Respiratory Complications After Solid-Organ Transplantation

Pınar Zeyneloğlu

Abstract

The risk for respiratory complications after solid-organ transplantation continues to be high, even though progress has been achieved with surgical techniques, immunosuppressive agents, and perioperative treatment of transplant recipients. This review is an overview of infectious and noninfectious respiratory complications in liver, kidney, heart, and lung transplant patients. Postoperative respiratory complications are more frequent after liver, heart, and lung transplant recipients, but the incidence is lower in kidney transplant recipients. Lung infiltrates due to multidrug-resistant bacterial infections are increasing and may cause respiratory failure associated with high morbidity and mortality. Treatment strategies including early, broad-spectrum empiric antibiotic therapy, lung protective mechanical ventilation, and appropriate timing of tracheotomy for patients who need prolonged mechanical ventilation. Early recognition and aggressive treatment of these respiratory complications may improve outcomes.

Key words: Heart, Lung, Liver, Kidney, transplant recipient, Respiratory failure

Introduction

Solid-organ transplantation (SOT) has been known as the standard of care for patients with end-stage organ failure. According to 2009 Global Data in Organ Donation and Transplantation from 98 countries, representing 90% worldwide population, 104 065 SOTs are performed annually worldwide including 71 418 kidney, 21 027 liver, 5403 heart, 3649 lung, 2316 pancreas, and 252 small bowel transplants. Although the immunosuppressive agents, surgical techniques, and graft survival have improved, respiratory complications are still among the important contributors to morbidity and mortality in SOT recipients.

Transplant recipients have high risk for respiratory complications after SOT due to their immunosuppressed status and surgical techniques used during transplant surgery. In adult liver transplant recipients, the incidence of respiratory complications during the early postoperative period was 59.1%, and older age and higher intraoperative transfusion requirements were noted as risk factors by Pirat and associates. Hong and coworkers found that pulmonary infiltrates were detected in 42.7% liver transplant recipients, and the etiology of the infiltrates was pleural effusion in 73.5%, pneumonia in 8.8%, atelectasis in 8.8%, pulmonary edema in 7.4%, and acute respiratory distress syndrome (ARDS) in 1.5% patients. Feltracco and associates demonstrated most commonly identified perioperative risk factors for respiratory complications after orthotopic liver transplant (Table 1).

In adult kidney recipients, respiratory complications are less frequent (3%-17%) and mostly secondary to noninfectious reasons early after surgery, whereas late respiratory failure frequently is due to infectious causes. In heart transplant recipients, pulmonary complications occur in 29.9% cases and are due to pneumonia, primarily bacterial in half the patients. Risk factors for pulmonary complications in heart transplant recipients are duration of heart failure, multiple organ failure, need for postoperative extracorporeal therapies, and intensive immunosuppression.
Pulmonary infection and acute rejection are the most common and serious complications after lung transplant. Major risk factors for postoperative pulmonary complications in lung transplant recipients include technical problems at the bronchial or vascular anastomoses, prolonged ischemia time, lung denervation, severe graft dysfunction, lung denervation, and impaired mucociliary function and lymphatic disruption.

Respiratory complications can be classified as either infectious or noninfectious and according to the time after transplant (early [< 100 d] or late [> 100 d] after surgery). These infectious and noninfectious situations may or may not be associated with respiratory failure, and definitions of these postoperative complications are outlined (Table 2).

There are various SOT procedures performed with organs including liver, kidney, heart, and lung. This review offers an overview of the respiratory complications after these SOTs.

**Infectious respiratory complications**

Despite a reduction in pulmonary infections due to prophylactic strategies and advances in diagnosis, treatment, and prevention, infectious respiratory complications still remain a life-threatening complication. Approximately two-thirds of lung infiltrates observed after transplantation are of infectious origin. The lung is the leading infectious site in lung and heart transplant recipients, second most common site (after intraabdominal infection) in liver transplant recipients, and lowest in frequency in kidney transplant recipients.

