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LUNG TRANSPLANT (MR ZAMORA, SECTION EDITOR)

Critical care management of the lung transplant recipient

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Abstract Lung transplantation provides the prospect of improved survival and quality of life for patients with end stage lung and pulmonary vascular diseases. Given the severity of illness of such patients at the time of surgery, lung transplant recipients require particular attention in the immediate post-operative period to ensure optimal short-term and long-term outcomes. The management of such patients involves active involvement of a multidisciplinary team versed in common post-operative complications. This review provides an overview of such complications as they pertain to the practitioners caring for post-operative lung transplant recipients. Causes and treatment of conditions affecting early morbidity and mortality in lung transplant recipients will be detailed, including primary graft dysfunction, cardiovascular and surgical complications, and immunologic and infectious issues. Additionally, lung donor management issues and bridging the critically ill potential lung transplant recipient to transplantation will be discussed.

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Introduction

Since the modern era of lung transplantation began in 1983 with the first series of successful human lung transplants [1], there have been remarkable advances in this potentially life-saving procedure for thousands of patients with end-stage lung and pulmonary-vascular diseases. However, the overall survival rates of lung transplant recipients in comparison to other solid organ transplant recipients is lagging, due in part to the unique technical, immunogenic, and infectious aspects of transplanting human lungs [2]. In more recent eras, survival has improved, largely due to improvements affecting the early post-transplant period [2]. Despite these improvements, early morbidity and mortality remain important limiting factors for long term success; therefore, early recognition and management of problems that arise before and after lung transplantation in the intensive care unit setting are key to the long term success of the recipient. This review aims to summarize the most important aspects of the critical care management of the lung transplant recipient in the peri-operative time period [3–6].

Preoperative issues

Donor management in the ICU

The continued relative lack of supply of organs in contrast to the increasing demand for lung transplantation has spurred

interest in expanding the traditionally accepted definition of the "ideal" lung donor, whose criteria of age <55, PaO_2 >300, minimal smoking history, and clear chest x-rays have contributed to lung acceptance rates of less than 20 % [7]. One avenue to expand the pool beyond this seemingly restrictive definition is the use of "extended donors" with liberalized selection criteria. Some transplant centers have shown that the use of these donors have comparable short-term outcomes to "ideal donors." Other centers have described prolonged ICU stays and increased early mortality with the use of donor lungs with infiltrates and/or purulent secretions [8–12]. Aggressive donor management by the team caring for a potential lung donor may result in the improvement of the function of "extended" donor lungs closer to the range of "ideal" organ and thus increasing lung donor conversion rates [13–15]. A protocol-based approach for the management of potential organ donors, and particularly the ventilator management of potential lung donors, is an effective way to standardize variation in practice styles in the community as well as improve donor conversion rates. The University of Texas at San Antonio showed that with protocols designed to incorporate standardized lung recruitment maneuvers, aggressive donor fluid management, and aspiration-reduction precautions, rates of lung procurement can be significantly increased. Of 98 actual donors during a 4 year protocol period, 54 % were lungs from patients initially considered poor donors [16]. A similar experience in Quebec showed that simple lung recruitment protocols can be instituted safely and effectively to increase procurement rates and organ availability, of particular importance in large geographic areas with limited donors [17].

Education of intensivists on care of the brain dead patient is key, as proper management of such patients may affect both procurement rates as well as lead to improved immediate post-transplant outcomes. Reviewed recently by Naik and Angel [18•], brain death elicits hemodynamic instability, activation of inflammatory pathways, and endocrine dysfunction that can profoundly impacts the quality and function of the donated lungs. In conjunction with an active local donor procurement organization, active donor management is necessary to treat these homeostatic derangements. Mascia et al. showed in a survey of 15 ICUs in Italy, that there is a clear tendency towards maintaining potentially injurious ventilatory management strategies and not performing recruitment maneuvers after the pronouncement of brain death [19]. This same group also recently demonstrated beneficial effects of employing lung protective ventilatory strategies (tidal volume 6–8 mg/kg predicted body weight, PEEP 8–10 cm H_2O) on potential lung donors in a randomized controlled trial compared to conventional ventilatory parameters (tidal volume 10–12 mg/kg predicted body weight, PEEP 3–5 cm H_2O) [20]. Of 118 patients enrolled into the study, 54 % of donors from the lung protective ventilator strategy group went on to donate lungs vs. 27 % of conventional ventilatory strategy group. Six month outcomes of lung recipients from both groups did not differ [20].

