immunosuppression to suppress the allograft rejection (Kramer et al. 1993a).

5.2.3.1.2.1 Bacterial Infection

Bacterial infection with Gram-negative bacteria of the lower respiratory tract is the most common in the early post transplant phase, and typically *Pseudomonas aeruginosa* are isolated (Cahill et al. 1997; Paradowski 1997). Although the incidence of bacterial pneumonia is highest in the first 3 months after transplantation and especially in the first month, the risk persists throughout the recipient's life (Trulock 1997).

The most frequent patterns seen in CT examinations with bacterial pneumonia are consolidation and ground glass opacification (Fig. 5.2.10) (Collins et al. 2000).

Other common findings are nodules varying in size and distribution and "tree-in-bud" patterns. If only ground glass opacification is seen on CT examinations, the differential diagnosis must include *Pneumocystis jiroveci* (PCP), formerly known as *Pneumocystis carinii* pneumonia (Agarwal et al. 2006), and acute rejection. One helpful hint at eliminating PCP is the fact that PCP has been virtually eliminated in lung-transplant recipients by the use of antibiotic prophylaxis and that if it does occur it is almost always associated with noncompliance with prescribed medication (Collins 2002).

5.2.3.1.2.2 Cytomegalovirus Infection

The second most common cause of infection in lung-transplant recipients is cytomegalovirus (CMV) (Trulock 1997). CMV is common in the general

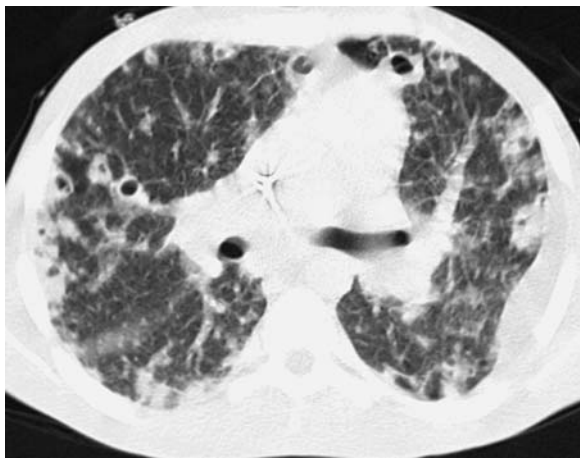


Fig. 5.2.10. Transverse CT scan in double-lung transplant recipient. CT scan shows multiple cavitary lesions corresponding to pneumatoceles after staphylococcal infection

population, and not all patients who present with CMV infection (i.e., identification of the organism in material obtained from any body site in the absence of symptoms and histological changes associated with CMV) also have CMV disease (i.e., identification of the organism in the material obtained from any body site in the presence of histological evidence of tissue damage). Patients who are seronegative for CMV before the procedure and in whom primary infection occurs as the result of the transplantation of an organ from a seropositive recipient are at greatest risk for severe infection, particularly pneumonitis (Ettinger et al. 1993). Pneumonitis is the most common presentation in CMV disease following lung transplantation, although hepatitis, gastroenteritis, or colitis can also occur (Shreeniwas et al. 1996).

A common way to prevent primary CMV infection in the lung-transplant recipient when either the donor or the recipient is seropositive is the initiation of ganciclovir prophylactically at the time of transplantation or preemptively when an increasing viral burden is detected (Palmer et al. 2004; Soghikian et al. 1996). Another strategy to prevent infection with CMV in the recipient is the use of seronegative donors and screened blood products. Unfortunately, although this reduces the risk of infection to negligible levels, this strategy is logically associated with increased waiting times before transplantation, since the majority of donors have been exposed to CMV (Arcasoy and Kotloff 1999).

5.2.3.1.3 Acute Rejection

5.2.3.1.3.1 Clinical and Imaging Diagnosis

Acute graft rejection is rare before the fifth postoperative day after lung transplantation, and the incidence is greatest within the first 100 days, usually within 3 weeks of surgery (Bando et al. 1995a). The clinical manifestations of acute rejection are poorly specific and include malaise, low-grade fever, dyspnea and coughing as well as impaired oxygenation and leukocytosis. Radiological findings which suggest acute rejection are new, worsening or persisting opacities 5–10 days after transplantation, new or increasing pleural effusions and septal lines without other signs of left ventricular failure (Fig. 5.2.11) (Bergin et al. 1990). Although these radiographic changes in the chest radiograph are common in early episodes of rejection, the chest film alone as a follow-up is nonspecific in early post transplant recipients. On the other hand, a "normal" postoperative chest radiograph does not rule out acute rejection. In a study by Kundu et al. for

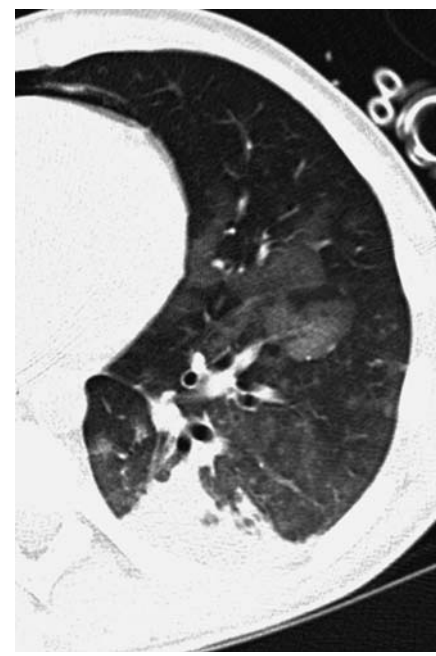


Fig. 5.2.11. Transverse CT scan of the left lung in a lung transplant recipient. The combination of ground glass opacities and gravity-dependent consolidations are highly suggestive of acute rejection and resemble features seen in early ARDS

instance, chest radiograph findings were found to be abnormal in only about 50% of instances of biopsy-proven acute rejection (Kundu et al. 1999). Because of poorly specific manifestations and chronological overlapping of other likely complications such as failure or infection, it is often very difficult to diagnose acute rejection and differentiate it from other complications that are also clinically similar. Further, retrospective epidemiologic analyses have demonstrated that three or more episodes of acute rejection are the major risk factors for the subsequent development of bronchiolitis obliterans (BO), which puts even more weight on correctly diagnosing and effectively treating acute rejection (Keller et al. 1995).

