Lung Transplant Complications

Michael K. Abraham and Robert L. Rogers

KEY POINTS

- All lung transplant recipients with respiratory complaints should be assessed for the possibility of rejection and parenchymal lung infection. In most cases, assessment leads to admission to the hospital.
- Rejection and pulmonary infection are frequently indistinguishable. The clinical manifestation of pneumonia and lung allograft rejection may be subtle, and admission is required to address both entities.
- Lung rejection is common and can occur anytime after transplantation.
- Transplanted lungs are highly susceptible to pneumonia. Cytomegalovirus pneumonia is the most common opportunistic pulmonary infection after lung transplantation.

SCOPE

A lung transplant recipient may seek care in the emergency department (ED) as a result of complications related to the surgical procedure, infections, or medication interactions. The main worry when dealing with transplant patients is to identify the threat for lung allograft rejection and begin treatment if necessary. To complicate matters, potent immunosuppressive regimens may mask serious or life-threatening infectious diseases in organ transplant recipients. This chapter provides information to arm the emergency physician (EP) with the knowledge necessary to take care of this complex group of patients.

More than 1500 lung transplants are performed each year in the United States; worldwide, approximately 3000 were performed in 2009. Survival rates had been rising in recent years because of technologic advances in surgical technique and immunobiology, but they seem to have reached a plateau. The current survival rate 1 year after transplantation is 79%. Multiple conditions necessitate lung transplantation, including cystic fibrosis, end-stage chronic obstructive lung disease, and interstitial lung disease (Box 53.1). The primary reason for bilateral lung transplantation is chronic obstructive pulmonary disease.

The number of patients who have undergone solid organ transplantation increases every year. In 2008 alone, 27,281 organ transplantations were performed in the United States. This figure represents a large number of patients who might seek medical care in an ED. In addition, current survival rates are rising. In 1998, 1-, 3-, and 5-year survival rates were 70.7%, 54.8%, and 42.6%, respectively, for lung transplant recipients. In 2009, the rates were 79%, 63%, and 52%. Although survival rates for lung transplantation lag behind those for other solid organ transplantations, enhancements in immunotherapy will probably continue to advance.

COMPLICATIONS RELATED TO THE SURGICAL PROCEDURE

The type of transplant (single lung, double lung, combined heart and lung, lobar) depends on the recipient’s disease and the particular transplant center where the procedure is performed. Single-lung transplantation requires a lateral thoracotomy incision, and double-lung transplantation requires a double thoracotomy (“clamshell”) incision. The heart may be transplanted along with one or both lungs. In some cases, a lobar segment of donor lung is transplanted. The surgical procedure includes anastomosis of the pulmonary arteries, veins, and bronchus.

EMERGENCY DEPARTMENT PRESENTATION

Patients who have undergone lung transplantation should be considered high risk when seen in an ED for evaluation. Because many patients live far from the facility where their surgery was performed, they are likely to go the nearest ED when problems arise. In a retrospective review of 131 lung and heart-lung transplant patients who visited an ED, the most common complaints were fever (37%), shortness of breath (13%), gastrointestinal symptoms (10%), and chest pain (9%).

ED manifestations of lung transplant recipients are commonly related to complications of the surgical procedure and immunosuppression. Disease unrelated to the transplant may also be present.
Lung allograft rejection is not usually diagnosed in the ED. Typically, patients are admitted and must undergo fiberoptic bronchoscopy and biopsy for diagnosis. Treatment of suspected lung transplant rejection begins with clinical suspicion. In all cases of suspected rejection, the patient’s pulmonologist or lung transplant surgeon should be contacted. This potentially life-threatening entity should be treated before the results of bronchoscopy become available. The biopsy indicates the presence and degree of tissue rejection and inflammation. The complex and histologically directed scale of rejection is beyond the scope of this chapter. The main ED treatment for patients with rejection is high-dose intravenous corticosteroids. Patients are usually given intravenous methylprednisolone at a dose of 0.5 to 1.0 g/day for 3 days, with the first dose given in the ED. If rejection is present, the symptoms should resolve rapidly. The therapy is then switched to oral corticosteroids. It is essential that rejection be diagnosed and treated in the ED in consultation with the patient’s transplant physician. Other interventions for acute rejection include methotrexate, muromonab-CD3, antithymocyte globulin, total lymphoid irradiation, and extracorporeal photopheresis.