Recipient risk factors: bridging to transplant

The management of the predisposing advanced lung diseases in lung transplant candidates who become acutely ill while awaiting lung transplantation can pose a challenge to the critical care practitioner. Given the sometimes unpredictable nature of donor availability, the ICU care of such patients has the potential to be prolonged, during which time-sensitive issues such as nutritional status, functional capacity, and infection avoidance in an effort to maintain listing eligibility become the focus of care. Since the institution of the Lung Allocation Score (LAS) in 2005 in the U.S. [21], the concept of net survival benefit as a balance of risk of death on the waitlist vs. chance of survival at 1 year has driven organ allocation, often assigning the highest scores to patients who are acutely ill and mechanically ventilated.

Traditionally, requirement for mechanical ventilation had been viewed as a contraindication for active listing at most lung transplant centers due to the fear for poor outcomes. As described by Mason et al., after querying the United Network for Organ Sharing for lung transplantation from October 1987 through January 2008, these fears are not unfounded [22••]. The authors showed that of 15,934 transplants performed, 586 patients were on mechanical ventilation and 51 were on extracorporeal membrane oxygenation (ECMO) at the time of transplantation, both factors that contribute to the highest LAS scores. Survival rates at 1, 6, 12, and 24 months were significantly worse in both mechanical ventilation and ECMO supported; patients; for example, 1 year survival was 72 % for the 51 ECMO bridged patients vs. 93 % for the unsupported patients. Those patients that received mechanical ventilation tended to be younger, have higher oxygen requirement, poorer renal function, and diagnoses other than emphysema such as cystic fibrosis. Of note, the increase in mortality seen in patients with pre-operative mechanical ventilation or ECMO support seemed to be limited to the early time period after lung transplant; patients who required aggressive support pre-transplant who survived the first 6 months had comparable long-term survival to those not requiring pre-transplant support [22••]. Therefore, these historical administrative data suggest that improvements in the pre-operative morbidity of these procedures, such as reducing sedation, paralytics, or immobility in the pre-operative critical-ill patients, could lead to reasonable long-term outcomes.

In recent years, pre-operative life support of the potential recipient has evolved. The concept of "bridging to

transplantation" involves the use of mechanical support systems to sustain a patient in respiratory failure until the lung transplant can be performed, often with concurrent aggressive rehabilitation and physical therapy if at all possible [23••, 24]. Similar to advances in mechanical circulatory support in heart transplantation, technical advances in the redesign of circulatory pumps, membrane oxygenators, and venous catheters has now made less invasive ECMO support feasible without immobilizing or paralyzing the patient in most cases. Smaller, bilumen catheters, introduced into the jugular vein and the inferior and superior vena cava to drain venous blood and simultaneously provide oxygenated blood into the right atrium [25], may potentially allow patients to be awake, non-ventilated, and ambulatory during ECMO support. As this field is rapidly evolving, further research will need to be done on selection of appropriate patients [26, 27•, 28–31].

Postoperative issues

The immediate post-operative period in the ICU remains the most critical for the lung transplant recipient, requiring continuous hemodynamic monitoring, often maximal ventilatory support, and close observation of chest tube output for evidence of bleeding or other surgical complications. Aggressive peri-operative antibiotic coverage is employed, often tailored to pre-transplant culture data, with consideration of induction immunosuppression. Often, newly instituted transplant medications have the potential for unforeseen side effects on the kidneys, central nervous system, and other organs. The following sections highlight the most important critical care issues in the post-operative lung transplant recipient. A comprehensive list of peri-operative complications is listed in Table 1.

Primary graft dysfunction

The various etiologies of respiratory failure following lung transplantation have been reviewed [32••, 33, 34] and will also be addressed in sections below. The most frequent and significant cause of early mortality after lung transplantation is primary graft dysfunction (PGD), a form of injury to the allograft resulting in large part from ischemia-reperfusion injury from the transplant process itself. PGD affects up to 30 % of all lung transplants, and it leads to prolonged mechanical ventilation and ICU length of stay, poor functional outcomes, and an increased risk of bronchiolitis obliterans syndrome (BOS) [35, 36]. In its most severe form, PGD presents as diffuse alveolar infiltrates in the allograft in the absence of cardiogenic pulmonary edema, infection, or cellular rejection that can lead to refractory hypoxia. Several clinical risk factors for PGD have been described, to which

