ANESTHESIOLOGY

Postoperative Management of Lung Transplant Recipients in the Intensive Care Unit

Matteo Di Nardo, M.D., Jussi Tikkanen, M.D., Shahid Husain, M.D., Lianne G. Singer, M.D., Marcelo Cypel, M.D., Niall D. Ferguson, M.D., Shaf Keshavjee, M.D., Lorenzo Del Sorbo, M.D.

Anesthesiology 2022; 136:482–99

ABSTRACT

The number of lung transplantations is progressively increasing worldwide, providing new challenges to interprofessional teams and the intensive care units. The outcome of lung transplantation recipients is critically affected by a complex interplay of particular pathophysiologic conditions and risk factors, knowledge of which is fundamental to appropriately manage these patients during the early postoperative course. As high-grade evidence-based guidelines are not available, the authors aimed to provide an updated review of the postoperative management of lung transplantation recipients in the intensive care unit, which addresses six main areas: (1) management of mechanical ventilation, (2) fluid and hemodynamic management, (3) immunosuppressive therapies, (4) prevention and management of neurologic complications, (5) antimicrobial therapy, and (6) management of nutritional support and abdominal complications. The integrated care provided by a dedicated multidisciplinary team is key to optimize the complex postoperative management of lung transplantation recipients in the intensive care unit.

(Anesthesiology 2022; 136:482–99)

Lung transplantation is a complex treatment for select patients with a diverse array of end-stage pulmonary diseases. The number of lung transplantations is progressively increasing worldwide, and in the last 5 yr, more than 4,000 were performed annually.[1] Improvements in donor management, organ preservation, recipient selection, antimicrobial prophylaxis, and immunosuppressive medications have resulted in durable and steady improvements in lung transplant outcomes. Survival of lung transplantation recipients, although lower than in other solid organ transplants, is currently at 60% at 5 yr.[2]

The expansion of lung transplantation provides new challenges in the perioperative management of the recipients in the intensive care unit (ICU). First, the number of lung transplantation centers and the number of admissions to the ICU posttransplant is increasing. Second, the increase of older lung transplantation recipients and those with associated comorbidities will undoubtedly increase the perioperative risk.[3] Third, severe primary graft dysfunction still occurs in up to 20 to 30% of the lung transplantation recipients, affecting outcome.[2,4,5] A complex interplay of unique pathophysiologic conditions and risk factors attributable to the characteristics of the donor, the recipient, and the interaction between them (fig. 1) affects the perioperative outcome of the lung transplantation. Thus, knowledge of these specific issues is fundamental to properly care for these patients, especially for those who require prolonged life support.

Potential Postoperative Complications in Lung Transplantation Recipients

Table 1 summarizes the main potential postoperative acute critical complications occurring in lung transplantation recipients in the ICU.

Among these complications, the most relevant is primary graft dysfunction, a particular form of acute respiratory distress syndrome (ARDS), mainly due to ischemia-reperfusion injury. It occurs in up to 20 to 30% of recipients. Several risk factors for primary graft dysfunction have been identified. The severity of primary graft dysfunction is graded according to the International Society for Heart and Lung Transplantation (Addison, Texas) working group guidelines, which propose a standardized definition of primary graft dysfunction based on the ratio of Pao_2 to inspired oxygen fraction (FIO_2) and infiltrates on the chest radiograph. Scores are calculated at specific time points (0, 24, 48, and 72 h) after reperfusion (table 1). Several studies have validated the International Society for Heart and Lung Transplantation grading system and demonstrated the discriminatory ability of primary graft dysfunction Grade 3 *versus* Grades 0, 1, and 2 to predict outcomes. Importantly, severe primary graft dysfunction is associated not only with short-term morbidity and mortality but also with an increased risk of chronic lung allograft dysfunction and overall mortality.[4,6]

Cardiac events, including heart failure, supraventricular tachyarrhythmias and pericarditis, delirium, and gastric content aspiration are other frequent complications in

This article is featured in "This Month in Anesthesiology," page A1.