**INFECTIOUS COMPLICATIONS**

Despite or possibly as a result of advances in immunosuppression, infection is a common complication after any solid organ transplantation, particularly of the lung. Because of the lung parenchyma’s interaction with the environment, the most common infection is pneumonia, but any opportunistic infection can occur.

Infectious complications after organ transplantation have been studied extensively and are related to multiple factors, the most important being the time since transplantation. Infections in organ recipients can be broken down into three periods (Fig. 53.1).

During the first month after transplantation, nosocomial infections predominate. Wound infections, urinary tract infections, pneumonia, and vascular access infections are common in this period. Opportunistic infections, such as those caused by *Pneumocystis* and *Nocardia* species, do not usually occur in the first month after transplantation. Infections that emerge 1 to 6 months after solid organ transplantation include many of the opportunistic infections, such as those caused by *Pneumocystis carinii* and *Listeria monocytogenes*. In addition,
immunomodulating viruses (particularly cytomegalovirus [CMV]) become important pathogens. Epstein-Barr virus, hepatitis B virus, hepatitis C virus, and human immunodeficiency virus can also produce infection during this time frame.

Viral infections that emerge after the first month following transplantation may be associated with chronic or progressive infection and may cause significant injury to the affected transplanted organ. Patients who experience chronic or recurrent bouts of organ rejection are invariably exposed to higher and prolonged periods of immunosuppressive therapy and thus tend to be vulnerable to these opportunistic pathogens.

### PULMONARY INFECTIONS

The lungs are particularly vulnerable to infection after solid organ transplantation. The highest risk for posttransplantation pulmonary infection occurs in lung transplant recipients. Pulmonary infections are the most common infectious complication in heart and lung transplant recipients and the least common in kidney transplant recipients. Multiple factors explain this higher incidence of lung infections (Box 53.3).

Organisms that commonly cause pulmonary infection in the postoperative period are gram-negative organisms (nosocomial) and *Staphylococcus aureus*. Community-acquired bacterial pneumonia tends to occur later in the posttransplantation period. Causative organisms include *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Legionella* species. Most cases of bronchiolitis obliterans syndrome are caused by *Pseudomonas aeruginosa*. Patients with this syndrome commonly have recurrent episodes of purulent bronchitis and pneumonia. Other infections to consider are fungal pneumonia and tuberculosis (Table 53.1).

Pulmonary infections in transplant patients may not cause the symptoms seen in other outpatients who have not received a transplant. As stated earlier, the symptoms may be subtle and may be as simple as a dry cough and mild upper respiratory tract discomfort. Fever in a patient receiving immunosuppressive treatment is a worrisome sign and may be the only manifestation of a serious underlying lung infection such as pneumonia. Many lung transplant recipients do not look that ill initially or do not have fulminant symptoms of pneumonia when first evaluated (Fig. 53.2).

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**Box 53.3 Factors Contributing to Risk for Pulmonary Infections in Lung Transplant Recipients**

- Impairment in cough because of lung denervation
- Narrowing of the bronchial anastomosis
- Disruption of pulmonary lymphatics
- Impairment of the mucociliary “escalator”
- Passive transfer of occult pneumonia from the donor

When a lung transplant recipient is being evaluated in an ED, pulmonary infection must be highest on the differential diagnosis, and the patient’s pulmonary or transplant physician should be contacted. Any suspicion of a pulmonary infection warrants the administration of broad-spectrum antibiotics that cover common community-acquired pathogens and healthcare–associated pathogens, including *Pseudomonas* species. In most cases, patients in whom pulmonary infection is suspected are admitted to the hospital or transferred to another facility where they will probably undergo fiberoptic bronchoscopy.