Table 1 Peri-operative complications in the lung transplant recipient

Category	Complication
Respiratory	Primary graft dysfunction (PGD)
	Pulmonary embolism
	Pleural effusions
	Chylous effusions
	Persistent air leak
	Atelectasis
	Auto-PEEP
	Native lung hyperinflation
	Poor airway clearance
Cardiovascular	Right heart dysfunction
	Hypotension
	Arrhythmias
	Myocardial infarction
Surgical	Thoracic bleeding: hemothorax
	Delayed chest closure
	Size mismatch
	Pulmonary arterial stenosis
	Pulmonary venous thrombosis
	Bronchial anastomosis dehiscence
Immunologic	Hyperacute rejection
	Acute rejection
	Immunosuppressant side effects
Infectious	Pneumonia: bacterial, viral, fungal, mycobacterial
	Mediastinitis
	Empyema
	Line and catheter associated infection
	Sepsis
Neurologic	Calcineurin inhibitor induced posterior leukoencephalopathy
	Lowered seizure threshold
	Hyperammonemia
	Phrenic nerve injury
	Critical illness delirium and myopathy/neuropathy
	Pain management
Gastrointestinal	Gastroparesis
	Reflux
	Dysphagia and aspiration risk
	Ileus
	Colonic perforation
Renal	Acute renal failure
	Electrolyte disturbance
Hematologic	Thrombotic thrombocytopenic purpura – hemolytic-uremic syndrome
	Deep venous thrombosis
	Transfusion-related acute lung injury (TRALI)
	Autoimmune hemolysis (blood type O to A, B or AB)
Other	Deconditioning
	Malnutrition

the ICU physician should be attuned in order to assess the possibility of PGD in the critically ill lung transplant recipient. These include donor characteristics such as female gender, African-American race, extremes of donor age, elevated pulmonary arterial systolic pressure at the time of transplant, obesity and pre-existing diagnoses of pulmonary arterial hypertension and idiopathic pulmonary fibrosis [37–40]. Surgical and intra-operative risk factors for PGD include blood product administration, single transplant procedure and use of cardiopulmonary bypass [41–45]. As most prior studies are hampered by small numbers, several of these risk factors have been inconsistently reported. Ongoing multi-centered prospective studies are underway to better understand the clinical risk factors for severe PGD.

Treatment of PGD is supportive. Other potentially reversible etiologies (Table 1) should be ruled-out utilizing the information available to the ICU physician such as pulmonary arterial catheter measurements, CVP, radiographs, bronchoscopy, and echocardiography. Mechanical ventilator support should be continued while simultaneously avoiding excessive colloid or crystalloid administration. Diuresis should be initiated with blood pressure support if needed, as the lung parenchyma is damaged with evidence of capillary leak [46]. Theoretical benefits of lung protective ventilator strategies (low stretch, high PEEP) are extrapolated from the ARDS literature. As a rescue therapy, pressure-controlled ventilation modes may be preferentially utilized to minimize barotrauma and airway/anastomosis complications. Inhaled nitric oxide, while not proven to be effective in preventing PGD [47], may have benefit in improving oxygenation, reducing mean pulmonary arterial pressure, and increasing mean systemic arterial pressure in the first 6–8 h after transplant [48]. Ventilator management of PGD in single lung transplants with COPD can be challenging. Acute hyperinflation and significant V/Q mismatch can occur, perhaps necessitating dual-lumen independent lung ventilation which can be logistically challenging for the ICU staff.

In severe and refractory cases, ECMO has been applied in those PGD cases not responsive to traditional mechanical ventilation. In 2009 the University of Pittsburgh published their experience with ECMO in heart-lung and lung transplant recipients over a 15 year period. Of 763 patients, 7.6 % required ECMO, instituted within the first 7 days after transplant; 39 of 58 patients were successfully weaned off ECMO. Thirty day-, 1 year-, and 5 year- survival in this group was 80 %, 59 %, and 33 % respectively [49•]. In this severely ill population, it has been shown that late institution of ECMO, or inability to wean off ECMO, has led to near universal poor outcomes [49•, 50]. Most recently, Hartwig et al. have investigated whether the use of venovenous ECMO and improvements in ICU technology have affected outcomes. At a center where venovenous ECMO was the routine treatment for severe PGD, over a 9 year period of time, 28 of 498 patients required ECMO. Patients were able to be weaned from ECMO 96 % of the time, and survival was better than in previous reports: 82 %, 64 %, and 49 % at 30 day, 1 year and 5 years, respectively. While encouraging, the authors did notice worse allograft function in ECMO survivors at 3 years [51••]. This study illustrates that with evolving technology and increased experience, venovenous ECMO may be successfully utilized in very select cases of profound respiratory failure following lung transplantation.