5.2.3.1.3.2 Histological Diagnosis of Acute Rejection

The diagnosis of acute rejection is made on the basis of histological findings. The histological hallmark is the presence of perivascular lymphocytic infiltrates, which in more severe cases spread over into the interstitium and alveolar air spaces (Yousem et al. 1996). When performing transbronchial biopsy, at least five pieces of alveolated parenchyma containing bronchioles and more than 100 air sacs should be obtained for optimal and accurate diagnosis of acute rejection (Yousem et al. 1996).

To ease the differential diagnosis when rejection is suspected, most institutions perform routine surveillance biopsies. A representative surveillance biopsy schedule is: 3 weeks; 3, 6, 9, 12 months; and annually thereafter (Trulock 1997).

If performed when based on clinical indications, transbronchial biopsy has been reported to reach a sensitivity for the detection of acute rejection of up to 94% (Trulock 1997). The rationale for surveillance biopsy protocols is based upon retrospective evidence that up to one-third of surveillance biopsies demonstrate evidence of allograft rejection (Chakinala et al. 2004) whereas only 40% of histologically confirmed grades II–IV acute rejections are associated with clinical signs or symptoms (Baz et al. 1996). There are reports in the literature however that suggest a much lower yield after 24 months, and some centers do not routinely perform biopsies after this point (Dransfield et al. 2004). In the study of Tamm et al. (1997) the benefit of surveillance biopsies was questioned. In this study, 51 heart-lung transplant recipients who underwent surveillance transbronchial biopsies were compared with 75 patients who received heart-lung transplants without routine surveillance biopsies. No significantly long patient survival rate was noted between the two groups, although the surveillance biopsy group received more steroid pulses (Tamm et al. 1997).

A less controversial method of monitoring allograft function is patient-administered home spirometry. Once postoperative function has been stabilized, the forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) should vary less than 5% from the baseline FEV_1 and FVC right after transplantation (Bjortuft et al. 1993; Morlion et al. 2002). A decline of 10% or more in spirometric values that persists for more than 2 days has been reported to indicate either rejection or infection.

5.2.3.1.3.3 Treating Acute Rejection

Treatment of acute rejection consists of high-dose parenteral corticosteroids, such as intravenous methylprednisolone (0.5–1.0 g IV per day) for 3 days. This is usually done in the inpatient setting, although selected patients who are clinically stable can be treated as outpatients. The outpatient regimen is the same, with intravenous methylprednisolone at home or in a chemotherapy infusion center (Chakinala and Trulock 2003). Resolution occurs rapidly in patients with clinical signs and symptoms of rejection. The clinical symptoms of acute rejection usually improve over 24–48 h, and the physiologic abnormalities begin to improve in the same time frame and return to baseline over several weeks. Since the risk of developing CMV is higher in patients receiving augmented immunosuppression, many centers administer ganciclovir (5 mg/kg IV bid) during the period of augmented immunosuppression. This practice has been successful in renal transplant recipients, for whom the risk of CMV disease is reduced when antiviral therapy is administered during intravenous steroid therapy for acute rejection (Hibberd et al. 1995).

5.2.3.1.3.4 Infection – Acute Rejection Surveillance

The clinical presentation of acute rejection and acute infection alone is nonspecific. Manifestations can include low-grade fever, shortness of breath, nonproductive cough, and changes in measured pulmonary function. In both entities, the chest radiograph may demonstrate perihilar infiltrates, interstitial edema,

focal consolidation, or pleural effusions (Shreeniwas et al. 1996). The point in time at which a disease manifests radiographically may provide clues to its etiology. CMV infection is rarely detected before the second week after transplantation, and the mean time to the initial episode of CMV pneumonitis is 55 days (Smith et al. 1998). In comparison, acute rejection has a variable time course, but may occur within the first 2–3 weeks after lung transplantation, when CMV infection would not be expected. For this reason, surveillance fiber optic bronchoscopy is usually performed whenever there is a clinical indication and decline of spirometric values in the absence of recently untreated organisms identified by sputum culture (Kukafka et al. 1997). However, it should be noted that even histologically the differentiation of rejection from infection can be at times difficult, since features suggesting rejection are also present in viral infection, and, most commonly, in CMV infection (Chakinala and Trulock 2003). In particular, the lymphocytic infiltrate that accompanies such infections or the presence of acute inflammatory cells, such as polymorphonuclear leukocytes, make the histological diagnosis difficult. Alveolar inflammation – as opposed to vascular or airway-centered inflammation – in combination with viral inclusions or the presence of infectious pathogens on special staining is more indicative of infection. In the presence of active infection, it is impossible to make the diagnosis of rejection with certainty. The approach in such situations is to treat the infection and then repeat the biopsies to assess any contribution of rejection to the patient's clinical syndrome (Chakinala and Trulock 2003). For all the above-mentioned reasons it is essential to understand the importance of interdisciplinary work-up of patients presenting with postoperative complications to achieve the correct diagnosis and treatment.