**Table 53.1** Differential Diagnosis of Fever and Pulmonary Infiltrates in Organ Transplant Recipients According to the Abnormality on Chest Radiographs and Rate of Progression of the Illness

<table>
<thead>
<tr>
<th>RADIOGRAPHIC ABNORMALITY</th>
<th>Cause</th>
<th>ACUTE ILLNESS*</th>
<th>SUBACUTE OR CHRONIC ILLNESS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consolidation</td>
<td></td>
<td>Bacteria (including <em>Legionella</em>)</td>
<td>Fungi</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thromboembolism</td>
<td><em>Nocardia asteroides</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hemorrhage</td>
<td>Tumor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pulmonary edema</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Viruses</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Drug reactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Radiation exposure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>Pneumocystis carinii</em></td>
</tr>
<tr>
<td>Peribronchovascular abnorality</td>
<td>Pulmonary edema</td>
<td>Viruses</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Leukoagglutinin reaction</td>
<td><em>P. carinii</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bacteria</td>
<td>Irradiation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Viruses (influenza)</td>
<td>Drug reactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Occasionally <em>N. asteroides</em>, tumor, fungi, tuberculosis</td>
</tr>
<tr>
<td>Nodular infiltrate†</td>
<td>Bacteria (including <em>Legionella</em>)</td>
<td>Fungi</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pulmonary edema</td>
<td><em>N. asteroides</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tuberculosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>P. carinii</em></td>
</tr>
</tbody>
</table>


*Acute illness develops and requires medical attention in less than 24 hours. Subacute or chronic illness develops over a period of several days to a week.
†A nodular infiltrate is one or more focal defects greater than 1 cm² in area on chest radiographs with well-defined borders and surrounded by aerated lung. Multiple tiny nodules are seen in a wide variety of disorders (e.g., cytomegalovirus, varicella-zoster virus infection) and are not included here.

**Fig. 53.2** Computed tomography (CT) scan of the chest showing an atypical infection. This is a CT scan of the chest with intravenous contrast enhancement in a bilateral lung transplant recipient. The patient came to the ED with a complaint of shortness of breath. The patient’s plain chest radiograph was interpreted as normal. The CT scan was negative for pulmonary embolism but shows diffuse inflammation. Bronchoscopy performed as an inpatient procedure was positive for *Pseudomonas aeruginosa* infection.
**Box 53.4 Clinical Findings in Cytomegalovirus Disease**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>Cough</td>
</tr>
<tr>
<td>Malaise</td>
<td>Dyspnea</td>
</tr>
<tr>
<td>Myalgia</td>
<td>Unexplained leukopenia</td>
</tr>
</tbody>
</table>

**Cytomegalovirus Infection**

CMV causes one of the most important and lethal infections in solid organ recipients. This virus, referred to as the “troll of transplantation,” is the second most common infection in lung transplant recipients after bacterial pneumonia. The overall likelihood of CMV infection in a lung transplant recipient is approximately 50% and is related to the CMV status of the donor and recipient.

CMV infection generally occurs 1 to 3 months after transplantation. Any episode of acute rejection raises the patient’s risk for continued CMV infection because of the immunosuppression required. The clinical findings may range from asymptomatic viremia to overwhelming sepsis and multiorgan failure. True clinical disease may be manifested as a mononucleosis-like syndrome with fever, malaise, and leukopenia (Box 53.4). There may also be organ-specific involvement in the lungs (pneumonitis), gastrointestinal system (colitis and hepatitis), and central nervous system. Over time, CMV infection leads to a high level of immunosuppression and the subsequent development of chronic allograft dysfunction and possibly failure.

Pneumonitis is the most common manifestation of CMV disease after lung transplantation. Clinically, CMV pneumonitis may look like acute rejection. Patients with either acute lung allograft rejection or CMV pneumonitis may have low-grade fever, a nonproductive cough, and shortness of breath. Further inpatient work-up (i.e., bronchoscopy) is generally required to distinguish the cause. CMV pneumonitis is diagnosed through serologic testing and the results of bronchoscopy, discussion of which is beyond the scope of this chapter. As many as 10% to 15% of patients with CMV pneumonitis are asymptomatic initially. A prodrome consisting of fever, malaise, and myalgias frequently precedes the onset of pneumonitis (cough and dyspnea). The disease may appear as opacities, nodules, or lobar infiltrates on chest radiographs.