Factors that may contribute to the type, severity, and outcome of the infection include underlying condition, comorbidity (especially diabetes mellitus and renal failure), degree of end-stage organ dysfunction, transfusion need, invasiveness of the surgical procedure, and duration of mechanical ventilation. Recent nosocomial exposures, remote latent infections in the recipient, and latent or unknown donor infections transmitted by the graft are possible sources.

Posttransplant infections occur at a predictable time (Table 3). The risk of infection is usually related to surgery, intensive care, invasive procedures, and hospitalization during the first month. Nosocomial bacterial infections including gram-negative pathogens and multidrug resistant (MDR) microorganisms are frequent, and fungal infections are infrequent but associated with high mortality. During the first to sixth months after SOT (a period of maximum sustained immunosuppression), immunomodulating viruses and opportunistic infections are high. After 6 months, community-acquired infections are common because the level of immunosuppression can be reduced due to sufficient allograft function. Opportunistic pathogens are less frequent in this period, except in the subgroup of patients who have immunosuppression increased due to treatment of acute or chronic rejection.

The diagnostic approach to pulmonary infiltrates in SOT recipients must be early and aggressive for the differential diagnosis of pulmonary infections. In addition to chest radiography and computed tomography (CT), fiberoptic bronchoscopy should be

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**Table 1. Perioperative Risk Factors for Respiratory Complications After Orthotopic Liver Transplantation**

<table>
<thead>
<tr>
<th>Preoperative</th>
<th>Intraoperative</th>
<th>Postoperative</th>
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<tbody>
<tr>
<td>Recipient age</td>
<td>Surgical procedure (wide incision)</td>
<td>Excessive perioperative fluid administration</td>
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<tr>
<td>Female sex</td>
<td>Fluid transfusion volume</td>
<td>Duration of mechanical ventilation</td>
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<tr>
<td>Smoking history</td>
<td>Blood transfusion volume</td>
<td>Acute rejection during the hospital stay</td>
</tr>
<tr>
<td>Severity of liver dysfunction (Child-Pugh class, MELD score)</td>
<td>Perioperative fluid balance</td>
<td>Postoperative acute renal failure</td>
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<tr>
<td>Cirrhosis</td>
<td>Fluid retention</td>
<td>Postoperative hypoproteinemia</td>
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<tr>
<td>Cerebral dysfunction</td>
<td>Bleeding volume</td>
<td>Poor postoperative myocardial function</td>
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<tr>
<td>Acute renal failure</td>
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<td>Right hemidiaphragm paralysis</td>
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<tr>
<td>Emphysema</td>
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<td>Greater exposure to nosocomial agents</td>
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<td>High systolic pulmonary artery pressure</td>
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<td>Decline in recipient immune function</td>
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<td>Hypoxia, orthodeoxia</td>
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<td>Surgical complications</td>
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<td>Hepatopulmonary syndrome</td>
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<td>Reintervention or need for revision transplant</td>
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<tr>
<td>Pre-existing pulmonary abnormalities</td>
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<td></td>
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<tr>
<td>Cardiopulmonary disease (intrinsic or specific to liver disease)</td>
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<td>Restrictive pulmonary syndrome</td>
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<td>Abnormal spirometry findings</td>
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<td>Preoperative ventilator support due to respiratory failure</td>
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<td>High INR value</td>
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<tr>
<td>Pre-existing diabetes mellitus</td>
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<tr>
<td>Impaired renal function</td>
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<td>Preoperative MARS use</td>
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<td>Deceased-donor source of organ transplant</td>
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**Abbreviations:** INR, international normalized ratio; MARS, molecular adsorbent recycling system; MELD, model for end-stage liver disease
considered. Eyüboğlu and colleagues reported that suspected pulmonary infection is the most common indication for fiberoptic bronchoscopy in transplant recipients, and bronchoscopy may identify the causative organism in > 30% patients. While starting broadspectrum empiric antimicrobial therapy, in addition to local microbiological data, biomarkers such as procalcitonin and galacto-mannan may help as part of a promising diagnostic approach for detecting infection after SOT.