5.2.3.2 Complications in the Nonacute Phase

5.2.3.2.1 Bronchiolitis Obliterans

5.2.3.2.1.1 Definition, Cause and Clinical Presentation

Chronic rejection, histologically defined as a fibroproliferative process that targets the small airways, is a major limiting factor in the long-term survival of lung-transplant patients (Sundaresan et al. 1995). Synonymous with bronchiolitis obliterans (BO), it leads to a submucosal fibrosis of the small airways, and consequently to luminal obliteration and often to obstructive airflow limitation (Arcasoy and Kotloff 1999; Boehler and Estenne 2000; Chamberlain et al. 1994). This chronic lymphoproliferative process is multifocal and may spare whole parts of the affected lung, while literally destroying the lung function (Boehler and Estenne 2000). Therefore, while the diagnosis of BO is based on the histological findings obtained at biopsy, a negative transbronchial biopsy does not exclude BO (Boehler and Estenne 2000; Chamberlain et al. 1994). Therefore, the International Society for Heart and Lung Transplantation devised a standardized nomenclature proposing the use of a spirometric definition for a clinical diagnosis (Cooper et al. 1993; Estenne et al. 2002). They also made a distinction between histologically proven BO and bronchiolitis obliterans syndrome (BOS). The latter is a clinical term and is applied to the situation in which there is "graft deterioration secondary to progressive airways disease for which there is no other cause" in the absence of histological evidence of BO with sustained fall in FEV_1 to a level of 80% or less of the peak value after transplantation (Estenne et al. 2002). The mortality rate associated with BOS ranges from 25% to 56%; the risk increases with the time elapsed after diagnosis has been made (Bando et al. 1995a; Keller et al. 1995; Nathan et al. 1995; Sundaresan et al. 1995). Because the occurrence of BOS increases with time, centers with a longer experience report higher prevalence rates, and centers that have presented their results in multiple publications report higher prevalence rates in a later publication (Trulock et al. 2003). Usually the onset of BOS is at 3 months after transplantation. The natural evolution of BOS has been described to follow one of three patterns: (1) rapid, relentless decline after onset; (2) initial rapid deterioration followed by stabilization; and (3) subtle onset and slow, relentless progression (Levine and Bryan 1995; Nathan et al. 1995). Retrospective epidemiologic analyses have demonstrated that three or more episodes of acute rejection are the major risk factor for the subsequent development of BO (Bando et al. 1995b; Boehler et al. 1998; Keller et al. 1995).

Gastroesophageal reflux (GER) appears to be common in patients following lung transplantation, and may contribute to chronic allograft rejection.

The frequency and clinical importance of GER were evaluated in a study of 128 lung-transplant recipients at a single institution: 93 (73%) had abnormal esophageal acid contact times based upon 24-hambulatory pH probe monitoring (Davis et al. 2003). From this group, 26 patients met diagnostic criteria for BO and underwent fundoplication. Following the procedure, 16 patients had lower BOS scores, and 13 no longer met criteria for the diagnosis of BOS. Long-term follow-up of these patients suggests that early fundoplication can result in a lower incidence of BOS and improved survival (Cantu et al. 2004).

5.2.3.2.1.2 Histological Diagnosis

Transbronchial biopsy is still considered the final proof of BO. However, the reported sensitivity and sensibility of transbronchial biopsy in diagnosing BOS have been diverting (Chamberlain et al. 1994). For example, one study reported a sensitivity of 17% and a specificity of 94.5% for a single set of transbronchial biopsies (Chamberlain et al. 1994). Another study reported a rate of 15% histological confirmation in patients clinically diagnosed with BOS (Kramer et al. 1993b). Another study concluded that transbronchial biopsies confirmed the diagnosis in 82% of their patients who developed clinical BOS (Bando et al. 1995b). In contrast Sundaresan et al. (1995) noted that among 77 patients diagnosed with chronic rejection, the diagnosis was made on the basis of declining FEV_1 in 52%. Only 9% of patients had a histologically proven diagnosis without the typical clinical physiologic abnormalities, whereas 39% had both positive histology and declining spirometry (Sundaresan et al. 1995). Because of these differing data, centers have adopted different approaches to making the diagnosis of BOS. Although the use of transbronchial biopsy in this setting is debated, many lung transplantation centers feel that it may aid in earlier diagnosis and therefore facilitate earlier therapy (Kukafka et al. 1997). Reasons for a confirming biopsy include exclusion of other causes of the clinical syndrome and establishment of the diagnosis prior to attempting therapy and/or retransplantation. Although no therapy has a good track record, many institutions have clinical protocols examining the efficacy of new approaches such as photopheresis, total lymphoid irradiation, plasmapheresis, and inhaled ciclosporin (Iacono et al. 2004).

5.2.3.2.1.3 Imaging of BO

Areas of air trapping caused by small airways are seen as regional inhomogeneities that fail to decrease in volume and remain relative lucent compared to normal lung parenchyma on expiratory CT sections. Areas of decreased attenuation, very often in the early onset of disease not seen on inspiratory CT sections, are easier detected on end-expiratory CT sections (Figs. 5.2.12, 5.2.13) (Arakawa and Webb 1998; Desai and Hansell 1997; Lucidarme et al. 1998; Ng et al. 1999; Verschakelen et al. 1998). The unchanging low attenuation in expiratory CT sections, and also the absence of a decreasing cross-sectional area of the affected part of the lung are helpful in detecting air trapping (Stern and Frank 1994). Expiratory CT can also be used in differentiating between the three main causes of a mosaic pattern (small airways disease, i.e., BO, infiltrative lung disease, and occlusive pulmonary vascular disease) in cases where inspiratory CT is problematic (Arakawa and Webb 1998; Stern et al. 1995). It is important however to keep in mind that in patients with widespread BO, end-expiratory CT sections may appear almost identical to the inspiratory CT sections, simply because of the severity of the air trapping (Fig. 5.2.14). In these cases there is no inhomogeneity of attenuation or change in cross-sectional area of any part of the lung. This important sign of air trapping on HRCT sections obtained at end-expiration in comparison to inspiratory HRCT sections is becoming a routinely performed examination (Arakawa and Webb 1998).

5.2.3.2.1.4 Developing Role of HRCT in the Diagnosis of BO

In one of the first CT studies of BO, Turton et al. (1981) examined 15 patients who fulfilled the criteria of "obliterative bronchiolitis" with thin-section CT (interspaced 3-mm sections, contiguous 10-mm sections). In 5 of the 15 patients the chest radiographs were normal and the remaining 10 patients showed "limited vascular attenuation and hyperinflation". In 13 of the 15 patients "patchy irregular areas of high and low attenuation in variable proportions, accentuated in expiration" were observed. These findings, together with two cases by Eber et al. (1993) were the first reports to identify regional inhomogeneity of the density of the lung parenchyma as the key CT feature of BO. This noninvasive ap-