Treatment of CMV infection may start in the ED. The diagnosis of CMV infection may not be established on initial evaluation, but a presumptive diagnosis is frequently made and empiric therapy started. Standard treatment of CMV infection consists of a 2- to 3-week course of intravenous ganciclovir. In some cases, ganciclovir is combined with CMV hyperimmune globulin. These therapies are usually started after the patient has been admitted.

All lung transplant recipients seen in an ED within the vulnerable period of 1 to 3 months after surgery should be evaluated carefully for CMV disease. It should be assumed that any lung transplant recipient who underwent transplantation less than 3 months previously and who has fever, cough, or other suspicious findings may have active CMV disease. In many cases, therapy is started in the ED in consultation with the patient’s physician.

**Medical Complications**

Patients who have undergone single-lung transplantation are at increased risk for bronchogenic carcinoma in their native lung. Venous thromboembolism (VTE) is a potential complication of any surgery, and lung transplantation increases the risk 8% to 29% over other forms of organ transplantation. Thus, the diagnosis of VTE and pulmonary embolism should be entertained when the initial complaint is shortness of breath or chest pain.

Patients who undergo long-term immunosuppression are at risk for posttransplant lymphoproliferative disorder (PTLD). Its prevalence is higher in lung transplant recipients than in other solid organ transplants. PTLD is typically manifested as non-Hodgkin lymphoma, which results from infection with Epstein-Barr virus, and nodules or masses can be seen on the chest film.

**Diagnostic Testing**

Diagnostic imaging in the ED is usually limited to plain film chest radiography and, occasionally, computed tomography (CT). EPs should maintain a low threshold for obtaining a CT scan of the chest in lung transplant recipients. CT has been shown to be far superior to chest radiography in detecting subtle cases of pneumonia in transplant patients.

**Immunosuppressive Therapy**

Because transplant recipients undergo long-term immunosuppressive therapy, they are prone to multiple drug side effects, drug-drug interactions, and higher risk for opportunistic infections. EPs must use caution when prescribing any new medication to transplant patients in the ED because potentially serious drug side effects and drug-drug interactions may result. It is best to discuss medication issues with the patient’s physician or a pharmacist.

Medications commonly used in lung transplant patients are calcineurin inhibitors (e.g., cyclosporine), cell cycle inhibitors, and corticosteroids. Their side effects are listed in Table 53.2. Most patients are maintained on a combination of these classes of medications.

Many commonly used medications may interfere with drugs used for long-term immunosuppression. Medications known to increase the blood levels (and thus toxicity) of certain medications include cyclosporine (Neoral) and tacrolimus (Prograf). In particular, erythromycin, doxycycline, and azole antifungal agents (ketoconazole, fluconazole, itraconazole) all raise serum concentrations of cyclosporine and tacrolimus. In contrast, other medications, such as isoniazid, rifampin, and rifabutin, lower the blood levels of these two immunosuppressants and may put the patient at risk for organ rejection. Sulfonamides, ganciclovir, and acyclovir potentiate the bone marrow toxicity of azathioprine and mycophenolate mofetil.

**Treatment and Disposition**

All patients with suspected lung transplant rejection or infection should be admitted to the hospital for further diagnostic
testing and evaluation. The importance of appreciating the subtle nature of these complications cannot be overemphasized. It is wise to seek consultation with the patient’s pulmonary physician or surgeon. A safe way to evaluate any lung transplant recipient seen in the ED is to assume that infection or rejection is present until proved otherwise (Box 53.5).

Lung transplant recipients are maintained on multiple immunosuppressive medications that interfere with many commonly used medications, such as antibiotics. EPs should never take it on themselves to add a drug to a transplant recipient’s regimen or alter the dose of an immunosuppressant without first consulting with the patient’s physicians.

By understanding the subtleties of rejection and pneumonia and the importance of drug side effects and interactions in lung transplant recipients, the EP will be in a better position to take care of this complex group of patients in the ED.

### SUGGESTED READINGS


### REFERENCES

References can be found on Expert Consult @ www.expertconsult.com.
REFERENCES