### Bacterial pneumonia

Pneumonia is the most common lower respiratory tract infection after SOT. Bacterial pneumonia may be nosocomial or community acquired. Nosocomial pneumonia is almost always a perioperative complication. Responsible pathogens usually are gram-negative, but hospital-acquired MDR pathogens are increasing and methicillin-resistant *Staphylococcus aureus* and *Legionella* infections may be observed. Among SOT recipients, some of the risk factors to acquire MDR *Enterobacteriaceae* and *Acinetobacter* include previous use of antibiotics, prolonged intensive care unit (ICU) stay, and renal failure with or without dialysis. The major risk factor for nosocomial pneumonia is the requirement of prolonged mechanical ventilation after SOT. Liver transplant recipients may have massive intraoperative bleeding during transplantation, persistence of severe encephalopathy, postoperative acute respiratory distress syndrome, and acute renal injury that may be related to prolonged mechanical ventilation and development of infectious complications. Lung transplant recipients have other risk factors such as impairment of mucociliary activity and pulmonary lymphatics, absent cough reflex, and narrowing of
bronchial anastomosis that may compromise their local pulmonary defenses.\(^2\) Community-acquired bacterial pneumonia is observed later after transplantation; responsible pathogens include \textit{Streptococcus pneumonia}, \textit{Haemophilus influenzae}, and \textit{Legionella}.\(^2\)

In liver transplant recipients, the incidence of nosocomial pneumonia is documented at 15\% to 20\%, and acute respiratory failure due to pneumonia after liver transplantation may occur in 50\% to 70\% patients.\(^{16,17}\) Ikegami and associates reported that 14.5\% living-donor liver transplant recipients had early-onset bacterial pneumonia that was associated with prolonged mechanical ventilation, intensive care unit stay, graft dysfunction, and mortality of 25.7\%.\(^18\) Early-onset hospital-acquired and ventilator-associated pneumonia may occur within the first 4 to 6 postoperative days, and late infections are observed after postoperative day 6.\(^6,19\) Pathogens including \textit{Pseudomonas aeruginosa}, \textit{Escherichia coli}, \textit{Klebsiella}, \textit{Acinetobacter}, and \textit{Staphylococcus aureus} may be isolated in bronchoalveolar lavage samples of liver transplant recipients.\(^20,21\) Empiric antibiotic therapy should be based on local epidemiologic data, and de-escalation should be performed according to the diagnostic evaluation.

In renal transplant recipients, infectious problems are not frequently observed early after surgery because early respiratory failure is mainly non-infectious in origin (cardiogenic pulmonary edema), but late respiratory failure may occur due to pneumonia within the subsequent months to years after transplant. Some of the risk factors for bacterial infections in renal transplant recipients include delayed graft function, years of dialysis before transplant, diabetes, lupus, and female sex.\(^12,22\) In retrospective studies, bacterial pneumonia was the main respiratory infection problem observed within the first 5 months after transplant.\(^23\) Candan and coworkers reported that pneumonia was the main infectious reason for admission to the ICU, and \textit{Escherichia coli} was the main pathogen in renal transplant recipients admitted to the ICU during long-term follow-up.\(^24\) In another retrospective multicenter study, the reason for ICU admission was acute respiratory failure in approximately half of the kidney transplant recipients admitted; the most common cause of acute respiratory failure was bacterial pneumonia in 35.5\% patients, and \textit{Escherichia coli} and \textit{Streptococcus pneumonia} were the most frequently recovered pathogens.\(^25\) The first-line antibiotic regimen should be chosen according to risk factors and local epidemiology and should be de-escalated when appropriate.