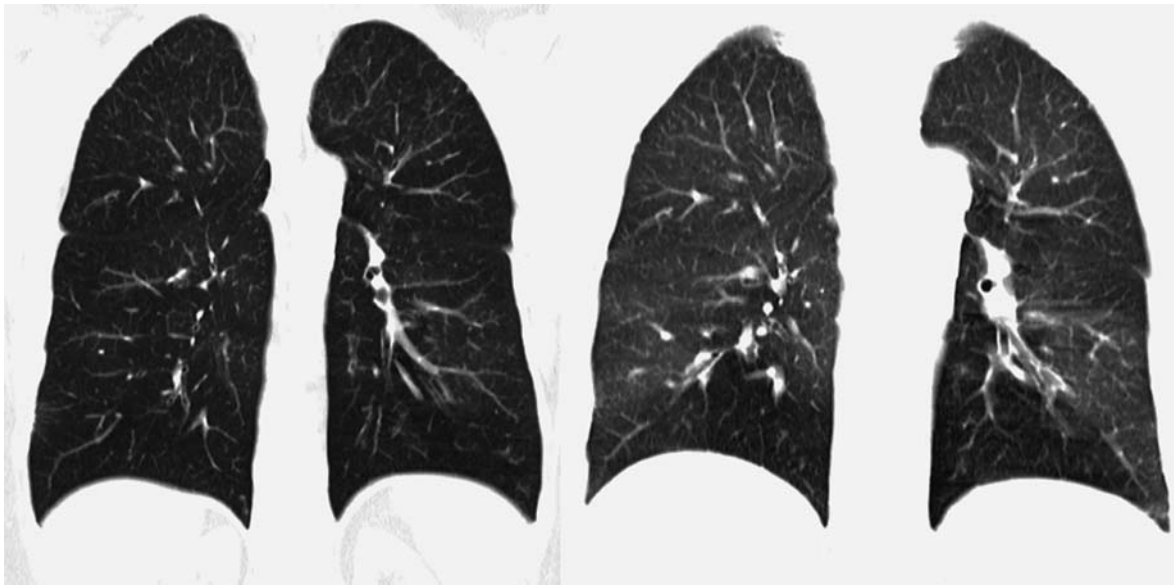


Fig. 5.2.12. Coronal multiplanar reformation CT section of a double-lung transplantation recipient in inspiration (*left*) and expiration (*right*). Whereas lung density in inspiration is normal, expiration shows extensive basal air trapping

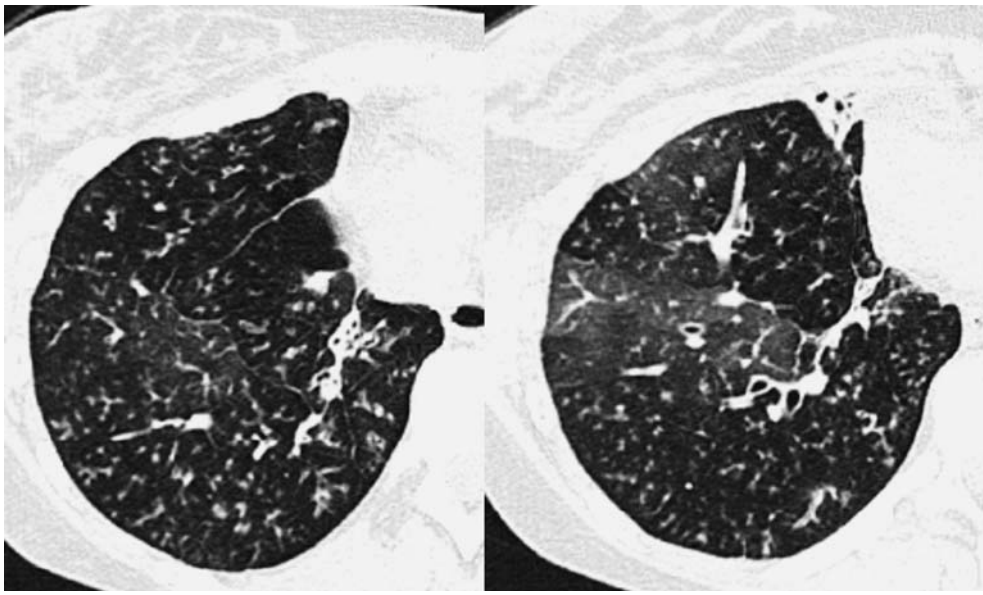
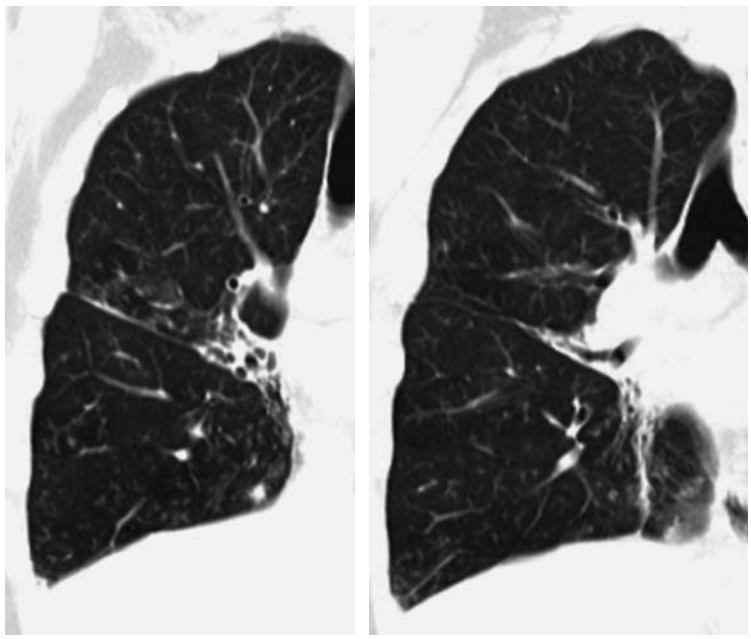


Fig. 5.2.13. Transverse CT section through the right lower lobe in a lung transplantation recipient in inspiration (*left*) and expiration (*right*). Inspiration section shows peripheral tree-in-bud and subtle inhomogeneity of the lung density. Inhomogeneities are accentuated in expiration and extended air trapping becomes apparent

proach to early diagnosis and follow-up of air trapping on HRCT scans has become more accepted recently (Bankier et al. 2001; Knollmann et al. 2004; Konen et al. 2004). The identification of areas of ground glass opacification on HRCT after transplantation, with an inclining incidence 6 months after transplantation, was described as very suggestive but nonspecific (Loubeyre et al. 1995). The reported sensitivity and specificity of HRCT for diagnosing BO associated with numerous other predisposing conditions or causative agents has already been presented; for example, MacLeod's syndrome,



a b

Fig. 5.2.14a, b. Coronal multiplanar reformation CT section of the right lung in lung transplantation recipient in inspiration (**a**) and expiration (**b**). Images show perihilar scarring and extensive peripheral tree-in-bud without any significant decrease in cross-sectional area in expiration