Cardiovascular considerations

The lung transplant recipient with elevated pulmonary arterial pressures at the time of transplant or an underlying diagnosis of pulmonary arterial hypertension requires particularly close attention immediately after lung transplantation. The proper care of such patients begins prior to surgery, as the anesthesiologist should be vigilant to avoid sudden rises in pulmonary vascular resistance and subsequent right heart failure [52•]. Intra-operative transesophageal echocardiography can be a useful tool to evaluate right ventricular function. Pulmonary vasodilators such as inhaled nitric oxide, milrinone, and inhaled prostacyclin can reduce right ventricular afterload and expedite recovery of the RV in the post-operative state [52•]. Most transplant recipients will require vasopressors during the surgical procedure, and it is not uncommon to return to the ICU with vasopressors being administered with the expectation of quick weaning of such agents. Fluid management should be aimed at maintaining cardiac output but also minimizing pulmonary edema with active use of pulmonary arterial catheter measurements or echocardiography if available.

Arrhythmias after lung transplant are typically supraventricular in origin and are common, ranging between 34 % and 74 %. Older patients seem particularly at risk for this complication [4]. In a recent review of 200 lung transplant recipients, atrial fibrillation occurred in 39 % of patients within 14 days after surgery, with a mean onset at 3.8 +/- 3 days. Mean ICU stay and hospital stays are lengthened when atrial arrhythmias are experienced [53]. In the ICU, hemodynamically significant arrhythmias should be treated aggressively with cardioversion when indicated; otherwise, medical management will usually suffice. If these issues persist, consideration should be given to antiarrhythmic administration such as amiodarone, as well as initiation of anticoagulation. When bleeding complications are concurrent, this can be problematic.

Surgical complications

The propensity for intra-operative bleeding in lung transplant recipients can often be anticipated prior to the surgical

procedure, with proper precautions taken. Recipients with an underlying history of heart disease with coronary stents in place may chronically be on antiplatelet agents such as clopidogrel, which will increase the risk of bleeding substantially. Additionally, patients with severe pulmonary hypertension may be on warfarin therapy that requires reversal. The explantation of native lungs can also lead to substantial bleeding; scarred lung parenchyma may be fibrotic and adherent to pleural surfaces, or inflamed and associated with chronic foci of infection such as in sarcoidosis or cystic fibrosis patients. Other infections such as aspergillomas with reactive pleural involvement sometimes pose a prohibitive risk for bleeding during the explantation of native lungs and can lead to operative demise if significant. In the post-operative setting, bleeding risk must be monitored through serial laboratory studies, chest tube drainage measurements, and radiographs. Rapidly enlarging effusions or "white out" of a lung field may indicate a significant pleural bleed, which may not be appreciated based on recorded output alone should the chest tube malfunction or be improperly positioned.

Differences in size matching present special challenges for management of the lung transplant recipient. Lung transplant recipients with fibrotic lung diseases will tend to have smaller thoracic cavities for their height, and because of this, there may be difficulties finding properly size-matched donors. Donor lungs may be volume reduced intraoperatively using linear stapling, though potential complications from this type of procedure include air leaks and bronchopleural fistula formation [5]. If lungs are too big for the chest cavity in the immediate post-operative period, the team may choose to delay chest closure if the median sternotomy approach is used, for instance. In the post-operative state, patients with open chests require specialized nursing attention and broadened antibiotic and antifungal coverage. Size mismatches of donor lungs that are too small for a thoracic cavity may lead to persistent pleural effusions and high chest tube output. In these situations, chest wall remodeling may occur over time or the recipient may be left with chronic post-operative effusions.

Vascular anastomotic complications can lead to severe and sudden compromise in the lung transplant recipient. Fortunately, these are rare, but may carry high mortality. Pulmonary arterial stenosis or thrombus formation typically presents with hypotension and evidence of right heart failure. Pulmonary venous thrombosis, usually in proximity to the pulmonary vein-left atrial anastomosis typically presents with hypotension and either lobar or diffuse pulmonary edema with refractory hypoxemia (Fig. 1) [6]. Because of the rarity of these conditions, diagnosis can be difficult and requires a high index of suspicion. Urgent transesophageal echocardiography should be performed at the bedside for patients with a rapid change of course for diagnosis before potential surgical intervention. Thrombolysis is a high-risk intervention that can be considered for pulmonary vein thrombosis [54]; however, management usually involves surgical re-exploration.