In heart and lung transplant recipients, pneumonia is a major cause of morbidity and mortality. During the first month after heart transplantation, the risk for bacterial pneumonia is highest in patients with prolonged mechanical ventilation, pulmonary edema, and \textit{cytomegalovirus} (CMV) infection.\(^26\) The incidence of pneumonia ranges from 20\% to 30\%, and nosocomial MDR pathogens, community-acquired bacteria, and opportunistic microorganisms are observed within the first 6 months after transplantation.\(^8\) In a retrospective review, Lenner and coworkers reported that the most common pulmonary complication in cardiac transplant recipients is bacterial pneumonia, and this occurs with similar frequency in the first month and at > 6 months after transplantation.\(^7\) Late-onset community-acquired pneumonia had good prognosis with empiric antibiotic therapy, but bacterial pneumonias within the first 6 months after transplant were nosocomial in origin and had high mortality.\(^7\) In lung transplant recipients, pneumonia has high incidence and is associated with mortality, and risk factors for pneumonia include high-level immunosuppression, altered local pulmonary host defenses, and direct access of environmental pathogens to the allograft.\(^27,28\) The incidence of nosocomial pneumonia early after transplantation was 15\%, and the most frequent organisms were drug-resistant gram-negative bacteria. Nosocomial pneumonia is observed in 47\% lung transplant recipients during their ICU stay, and 40\% of patients who had nosocomial pneumonia had pneumonia recurrence.\(^29\) Most frequently isolated organisms were Enterobacteriaceae, \textit{Pseudomonas aeruginosa}, and \textit{Staphylococcus aureus}. Another retrospective study reported that in lung transplant recipients, new pulmonary infiltrates occurring after the first month are most likely due to infection, with bacterial pathogens responsible in 50\% pneumonias.\(^8\) Lung transplant recipients with new pulmonary infiltrates should be assessed with high suspicion of pneumonia and require early diagnosis and specific treatment.

Nocardia infections are rarely reported (0.7\%-3\%) in patients after SOT due to reduced doses of corticosteroids used and widespread sulfonamide use for \textit{Pneumocystis} pneumonia prophylaxis.\(^2\) Concomitant infection with CMV, profound hypogammaglobulinemia, and aggressive immunosuppression...
(use of antilymphocyte immunoglobulins) are major risk factors for nocardial infections. Infection occurs within 1 to 6 months after transplant. Pulmonary nocardiosis may cause granulomatous and pyogenic processes with several nodules that often progress to cavitation on radiographs or CT scans. Dissemination to brain, skin, and soft tissue may occur, and sulfonamides are the treatment of choice.

Legionella species are important causes (25%-50% cases) of hospital- and community-acquired pneumonias after SOT. Most cases are observed early after transplantation and during augmented immunosuppression. In the peritransplant period, Legionella may be transmitted through mechanical ventilators and nasogastric tubes. Legionella should be suspected in all transplant recipients with community-acquired pneumonia, especially when they do not respond to betalactam antibiotics. Legionella infection should be diagnosed with both culture and urinary antigen, and prompt empiric therapy in suspected patients includes azithromycin or a fluoroquinolone.

Tuberculosis is more frequent in transplant recipients than the general population. Mycobacterium tuberculosis infections are mainly observed in areas that are highly endemic. The prevalence is 0.5% to 6.4% in low-endemic areas but 15.2% in endemic areas. Most patients with tuberculosis infection present in the first 6 months after transplant, but the onset is later in renal transplant recipients. Most transplant recipients with tuberculosis infection have pulmonary tuberculosis (51%), and fever is the most common presenting symptom. Radiographic changes include focal infiltrates, miliary pattern, pleural effusions, diffuse interstitial infiltrates, and cavitary lesions. Diagnosis of active tuberculosis in SOT recipients is challenging due to unusual manifestations of the disease. Although the treatment involves combination therapy as in the general population, interaction between antituberculosis and antirejection medications may increase the risk of rejection because of difficulty in drug dosing. Mortality of transplant recipients with tuberculosis is 25% to 40%. In transplant patients, routine skin testing and preemptive treatment of the latent infection is recommended. Isoniazid is preferred for the treatment of latent tuberculosis and can be used with caution in liver transplant candidates.

Nontuberculous mycobacterial pulmonary infections are more common in heart and lung transplant recipients than other SOT recipients, and onset of the infection usually is ≥ 1 year after transplant.

Viral infections

The CMV is the most common viral pathogen observed in solid organ transplant recipients. The CMV disease is CMV infection accompanied by clinical signs and symptoms. The CMV disease is categorized as (1) CMV syndrome that manifests as fever and/or malaise, leukopenia, and thrombocytopenia and (2) tissue-invasive CMV disease (pneumonitis, myocarditis, nephritis, gastrointestinal disease, or other). Without prevention, CMV disease occurs during the first 3 months after transplantation, but onset is delayed in patients after SOT receiving CMV prophylaxis.