a form of constrictive bronchiolitis that occurs typically following a viral infection acquired in childhood. Here the inhomogeneous nature of lung involvement, similar to the post transplant lung, is particularly well demonstrated on CT (Lucaya et al. 1998; Marti-Bonmati et al. 1989; Moore et al. 1992; Zhang et al. 1999). Later studies went further to apply these findings specifically to BO in lung-transplant patients and provided further evidence that air trapping on expiratory CT scans is an accurate indicator of BO (Leung et al. 1998; Worthy et al. 1997). These findings were, however, based on a small number of patients and a control group was not used. Later on larger study groups reported the reliable accuracy of expiratory thin-section CT to diagnose BOS and complemented the clinical follow-up of lung-transplant recipients (Fig. 5.2.15) (Bankier et al. 2001). Other studies found that the diagnosis of BOS on expiratory thin-section CT was not accurate enough to warrant a role in the follow-up of these patients (Konen et al. 2004; Lee et al. 2000; Miller et al. 2001). These diverting findings however, for the most part, probably reflect differences in examination protocols and scoring systems, and varying patient populations. Bankier et al. (2001) took on this uncertainty by examining more patients and analyzing longer periods of follow-up CT examination, and proved that air trapping at a certain threshold is a relatively sensitive, specific, and accurate method for diagnosing BOS. In a later study Bankier et al. (2003) also examined whether changes in air trapping at sequential CT examinations result from an inherent variability of air trapping or from the variability of the underlying BOS. In this study, Bankier et al. (2003) showed that the anatomic distribution and extent of air trapping in functionally stable heart-lung transplant patients are reproducible characteristics and hence may contribute to the early detection of subclinical chronic rejection of the allograft lung and may be a major tool in the follow-up of such patients (Bankier et al. 2003).

Although some lung transplant centers use HRCT and air trapping in the screening of possible BO, there are still many more centers that doubt these findings because of the lack of a multi-center study proving the value and impact on clinical management of the above-mentioned findings.

5.2.3.2.1.5 Treatment of BO

A variety of treatments have been tried for BO. A study of 32 patients with BO found that conversion from ciclosporin to tacrolimus was associated with spirometric stabilization over 12 months of follow-up (Cairn et al. 2003), and a second study of 13 patients reported similar outcomes when mycophenolate mofetil was introduced (Whyte et al. 1997). Other studies have reported similar results after in-

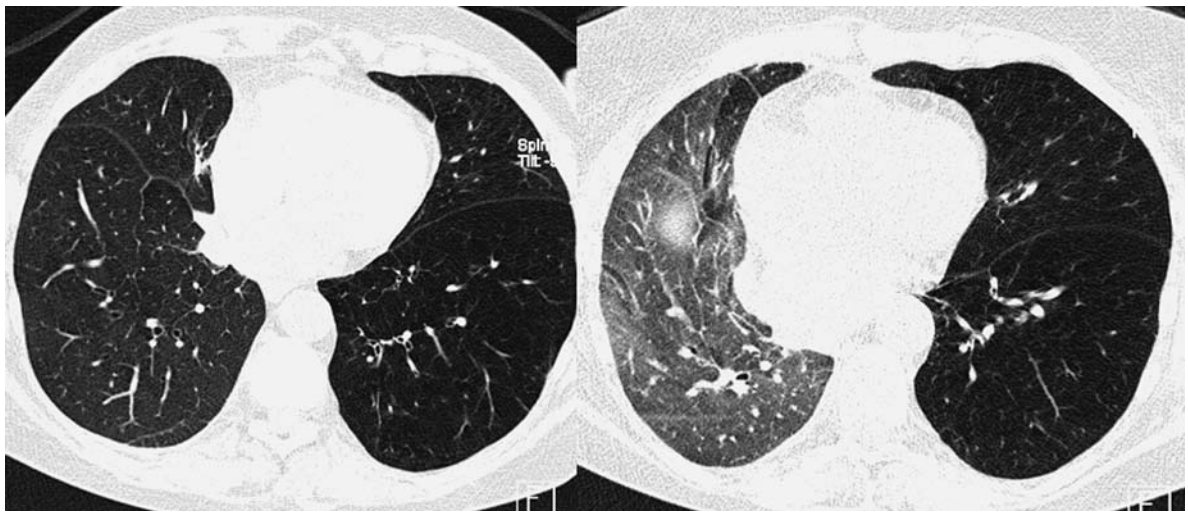


Fig. 5.2.15. Transverse CT section after right single-lung transplantation in inspiration (*left*) and expiration (*right*). Native emphysematous lung does not change in density between inspiration and expiration, suggestive of extensive air trapping. Transplanted right lung increases in density in expiration and shows only a peripheral area of air trapping

troducing substitutions in the immunosuppression regimen (Revell et al. 2000; Verleden et al. 2003). Limited evidence suggests that high-dose inhaled corticosteroids are not effective in slowing or preventing the development of BOS (Whitford et al. 2002). Two reports assessed the value of prolonged oral azithromycin therapy (250 mg PO × 5 days, then 250 mg PO every other day) in patients with BOS (Gerhardt et al. 2003; Verleden and Dupont 2004; Yates et al. 2005). This approach was associated with significant improvements in FEV_1 for some, but not all, patients. These reports have involved only small numbers of patients, and there is little convincing evidence that any of the treatment modalities can be considered effective therapy that dramatically changes the natural history of BOS. It seems that the best strategy to deal with BOS is attempted primary prevention, i.e., aggressive early immunosuppression to eliminate early episodes of acute rejection, since there is no reliable therapy once patients develop symptomatic airflow obstruction.

The issue of retransplantation after the development of BOS is controversial. Early experience suggested that the outcome was not as good as with the first transplant, and some believe that BOS tends to recur in retransplant recipients in an accelerated fashion (Novick et al. 1998). The risk, however, does not appear to be significantly different from that with the first transplant. In a review of 230 retransplantation cases performed in 47 centers between 1985 and 1996 1-year survival was significantly lower (47%) than for the initial transplant (Novick et al. 1998). Among the long-term survivors, however, the risk of developing BO by 2 years was 38%, a rate similar to that of first transplants. Similarly in a single-center series of 15 patients undergoing retransplantation for BOS it was noted that 60% were still alive at 1 year. Surviving patients had a 28% likelihood of recurrent BOS within 3 years after transplantation (Brugiere et al. 2003). Opinions concerning the appropriateness of retransplantation as a treatment of BOS vary widely, in part shaped by the recognition that most centers have more potential first-time recipients than donors, and that mortality on the waiting list is a significant problem. As a result of these considerations, transplant programs vary in policy concerning the availability of retransplantation as a therapeutic option.