Submitted for publication May 23, 2021. Accepted for publication September 28, 2021. Published online first on December 15, 2021. From the Pediatric Intensive Care Unit, Bambino Gesù Children's Hospital, Scientific Institute for Research, Hospitalization and Healthcare, Rome, Italy (M.D.N.); and the Toronto Lung Transplant Program, Toronto General Hospital (M.D.N., J.T., S.H., L.G.S., M.C., S.K., L.D.S.), and Interdepartmental Division of Critical Care Medicine (N.D.F., L.D.S.), University Health Network, University of Toronto, Toronto, Ontario, Canada.

 Anesthesiology 2022; 136:482–99. DOI: 10.1097/ALN.0000000000004054

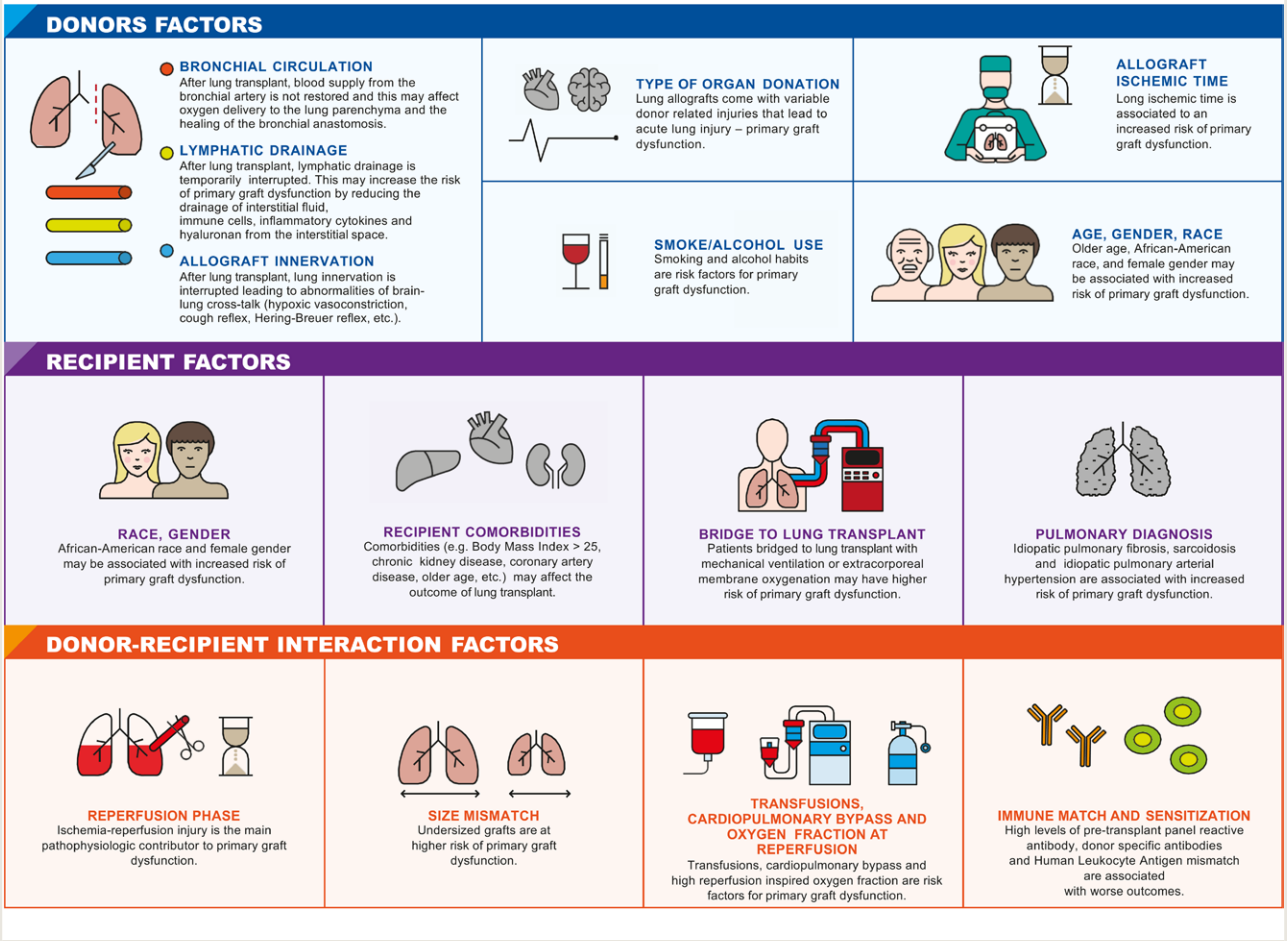

Fig. 1. Donor, recipient, and donor–recipient interaction—associated risk factors for primary graft dysfunction (adapted from Diamond *et al.*[4]).