The incidence of CMV pneumonitis is 0% to 9.2% in liver transplant recipients, 0.8% to 6.6% in heart transplant recipients, < 1% in renal transplant recipients, and 15% to 55% in lung transplant recipients because the lung is a major site of CMV latency. The presence of CMV pneumonitis is characterized by nonproductive cough and dyspnea; ground glass opacities, consolidation, or nodules on radiography; and leukopenia, thrombocytopenia, and elevated liver enzymes in biochemistry tests. Histopathology confirms the presence of tissue-invasive CMV disease. Molecular tests that detect CMV DNA or RNA are the preferred methods for diagnosis of CMV after SOT, and higher viral load values are associated with tissue-invasive disease. Antiviral drugs for CMV prophylaxis are valganciclovir and ganciclovir, and these drugs should be started within the first 10 days after transplantation. For kidney transplant recipients, valacyclovir is an alternative. The standard treatment of CMV disease in transplant recipients includes intravenous ganciclovir or valganciclovir.

Community respiratory viruses including influenza, parainfluenza, adenovirus, and respiratory syncytial virus may cause lower respiratory tract infection and severe respiratory insufficiency. Lung transplant recipients have the highest risk for respiratory viral infections. Treatment is mostly supportive, and prevention with amantadine or rimantadine is important in influenza outbreaks involving transplant recipients.

Fungal infections

Aspergillosis is the most common and fatal fungal pathogen in transplant recipients. The incidence of
invasive aspergillosis is 1% to 15% SOT recipients and has a 22% mortality rate. Invasive disease may be observed as localized (pulmonary or extrapulmonary disease) or disseminated aspergillosis. Invasive disease generally is diagnosed within the first 6 months after transplantation and usually involves the lung. Symptoms are nonspecific, and fever, cough, pleuritic chest pain, and hemoptysis can be observed. In pulmonary aspergillosis, single or multiple nodular opacities, cavities, or alveolar consolidation can be observed on radiographs. Most important risk factors for invasive aspergillosis are retransplantation and renal failure in liver transplant recipients; graft failure requiring hemodialysis and high and prolonged duration of corticosteroids in kidney transplant recipients; receipt of single lung transplant, relative ischemia at the anastomosis, CMV infection, and pre/post colonization of the airways with Aspergillus in lung transplant recipients; and the isolation of Aspergillus fumigatus from bronchoalveolar lavage, reoperation, CMV disease, and posttransplant hemodialysis in heart transplant recipients. Invasive Aspergillus infections are more frequent (15%) in lung but rare (< 5%) in liver transplant recipients. High fatality is observed in heart transplant patients. Diagnosis of invasive aspergillosis is challenging. Diagnostic criteria have been reported for fungal infections in immunocompromised hosts. Cultures of respiratory tract secretions can be detected in the late stages of the disease, and the sensitivity of the galactomannan test can be improved by testing bronchoalveolar lavage. The CT findings for invasive fungal infection are a halo sign (poor sensitivity), multiple nodules, masses, or cavitation (air-crescent sign), and these are more frequent in stem cell transplant recipients. Prompt initiation of antifungal therapy (intravenous voriconazole as primary therapy) is important for optimal outcomes in transplant recipients.

Pneumocystis pneumonia can be effectively prevented with the use of trimethoprim-sulfamethoxazole prophylaxis. Other fungal organisms including Cryptococcus neoformans are rare causes of pulmonary disease and present with disseminated disease. Candida species may commonly cause bloodstream, intraabdominal, and urinary tract infection in organ transplant recipients. Candida albicans is the dominant invasive pathogen. Pulmonary candidiasis is rare, even among lung transplant recipients, and histopathologic evidence is necessary to confirm diagnosis. Isolation of Candida species from the respiratory tract rarely indicates invasive candidiasis and usually is not treated with antifungal therapy, but lung transplant recipients with anastomotic tracheobronchitis due to Candida may be an exception.