5.2.3.2.2 Infection in the Nonacute Phase

5.2.3.2.2.1 Fungal Infections

The isolation of *Candida* or *Aspergillus* species from pulmonary specimens is not unusual. The majority of isolates represent colonization without invasive or clinically apparent disease, but these fungi also may produce major complications and death (Fig. 5.2.16)

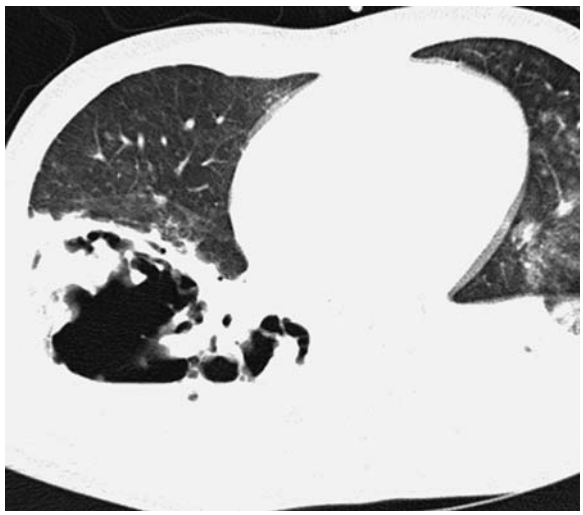


Fig. 5.2.16. Transverse CT section after double-lung transplantation. CT shows extensive cavitation in the right lower lobe following necrotizing pneumonia

(Dauber et al. 1990; End et al. 1995; Kramer et al. 1993a; Mannes et al. 1995; Maurer et al. 1992; McDougall et al. 1993; Paradis and Williams 1993; Westney et al. 1996; Winter et al. 1994; Yeldandi et al. 1995). Since effective, nontoxic antifungal drugs have become increasingly available, most centers have had a low threshold for preventive or preemptive treatment (Dummer et al. 2004).

5.2.3.2.2.2 Candida *Infection*

Candida infection occurs relative frequently, perhaps because colonization is common both in donor lungs and in hospitalized, immunosuppressed patients (Low et al. 1993; Zenati et al. 1990). Before the era of prophylaxis or preemptive therapy, *Candida* infection in the donor was associated with fatal, invasive complications in the recipient (Dauber et al. 1990; Zenati et al. 1990). Although *Candida* is often isolated from respiratory tract specimens, pneumonitis is rare. Disseminated or locally invasive infection with *Candida* can be treated with fluconazole or amphotericin B.

5.2.3.2.2.3 Aspergillus *Infection*

Aspergillus is a ubiquitous organism and is transmitted by inhalation of spores. It can be a devastating pathogen in an immunocompromised host. Surveys have reported a frequency of infection in lung-transplant recipients in the range of 20%–45% (Cahill et al. 1997; Flume et al. 1994; Nunley et al. 1998; Westney et al. 1996; Yeldandi et al. 1995). *Aspergillus* infection after lung transplantation can be classified into two major categories, saprophytic colonization and disease. Particularly devitalized cartilage and foreign suture material of the fresh bronchial anastomosis may create vulnerable sites for *Aspergillus*. *Aspergillus* may also diffusely infect the airways and cause mucosal edema, ulceration and the formation of pseudomembranes (Kramer et al. 1991). One series including 101 patients reported the development of invasive aspergillosis in 14% (Husni et al. 1998). The primary site of lung disease is usually the allograft, but the native lung has been the nidus in some single-lung recipients (McDougall et al. 1993; Westney et al. 1996; Yeldandi et al. 1995). The infection itself has not always been reported to be the ultimate cause of death, however up to 30%–75% mortality rates have been connected with *Aspergillus* disease. Most of the deaths have occurred in recipients with pneumonia or disseminated aspergillosis (Cahill et al. 1997; Kramer et al. 1991; Westney et al. 1996; Yeldandi et al. 1995).

Risk factors for *Aspergillus* infection have not been extensively analyzed, but a strong association with CMV disease was noted in several studies (Husni et al. 1998; Monforte et al. 2001; Yeldandi et al. 1995). No relationship of *Aspergillus* infection to rejection or augmented immunosuppression has been proven, and retransplantation infection with *Aspergillus* does not predict post transplantation illness (Flume et al. 1994). The risk of developing an invasive disease, however, is strongly associated with early post transplant colonization. One study of 151 lung transplant recipients found that patients who had *Aspergillus fumigatus* isolated from the airway within the first 6 months of transplantation had an 11-fold greater risk of developing invasive disease compared with those not colonized during this period (Cahill et al. 1997).

The diagnosis of aspergillus bronchitis is usually made on the basis of a compatible bronchoscopic appearance and isolation of the organism from a biopsy or lavage specimen (Kramer et al. 1991). The definitive diagnosis of pneumonia requires biopsy demonstration of invasion, but a presumptive diagnosis may be made if *Aspergillus* is present in bronchoalveolar lavage (BAL) or sputum and the clinical picture is consistent. The most common CT findings

in patients with fungal pneumonia in general are a combination of nodules, consolidation, and ground glass opacities (Collins et al. 2000). Nodules are mostly multiple and vary in size, have irregular margins and involve all lung zones (Fig. 5.2.17). Bronchitis due to *Aspergillus* infection has responded well to itraconazole or aerosolized amphotericin (Kramer et al. 1991; Mehrad et al. 2001; Westney et al. 1996; Yeldandi et al. 1995). The standard treatment for pneumonia or disseminated aspergillosis is intravenous amphotericin B, but the outcome has been disappointing.