the postoperative phase, and their incidence will probably increase in the future due to the progressively older age of the patients receiving lung transplantation.

Risk Factors for Primary Graft Dysfunction

Donor lungs do not have bronchial circulation, which may affect oxygen delivery to the parenchyma and bronchial anastomosis, and also lack innervation, which precludes brain–lung crosstalk and may result in abnormal cough reflexes, hypoxic vasoconstriction, and Hering–Breuer reflex. Lymphatic drainage is interrupted for a few weeks after lung transplantation, and hence the drainage of interstitial fluid, immune cells, inflammatory cytokines, and hyaluronan is at least temporarily impaired. The type of lung donor (brain death donors or donation after cardiac death) may also affect the risk of primary graft dysfunction. In brain death donors, lungs are particularly susceptible to injury due to the systemic inflammatory response induced by brain death. This response may cause lung edema and potentially increase the risk of ventilator-induced lung injury.[4] Grafts from controlled donation after cardiac death may have an increased risk of primary graft dysfunction proportionally to the duration of withdrawal of life-sustaining therapy.[7] Ischemic time is associated with increased risk of primary graft dysfunction. Currently, a warm ischemic time less than 60 min is considered a cutoff for lung retrieval by many centers; however, improvement in organ preservation techniques and the use of *ex vivo* lung perfusion to assess donor lung function before lung transplantation have moved this cutoff up to 120 min.[8] Size matching is an important variable affecting lung transplantation outcomes.[9] In undersized allograft (donor to recipient predicted total lung capacity ratio less than 1), a reduced pulmonary vasculature may result in high pulmonary arterial pressure and increase the risk of primary graft dysfunction; this risk may be further increased by the use of high tidal volumes compared to the donor lung size during invasive ventilation. Contrarily, oversized grafts may present a reduced risk of primary graft dysfunction.[9] Identification of recipient and intraoperative risk factors for primary graft dysfunction is also of clinical importance. Incidence of primary graft dysfunction is higher in recipients with diagnosis of sarcoidosis,

Table 1. Postoperative Acute Critical Complications Associated with Lung Transplantation

Respiratory Failure	Shock	Others
• Primary graft dysfunction[2] ◦ Primary graft dysfunction 0: no edema on chest X-ray with any Pao_2/Fio_2 ◦ Primary graft dysfunction 1: edema on chest X-ray with $Pao_2/Fio_2 > 300$ ◦ Primary graft dysfunction 2: edema on chest X-ray with Pao_2/Fio_2 200–300* ◦ Primary graft dysfunction 3: edema on chest X-ray with $Pao_2/Fio_2 < 200$† • Donor-associated pneumonia • Ventilator-associated pneumonia • Acute rejection • Bronchial anastomotic complications (dehiscence) • Cardiogenic pulmonary edema • Pulmonary vein anastomotic obstruction • Pulmonary embolism • Hemothorax • Whole lung or lobar torsion • Phrenic nerve injury	• Hemorrhagic • Distributive (septic) • Cardiogenic (right ventricular failure, left ventricular failure) • Obstructive (tamponade, pulmonary embolism)	• Infection • Arrhythmias • Postoperative pericarditis • Gastroesophageal reflux • Bowel obstruction, perforation, ischemia • Immunosuppression side effects • CNS complications • ICU acquired weakness

Primary graft dysfunction is graded at four timepoints, every 24 h, over the first 72 h after transplantation (0, 24, 48, and 72 h). Primary graft dysfunction in recipients treated with noninvasive ventilation should be graded according to Pao_2/Fio_2 ratio as for invasive mechanical ventilation.