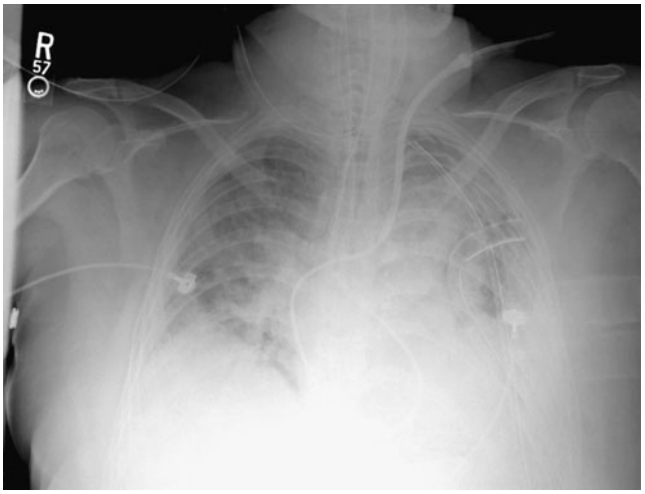

Fig. 1 This 65-year-old woman underwent left single lung transplant for advanced IPF. Within the first 3 h post-operatively, she experienced frothy, blood-tinged sputum with profound hypoxia. Bedside bronchoscopy revealed no active bleeding and intact anastomosis. Worsening hypotension was observed. Urgent bedside TEE was performed which demonstrated inability to visualize the left pulmonary veins. Only the proximal-most confluence of the left pulmonary veins was seen, with minimal forward flow on Doppler. The patient was taken to the OR for VA ECMO, but suboptimal flows ensued. The patient was made DNR-C and expired

In the immediate post-operative state, the bronchial anastomoses are prone to complications due to the bronchial circulation being sacrificed during the transplant procedure. This relative ischemia may then be exacerbated by intra- or post-operative hypotension or other hemodynamic fluctuations, making the anastomosis susceptible to necrosis, dehiscence, and infection. Frank bronchial dehiscence is rare, on the order of 1 %; partial dehiscence can be addressed with the temporary placement of self-expanding wire stents to encourage granulation tissue growth and healing [32••, 55, 56]. In most lung transplant programs, it is the general practice to sacrifice the bronchial arterial supply when implanting the newly transplanted lung. In spite of concerns that bronchial artery revascularization (BAR) prolongs ischemic time and increases operative risk of bleeding, centers who routinely employ BAR argue for potential benefits of fewer airway complications and reduced BOS risk [57–60]. Before BAR can be advocated for widespread use, extension of these techniques to a broader range of centers with consistent surgical competency needs to be addressed.

Immunologic issues

Hyperacute and acute rejection

Hyperacute rejection is a distinct and rare form of lung rejection and is described mostly in case reports [61–66]. It is characterized by an early and rapid onset, minutes to hours after reperfusion, and is the result of preformed recipient antibodies causing profound allograft dysfunction via mechanisms such as complement activation from ABO incompatibility or unrecognized significant anti-HLA antibodies to the donor. Clinically, one sees pink frothy sputum, profound hypoxemia, and pathologically a coagulopathy with fibrin and platelet thrombi formation within minutes to hours of reimplantation. The first case report appeared in 1996 as described by Frost et al. and illustrates the typical presentation: the patient described was a single lung recipient who tolerated a few hours of hyperacute rejection [65]. The patient had a history of two pregnancies, no blood transfusions, and a calculated PRA was approximately 33 %. Three hours after implantation a donor specific class I antibody to B8 was identified. The patient underwent treatment with plasmapheresis, Cytoxan, and ultimately the allograft was removed and the patient relisted for re-transplant. The recipient died 10 days later before another donor could be identified [65]. Other case reports detail patient survival after suspected hyperacute rejection with similarly aggressive immunosuppression regimens [61].

Although traditionally thought not to occur in the days following transplantation, acute cellular rejection can be seen as early as a week after transplant, and it can make treatment of other ICU complications difficult. For instance, during treatment of profound infections in critically ill lung transplant recipients, targeted immunosuppression levels may be lowered or agents stopped altogether in efforts to allow the patient to fend off the current infection. Beyond the initial hospitalization, acute cellular rejection is a common occurrence especially in the first year post-transplant, monitored with surveillance bronchoscopy with transbronchial biopsies.