The threat of serious complications and the availability of effective, nontoxic drugs has led the majority of centers to undertake preventive therapy for *Candida* or *Aspergillus* infection (Dummer et al. 2004). The protocols are typically based on fluconazole for *Candida* and itraconazole for *Aspergillus*. Such strategies undoubtedly result in over treatment but have been justified by the reduction in serious fungal infections (Hamacher et al. 1999; Paradis and Williams 1993). The treatment of all respiratory isolates of *Candida* and *Aspergillus* infection with fluconazole or itraconazole reduced the lifetime incidence of fungal infections from 14% to 5% (Paradis and Williams 1993).

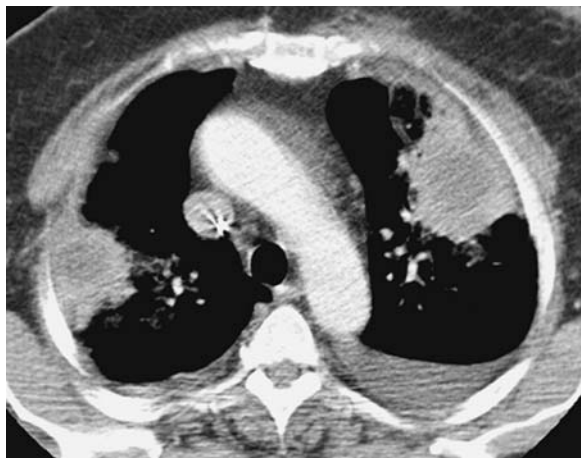


Fig. 5.2.17. Transverse CT section after double-lung transplantation. CT shows large peripheral enhancing masses corresponding to fungal infection

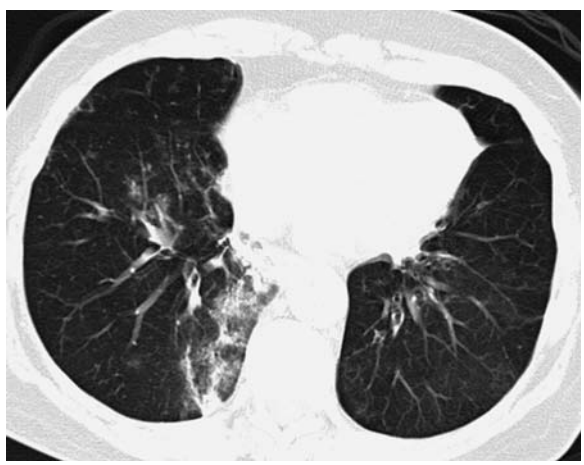


Fig. 5.2.18. Transverse CT section after double-lung transplantation. CT shows partly consolidated, partly ground-glass-like opacities in the right lung, corresponding to *Mycobacterium xenopi*

5.2.3.2.2.4 Other Fungal Infections

Other fungi, including *Cryptococcus*, *Mucor*, and endemically restricted organisms such as *Coccidioides immitis* or *Xenopi* (Fig. 5.2.18), have occasionally caused pulmonary or disseminated disease following lung transplantation (Dauber et al. 1990; Kramer et al. 1991; Paradis and Williams 1993). Prophylaxis should be considered for recipients who live within endemic areas.

5.2.3.2.2.5 Tuberculosis

The incidence of pulmonary tuberculosis after lung transplantation is estimated to be between 2% and 3.8% (Kesten and Chaparro 1999; Schulman et al. 1997). The transmission of pulmonary tuberculosis after lung transplantation is probably via the donor allograft (Collins 2002). The infection typically occurs 1.5–9 months after surgery. CT finding are nonspecific and include subtle bronchial narrowing, pleural effusions and bilateral small nodules, multiple bilateral upper and lower lobe cavitary lesions and consolidations as well as mediastinal lymph node enlargement (Collins 2002).

5.2.3.2.2.6 Bacterial Infection in the Nonacute Phase

Although bacterial infection is more common in the acute phase after lung transplantation, as mentioned above, it also reemerges as a late complication (Trulock 1997). Especially among patients in whom BOS develops, recurrent episodes of purulent tracheobronchitis are common (Arcasoy and Kotloff 1999). Radiographically these episodes of

bacterial infection are often associated with evidence of bronchiectasis (Kramer et al. 1993b).

5.2.3.2.3 Post Transplantation Malignancy

The chronic use of immunosuppressive agents to prevent allograft rejection increases the long-term risk of malignancy compared with that of the general population.

The most frequent malignancy in lung transplant recipients is post transplantation lymphoproliferative disease (PTLD) and occurs in 5%–20% of patients (Trulock 1997). The histological findings range from benign polymorphic hyperplasia of lymphocytes to malignant lymphoma. PTLD is thought to be caused by proliferation of Epstein–Barr-virus-infected donor B-lymphocytes and is more common in Epstein–Barr-virus-seronegative recipients who receive an Epstein–Barr-virus-seropositive donor lung (Collins et al. 1998). Patients may respond to a reduction in immunosuppressive therapy, but this response must be balanced against increasing allograft rejection.

Common radiographic findings of PTLD consist of single or multiple pulmonary nodules, hilar or mediastinal lymphadenopathy, pleural or pericardial effusions, and parenchymal consolidation (Fig. 5.2.19) (Collins et al. 1998; Dodd et al. 1992). Other neoplasms are skin and lip carcinomas, vulvar or perineal carcinomas, in situ cervical cancer, and Kaposi's sarcoma. The risk for cancers that are common in the general population (e.g., lung, breast, prostate, colon) is not increased in transplant recipients (Penn 1993). When lung cancer has occurred in patients undergoing lung transplantation, it has typically been described in patients with strong risk factors for lung cancer prior to transplantation (Fig. 5.2.20) (Arcasoy et al. 2001). In rare cases, the

