However, other factors have contributed as well. The mortality risk has been higher at centers with <20–30 transplantations per year.

Function Regardless of the disease, successful transplantation impressively restores cardiopulmonary function. After bilateral transplantation, pulmonary function tests are typically normal; after unilateral transplantation, a mild abnormality characteristic of the remaining diseased lung is still apparent. Formal exercise testing usually demonstrates some impairment in maximal work rate and maximal oxygen uptake, but few recipients report any limitation to activities of daily living.

Quality of Life Both overall and health-related quality-of-life scores are enhanced. With multidimensional profiles, improvements extend across most domains and are sustained longitudinally unless chronic rejection or some other complication develops. Other problems that detract from quality of life include renal dysfunction and drug side effects.

Cost The cost of transplantation depends on the health care system, other health care policies, and economic factors that vary from country to country. In the United States in 2011, the average billed charge for the period from 30 days before bilateral lung transplantation until 180 days after discharge from the transplantation admission was $797,300. The total cost included the following charges: all care during 30 days before transplantation, $21,400; organ procurement, $90,300; hospital transplantation admission, $458,500; physician fees during transplantation admission, $56,300; all inpatient and outpatient care for 180 days after discharge, $142,600; and all outpatient drugs (including immunosuppressants) for 180 days after discharge, $28,200.

COMPLICATIONS

Lung transplantation can be complicated by a variety of problems (Table 320e-3). Aside from predicaments that are unique to transplantation, side effects and toxicities of immunosuppressive medications can cause new medical problems or aggravate preexisting conditions.

TABLE 320e-3 MAJOR POTENTIAL COMPLICATIONS OF LUNG TRANSPLANTATION AND IMMUNOSUPPRESSION

Category	Complication
Allograft	Primary graft dysfunction; anastomotic dehiscence or stenosis; ischemic airway injury with bronchostenosis or bronchomalacia; rejection; infection; recurrence of primary disease (sarcoidosis, lymphangioleiomyomatosis, giant cell interstitial pneumonitis, diffuse panbronchiolitis, pulmonary alveolar proteinosis, Langerhans cell histiocytosis)
Thoracic	Phrenic nerve injury/diaphragmatic dysfunction; recurrent laryngeal nerve injury/vocal cord dysfunction; cervical ganglia injury/Horner's syndrome; pneumothorax; pleural effusion; chylothorax; empyema
Cardiovascular	Intraoperative or perioperative air embolism; postoperative pericarditis; perioperative myocardial injury/infarction; venous thromboembolism; supraventricular dysrhythmias; systemic hypertension
Gastrointestinal	Esophagitis (especially *Candida,* herpesvirus, or cytomegalovirus [CMV]); gastroparesis; gastroesophageal reflux; diarrhea (*Clostridium difficile*; medications, especially mycophenolate mofetil and sirolimus); colitis (*C. difficile*; CMV)
Hepatobiliary	Hepatitis (especially CMV or medications); acalculous cholecystitis
Renal	Calcineurin inhibitor nephropathy; hemolytic-uremic syndrome (thrombotic microangiopathy)
Neurologic	Perioperative stroke; tremors; seizures; reversible posterior leukoencephalopathy; headaches
Musculoskeletal	Steroid myopathy; rhabdomyolysis (cyclosporine + HMG-coA reductase inhibitor treatment); osteoporosis; avascular necrosis
Metabolic	Obesity; diabetes mellitus; hyperlipidemia; idiopathic hyperammonemia
Hematologic	Anemia; leukopenia; thrombocytopenia; thrombotic microangiopathy
Oncologic	Lymphoproliferative disease and lymphoma; skin cancers; other malignancies

Graft Dysfunction Primary graft dysfunction (PGD), an acute lung injury, is a manifestation of multiple potential insults to the donor organ that are inherent in the transplantation process. The principal clinical features are diffuse pulmonary infiltrates and hypoxemia within 72 h of transplantation; however, the presentation can be mimicked by pulmonary venous obstruction, hyperacute rejection, pulmonary edema, and pneumonia.

The severity is variable, and a standardized grading system has been established. Up to 50% of lung transplant recipients may have some degree of PGD, and ~10–20% have severe PGD. The treatment follows the conventional supportive paradigm for acute lung injury. Inhalation of nitric oxide and extracorporeal membrane oxygenation have been used in severe cases; retransplantation has also been performed, but when undertaken in the first 30 days this procedure is associated with a poor survival rate (~30% at 1 year). Most recipients with mild PGD recover, but the mortality rate for severe PGD has been ~40–60%. PGD is also associated with longer postoperative ventilator support, longer intensive care unit and hospital stays, higher costs, and excess morbidity, and severe PGD is a risk factor for the later development of chronic rejection (see below).

Airway Complications The bronchial blood supply to the donor lung is disrupted during procurement. Bronchial revascularization during transplantation is technically feasible in some cases, but it is not widely practiced. Consequently, after implantation, the donor bronchus is dependent on retrograde bronchial blood flow from the pulmonary circulation and is vulnerable to ischemia.

The spectrum of airway problems includes anastomotic necrosis and dehiscence, occlusive granulation tissue, anastomotic or bronchial stenosis, and bronchomalacia. The incidence has been in the range of 7–18%, but the associated mortality rate has been low. These problems usually can be managed bronchoscopically with techniques such as simple endoscopic debridement, laser photoresection, balloon dilation, and bronchial stenting.

Rejection Rejection is the main deterrent to higher medium- and long-term survival rates. In this immunologic response to alloantigen recognition, both cell-mediated and antibody-mediated (humoral) cascades can play a role. Cellular rejection is effected by T lymphocyte interactions with donor alloantigens, mainly in the major histocompatibility complex (MHC), whereas humoral rejection is driven by antibodies to donor MHC alloantigens or possibly to non-MHC antigens on epithelial or endothelial cells.

Rejection is often categorized as acute or chronic without reference to the underlying mechanism. Acute rejection is cell-mediated, and its incidence is highest in the first 6–12 months after transplantation. In contrast, chronic rejection generally emerges later, and both alloimmune and non-alloimmune fibroproliferative reactions may contribute to its pathogenesis.

Acute Cellular Rejection With current immunosuppressive regimens, ~30–40% of recipients experience acute rejection in the first year. Acute cellular rejection (ACR) can be clinically silent or can be manifested by nonspecific symptoms or signs that may include cough, low-grade fever, dyspnea, hypoxemia, inspiratory crackles, interstitial infiltrates, and declining lung function; however, clinical impressions are not reliable. The diagnosis is confirmed by transbronchial biopsies showing the characteristic lymphocytic infiltrates around arterioles or bronchioles, and a standardized pathologic scheme is used to grade the biopsies.

Minimal ACR on a surveillance biopsy in a clinically stable recipient is often left untreated, but higher grades generally are treated regardless of the clinical situation. Treatment usually includes a short course of high-dose glucocorticoids and adjustment of the maintenance immunosuppressive regimen. Most episodes respond to this approach; however, more intensive therapy is sometimes necessary for persistent or recurrent episodes.