Immunosuppression

The initiation of several immunosuppressive agents in the early post-operative period not only predisposes the transplant recipient to infectious complications, but can cause transient renal dysfunction that may be exacerbated by other concurrent medical complications. The calcineurin inhibitors tacrolimus and cyclosporine are the main culprits for acute renal dysfunction. These agents induce vasoconstriction of the afferent renal arteriole leading to reduction of renal blood flow and glomerular filtration rate. If the critically ill lung transplant recipient experiences peri-operative hypotension, aggressive diuresis for PGD, and is on numerous potentially other nephrotoxic medications, renal dysfunction may be prolonged and severe, leading to serious long-term complications. In a series of 219 lung and heart-lung transplant recipients surviving at least 6 months, 91.3 % had a decrease in kidney function, and end stage renal disease occurred in 7.3 % at a median duration of 28 months [67].

Infectious complications

Infectious complications are a frequent and important cause of morbidity and mortality in the post-operative lung transplant recipient. In addition to the relatively high levels of immunosuppression required by lung transplant recipients, the lungs are unique when compared to other solid organ transplants in that they are continually exposed to the external environment, thereby putting the allografts at risk for many more potential infectious insults. This section will focus on the infectious issues surrounding the care of the lung transplant recipient in the immediate post-operative time period.

Pre-transplant culture data are vitally important when caring for lung transplant recipients in the ICU. Ideally patients with underlying suppurative lung diseases such as bronchiectasis or cystic fibrosis will have recent culture data with which to guide immediate antibiotic therapy choices in the post-operative period. Organisms such as multi-drug resistant *Pseudomonas* species, methicillin resistant *Staph aureus*, rapidly-growing non-tuberculous mycobacteria (NTMB), and fungal organisms will directly impact peri-operative antibacterial and antifungal choices and will likely affect treatment duration as well. In patients with cystic fibrosis, the sinuses and upper respiratory tract may be a reservoir for ongoing infections and therefore aggressive antibiosis and prolonged therapy is often necessary. Cultures taken intra-operatively, from bronchoscopy performed after bronchial anastomoses are completed, as well as pleural and chest wall cultures can be very useful as well. The former provide up-to-date sampling of the potential donor flora, which can be used in conjunction with cultures obtained from the donor site to help guide antibiotic therapy. Chest cavity cultures can be helpful in recipients with structurally abnormal lungs (e.g. cavitary lesions) or parenchymal pulmonary nodules that may be suspicious for chronic infections such as *Aspergillus* species or NTMB.

Culture data from the organ donor may potentially affect post-transplant care in the ICU. As lung donors are ventilator-dependent, tracheal aspirate cultures are routinely

performed, as well as blood and urine cultures. However, such information may not be readily available at the time of transplant, so any significant change in post-operative course or concern for progressing infection in the recipient should prompt an investigation into the results of donor cultures. Empiric broad spectrum peri-operative antibiotic prophylaxis is often employed, but the decision to continue such treatment is on a case-by-case basis, often impacted by information derived from donor culture results.

Viral infections in the post-operative state are rare, but conceivably can either be transmitted via the donor or result from an early or subclinical respiratory virus in the recipient at the time of surgery and induction immunosuppression. Recipients may have been exposed to community acquired viruses such as respiratory syncytial virus, adenovirus, parainfluenza, and influenza, which may become clinically apparent in the peri-operative period as fulminant respiratory or systemic infections. In contrast, although CMV is a commonly seen viral pathogen in post-transplant patients, overwhelming CMV infection is rare in the immediate post-operative state in the modern era. Most centers will institute CMV prophylaxis of varying duration depending on the CMV status of the donor and recipient.

Due to the wide variety of common and opportunistic infections to which the lung transplant population is susceptible, it is often prudent for the ICU practitioner to employ the expertise of transplant infectious disease specialists to help manage such cases. In addition, the presence of a dedicated transplant pharmacist as part of the multi-disciplinary team is helpful in monitoring for significant medication interactions that affect serum drug levels and for side effects such as nephrotoxicity.

Conclusions

The care of the lung transplant recipient in the immediate post-operative period is a complex undertaking that requires a multidisciplinary team led by the ICU practitioner working in conjunction with the transplant medical and surgical teams. The lung transplant recipient is at risk for several categories of complications. With donor supply shortages and increasing numbers of patients awaiting transplant, the scenario of employing more extended criteria lungs in increasingly critically ill recipients at the time of transplant is becoming more likely. Great care must be taken to reduce the impact of immediate post-operative morbidity on long term outcomes in this population.

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- • Of importance
- •• Of major importance

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