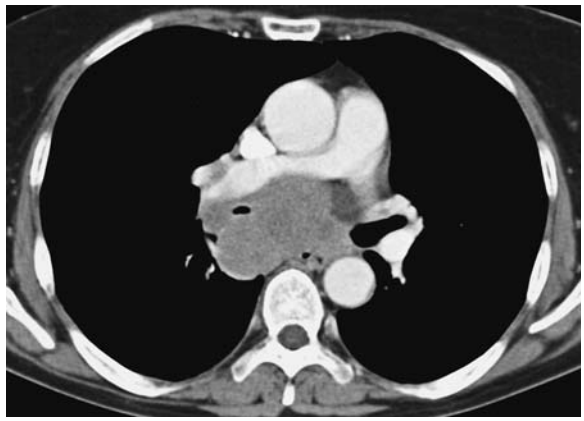
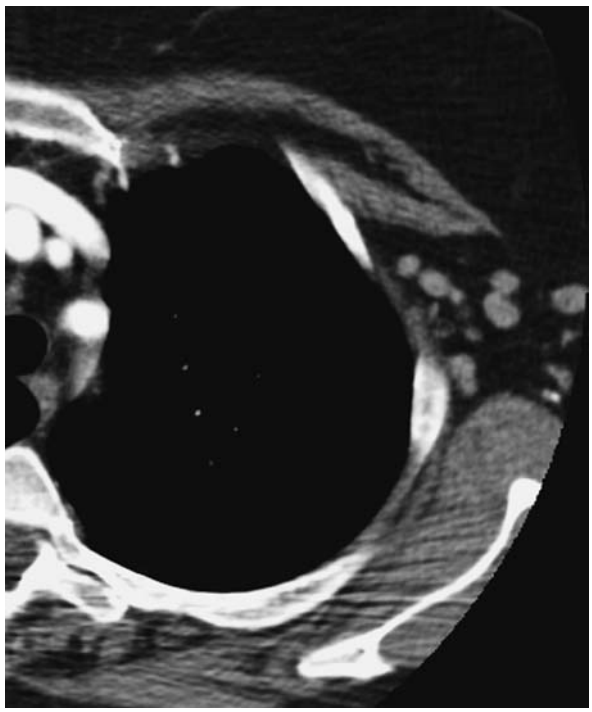
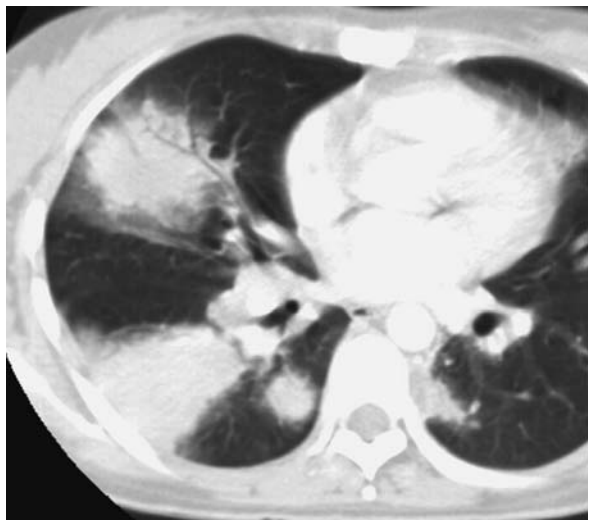


Fig. 5.2.20. Transverse CT section of a double-lung transplant recipient shows a large subcarinal mass suggestive of post transplant lymphoproliferative disease



a



b

Fig. 5.2.19a,b. CT shows large axillary lymph nodes (**a**) and focal pulmonary consolidation (**b**) in a patient with lymphoproliferative disease

tumor represents recurrent disease in patients who were transplanted for bronchoalveolar carcinoma (de Perrot et al. 2003; Garver et al. 1999). A single-center review of outcomes following lung transplantation identified bronchogenic carcinoma in 6 of 251 patients (2.4%). All 6 patients had a history of heavy smoking (mean of nearly 80 pack years), and 5 patients had COPD as their indication for transplantation (Arcasoy et al. 2001).

5.2.3.2.4 Recurrence of Primary Disease

A number of diseases have been reported to recur in the lung allograft, including sarcoidosis (Bjortuft et al. 1994; Johnson et al. 1993; Kazerooni et al. 1994; Milman et al. 2005; Walker et al. 1998), and bronchioloalveolar carcinoma (Dransfield et al. 2004; Paloyan et al. 2000). Other less frequently observed but reported disease recurrences after lung transplantation are idiopathic pulmonary hemosiderosis (Calabrese et al. 2002; Wroblewski et al. 1997), alpha-1-antitrypsin deficiency (Mal et al. 2004), pulmonary veno-occlusive disease (Izbicki et al. 2005), diffuse panbronchiolitis (Baz et al. 1995), pulmonary Langerhans' cell histiocytosis (Fig. 5.2.21) (Etienne et al. 1998; Gabbay et al. 1998; Habib et al. 1998), lymphangioleiomyomatosis (Nine et al. 1994; O'Brien et al. 1995), desquamative interstitial pneumonia (Verleden 1998), and pulmonary alveolar proteinosis (Parker and Novotny 1997). Particularly sarcoidosis has been described to have a high pathologic recurrence rate in some small series (Collins et al. 2001). It usually is discovered incidentally when granulomas are noted on lung biopsy specimens, but these pathologic recurrences have not adversely affected the long-term outcome (Johnson et al. 1993). As an example, a series of 12 patients found post transplantation recurrence of sarcoidosis in 3, but reported 3- and 5-year survival rates comparable to those of patients transplanted for other diseases (Walker et al. 1998). Because the history of lung transplantation is brief compared with the natural history of the underlying diseases, it would not be surprising for recurrence of other diseases to be described in the future among long-term surviving patients.

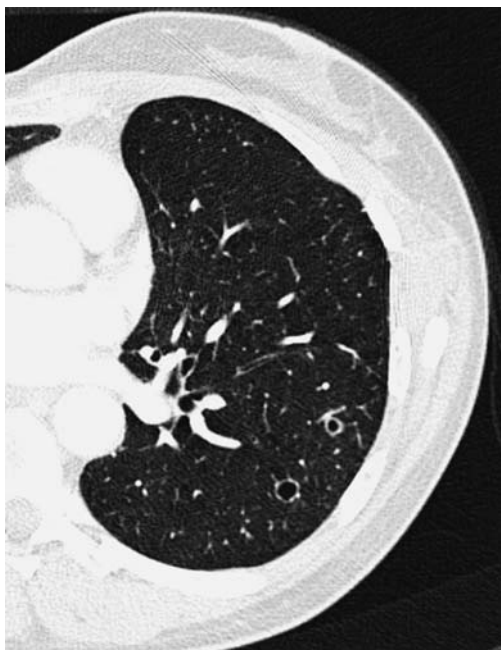


Fig. 5.2.21. Transverse CT section through the left lower lobe. Recurrence of histocytosis X in transplanted lung

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