Noninfectious respiratory complications
Recipients of SOT are at increased risk of developing noninfectious respiratory complications early or late after surgery, depending on the grafted organ and site of transplant (either abdomen or thorax). Pleural effusion, atelectasis, pulmonary edema, diaphragmatic dysfunction, and ARDS are complications that may cause respiratory failure. Postoperative respiratory complications are more frequent after liver, heart, and lung transplantation, but the incidence is lower in kidney transplant recipients. Postoperative respiratory complications are associated with the preoperative status of the recipient, functional recovery of the graft, surgical-trauma-induced systemic inflammatory response, intraoperative hemodynamic changes, ischemia-reperfusion injury, and toxicity of posttransplant medications.

Pleural effusion
In liver transplant recipients, pleural effusions are primarily right-sided (30%-50%), transudative, and not related to primary cardiovascular disease. The mechanisms are disruption of the lymphatics during hepatectomy, transfer of ascites to the thoracic cavity due to diaphragmatic defects, hypoalbuminemia, atelectasis, and volume overload. Effusions may expand during the first postoperative week but generally resolve by the following weeks. Drainage of the effusion is required in 10% to 20% patients due to respiratory failure or to rule out other causes when left-sided only. Persistent effusions may predispose to pneumonia by reducing dependent lung expansion and causing atelectasis. Persistent and enlarging effusions may be due to subdiaphragmatic processes and are considered accordingly.

In renal transplant recipients, volume overload is the primary reason for pleural effusions. Pleural effusion may be associated with atelectasis. Urinotherax is a rare cause of pleural effusion due to obstruction of the transplanted ureter. In heart transplant recipients, pleural effusions are common during the first week after transplant.
They result from postoperative hemorrhage, disruption of the lymphatic system, mediastinal blood, or graft dysfunction.6

In lung transplant recipients, pleural effusions early after surgery are common (25%) in the presence or absence of allograft rejection.45 They are bloody, neutrophil-predominant exudates due to surgical trauma and capillary leak pulmonary edema.46 Pleural space infection occurs in 25% lung transplant recipients who have early postoperative effusions, and elevated neutrophils in the pleural fluid has the greatest specificity for identifying the pleural space infection.45

Diaphragmatic dysfunction
Right-sided diaphragmatic dysfunction is a common perioperative complication after liver transplantation because of crush injury to the right phrenic nerve from clamping the suprahepatic vena cava during surgery.44

In heart and lung transplant recipients, diaphragmatic dysfunction due to phrenic nerve injury also is common. A retrospective study reported that 42.8% heart and 9.3% lung transplant recipients had phrenic nerve dysfunction, and this complication affected the number of ventilator days and ICU resource use.47

Pulmonary edema
In liver transplant recipients, severe pulmonary edema is unusual early after transplantation. Causes of acute pulmonary edema may include acute fluid overload due to massive amounts of fluid and blood products administered intraoperatively, postoperative acute kidney injury, and severe acute left ventricular dysfunction. Patients with pulmonary edema after liver transplantation stayed longer in the ICU and had longer duration of mechanical ventilation; when compared with hydrostatic-type pulmonary edema, permeability-type pulmonary edema was associated with increases in pulmonary arterial pressure and pulmonary vascular resistance.48,49

In kidney transplant recipients, pulmonary edema is the main cause of respiratory failure after transplantation. It is due to early graft dysfunction or acute rejection.6

In addition to complications such as pneumothorax, atelectasis, bronchitis, and mediastinitis seen in cardiac surgical patients, pulmonary edema is a pulmonary complication that may be observed after heart transplantation.

In lung transplant recipients, pulmonary edema is a type of acute noncardiogenic pulmonary edema that occurs as part of the primary graft dysfunction (PGD, previously known as pulmonary reimplant response or reperfusion pulmonary edema). Transient and mild pulmonary edema may be observed quite frequently (57%) because of increased vascular permeability due to allograft ischemia and reperfusion.50 However, severe edema persists in 10% to 25% recipients and can result in PGD, which is the leading cause of early death after lung transplantation.51,52 The PGD is characterized by severe hypoxemia, lung edema, and radiographic appearance of diffuse pulmonary opacities without an identifiable cause, and may develop within 72 hours. It represents a multifactorial injury to the transplanted donor lung by the transplant process (retrieval, preservation, implant, and reperfusion) and by other factors such as aspiration, pneumonia, and ventilator-associated lung injury including recipient factors.53 The typical histopathologic pattern is diffuse alveolar damage. The severity of PGD is graded based on the ratio of arterial oxygen pressure to inspired oxygen concentration (P_{O_2}/FiO_{2}). Patients who have PGD grade 3 (P_{O_2}/FiO_{2} < 200) have the worst short- and long-term outcomes.52 The PGD also is a risk factor for the development of chronic lung transplant rejection. Differential diagnosis includes pulmonary edema from volume overload or myocardial dysfunction, pneumonia, rejection, aspiration, pulmonary thromboembolism, and technical problems. The main treatment strategy is supportive care. Treatment is similar to treatment used in ARDS. In addition to conventional supportive treatment with lung protective ventilation and optimal fluid treatment, inhaled nitric oxide and extracorporeal membrane oxygenation can be used.51

Acute respiratory failure
Perioperative acute respiratory failure may be observed after SOT. The incidence is high in liver transplant recipients because of extensive upper abdominal surgery, perioperative intravascular volume shifts (with volume overload and massive blood products administered), preoperative status of the patient, and a high frequency of postoperative pneumonia.54 Risk factors for prolonged mechanical ventilation after orthotopic liver transplantation include acute liver failure before transplantation,
severe postoperative graft dysfunction, and retransplantation. González and colleagues reported that the risk factors for development of acute respiratory failure after liver transplantation were female sex, Child-Pugh class, pulmonary edema, postoperative acute renal failure, cerebral dysfunction, and respiratory infection. In another study, it was shown that acute respiratory failure was precipitated by pneumonia and pulmonary edema in liver transplant recipients.

Hepatopulmonary syndrome and portopulmonary hypertension are pulmonary complications of advanced liver disease and may complicate the postoperative period because they may not correct immediately after liver transplantation. Hypoxemia may persist after transplantation, and patients may require prolonged mechanical ventilation. Portopulmonary hypertension after liver transplantation is associated with posttransplant mortality. Prostacyclin has been reported to be successful in the posttransplant treatment of pulmonary hypertension. Extracorporeal membrane oxygenation may be used for refractory hypoxemia after liver transplantation in severe hepatopulmonary syndrome and as a rescue therapy in portopulmonary hypertension.

Acute respiratory failure may be due to ARDS within 24 hours or few days after liver transplantation. According to the Berlin Definition, ARDS is newly defined as a single entity of acute onset respiratory failure that (1) occurs within 1 week of known clinical insult or new or worsening respiratory symptoms, (2) is not fully explained by cardiac failure or volume overload, and (3) includes bilateral opacities with 3 levels of severity (mild, moderate, and severe) according to the degree of hypoxemia with P_{a}O_{2}/FiO_{2} ratio and positive end-expiratory pressure (PEEP) requirement. The reported incidence of ARDS is between 4.5% to 16.3%, and mortality rate is 70% to 80%. In a retrospective analysis, frequent causes of ARDS included fluid overload from crystalloid infusion or massive transfusion, and predisposing or contributing factors were sepsis, intravenous use of cyclosporine, fast tapering of corticosteroids, and gastric aspiration. Transfusion-related acute lung injury and reperfusion syndrome of the newly implanted liver were mentioned as other contributing factors. Pereboom and colleagues have reported that platelet transfusion during orthotopic liver transplantation is associated with higher postoperative mortality due to lung injury.

Treatment of ARDS is supportive and involves ventilatory and nonventilatory strategies. Lung-protective ventilation with low tidal volumes and attention to fluid balance are important. Rescue strategies in patients with refractory hypoxemia are recruitment maneuvers, airway pressure release ventilation, and high frequency ventilation. Nonventilatory strategies include corticosteroids, neuromuscular blockade, prone positioning, and, in severe cases, extracorporeal membrane oxygenation. The risk of acute respiratory failure is low after kidney and heart transplantation compared with liver transplantation. In a series of 6919 patients who received kidney allografts, 452 patients (6.6%) were admitted to the ICU, including 216 patients (47.8%) who were admitted for acute respiratory failure after a median 17 months (range, 3-67.3 mo) after transplantation. The median time from respiratory symptom onset to ICU admission was 2 days, and at admission, 62.3% patients were severely hypoxic, with P_{a}O_{2}/FiO_{2} ratio ≤ 200. Noninvasive mechanical ventilation was required in 32% patients, with 46.9% patient having success, and invasive mechanical ventilation was needed in 46.5% kidney transplant recipients. In addition, the authors concluded that in kidney transplant recipients, acute respiratory failure was associated with high mortality and graft loss rates, and early admission to the ICU might prevent graft loss. In a retrospective review of kidney transplant recipients, ARDS was documented in 0.2% patients, and graft failure and use of antilymphocyte globulin were identified as risk factors for the development of ARDS. In a series of 159 heart transplant recipients, prolonged respiratory failure requiring tracheotomy was reported in 4.4% cases.

In lung transplant recipients, acute pulmonary allograft rejection is an important problem in the first few months after lung transplantation. Patients often are asymptomatic, but when present, symptoms may be nonspecific, including fever, shortness of breath, and cough. The diagnosis is based on the characteristic histopathologic changes on transbronchial lung biopsy specimens. The usual treatment is intravenous methylprednisolone for 3 days. After clinical response, oral glucocorticoids are given and tapered to the patient’s baseline dose over several weeks.
Noninvasive ventilation (NIV) is an appropriate initial ventilator modality in selected SOT recipients who have acute respiratory failure. In a prospective randomized trial, early application of NIV in recipients of SOT with acute hypoxemic respiratory failure was associated with improvement in gas exchange. When compared with standard treatment with supplemental oxygen using a Venturi mask, patients with NIV had significantly lower rates of endotracheal intubation, septic and fatal complications, and ICU mortality.66

Cases of respiratory insufficiency due to infectious or noninfectious pulmonary complications frequently require endotracheal intubation or tracheotomy when prolonged mechanical ventilation is required. Protective mechanical ventilation of both recipient and donor with strategies to prevent postoperative pulmonary complications include preoperative pulmonary rehabilitation before transplantation, intraoperative lung protective strategies (low tidal volume and optimal positive end-expiratory pressure), and postoperative early extubation when appropriate with lung expansion maneuvers, execution of bronchial toilet during chest physical therapy, or use of NIV; if necessary, invasive mechanical ventilation is recommended with assisted modes, with minimal or no sedation.6,67,68 Prolonged mechanical ventilation after transplantation may be associated with a risk of pneumonia; therefore, efforts should be done to wean from invasive airways.

Tracheotomy has gained popularity as a way to facilitate weaning from the ventilator by reducing pulmonary dead space and providing access to enable clearing pulmonary secretions and improving patient comfort. Pirat and colleagues have proposed percutaneous dilational tracheotomy as a method of choice for prolonged airway treatment in SOT recipients, provided the patients are properly selected and the procedure is performed by an experienced operator with endoscopic guidance.69

Conclusion

Infectious and noninfectious respiratory complications are important contributors to early morbidity and mortality in SOT recipients. About two-thirds of lung infiltrates observed after transplantation are of infectious cause, and the increasing incidence of MDR bacterial infections warrants effective treatment strategies. Noninfectious problems early or late after surgery depend on the grafted organ and the site of transplant and may cause acute respiratory failure necessitating prolonged mechanical ventilation and ICU stay. It is of great importance to accurately identify the respiratory problem because a rapid and aggressive approach is important to prevent multisystem organ failure and increase survival. In addition, the final outcome of SOT recipients with respiratory complications requires close cooperation of the transplant team with intensivists, infectious disease specialists, pulmonologists, and physiotherapists.

References