*If Pao_2/Fio_2 ratio is not available, oxygen saturation/Fio_2 ratio 235 to 315 is used instead of Pao_2/Fio_2 ratio 200 to 300. †Use of extracorporeal membrane oxygenation with pulmonary edema is graded as primary graft dysfunction 3. Extracorporeal membrane oxygenation for cardiac indication (without pulmonary edema) is ungradable.

CNS, central nervous system; Fio_2, inspired oxygen fraction; ICU, intensive care unit.

idiopathic pulmonary fibrosis, or pulmonary hypertension, or with a body mass index greater than 25. Intraoperative factors, such as the type of lung transplantation (single *vs.* double), the use of cardiopulmonary bypass, prolonged ischemic time, and large volume of intraoperative blood transfusions (greater than 1 l) may also increase the risk of primary graft dysfunction.[5]

Postoperative Management of Lung Transplantation Recipients

The management of lung transplantation recipients in the ICU plays a critical role in improving their outcome. However, recommendations in the literature to guide the postoperative ICU management of lung transplantation recipients are outdated and often not comprehensive. As high-grade evidence-based guidelines are not yet available, the current practice in this field is mainly based on the results of observational studies, knowledge of the pathophysiology of lung transplantation, and an expertise-based approach.

The scope of this review is to address six important aspects of the postoperative management of lung transplantation recipients (table 2), in the context of the expertise of a large and very experienced lung transplantation center. We highlight the current practice and areas with opportunities for future investigation in the following: (1) management of mechanical ventilation, (2) management of fluids and hemodynamics, (3) prevention and management of neurologic complications, (4) immunosuppressive therapies, (5) antimicrobial strategies, and (6) management of nutritional support and of abdominal complications.

Management of Mechanical Ventilation

Mechanical ventilation represents an essential supportive measure in the management of patients receiving lung transplantation. Its goals in the postoperative phase are maintaining adequate gas exchange, monitoring lung allograft function, and facilitating early weaning while minimizing the risk of ventilator-induced lung injury to the graft.

Experimental data suggest that all lung transplantation recipients, not only those with primary graft dysfunction, are at risk of ventilator-induced lung injury,[10] and hence postoperative protective mechanical ventilation should be used.[11] However, despite the critical role of mechanical ventilation in lung transplantation, very few data are available in the literature to guide clinical practice.[9,12–16] Thus, the currently applied protective mechanical ventilation strategies in lung transplantation patients have been extrapolated from the management of ARDS patients,[17–20] as the benefits of lung-protective mechanical ventilation extend to both patients with ARDS and patients at risk for ARDS.[16]

The initial protective mechanical ventilation settings in all lung transplantation recipients limit tidal volume to 6 ml/kg of donor predicted body weight and plateau pressure less than 30 cm H_2O, aiming for a pH greater than 7.25, and oxygen saturation greater than 90% as measured by pulse oximetry.[15] Normalizing tidal volume to donor rather than recipient predicted body weight reduces the risk of delivering excessive tidal volume in undersized allografts.[9,13] Fio_2 is reduced as low as possible to reduce the risk of hyperoxia and oxidative stress.[21] Positive end-expiratory pressure (PEEP) is titrated following a prespecified table according to Fio_2 requirements (table 2). If these mechanical

Table 2. Main Goals of Postoperative Lung Transplant Management

Mechanical ventilation

Protective settings, early weaning, and extubation to minimize ventilator-induced lung injury.

Initial ventilator settings:

- Tidal volume: 6 ml/kg predicted body weight (donor)
- Inspiratory plateau pressure < 30 cm H_2O
- Spo_2 > 90% and pH > 7.25
- PEEP (cm H_2O) adjusted according to the ARDS network table*, but avoiding PEEP level > 12–14 cm H_2O

If Pao_2/Fio_2 > 200 and pH > 7.25

- Wean sedation
- Tidal volume: 6–8 ml/kg predicted body weight (donor)
- PEEP: 5 cm H_2O
- Inspiratory plateau pressure: < 25 cm H_2O
- Early extubation

If Pao_2/Fio_2 < 200

- Maintain sedation
- Initial ventilator settings with tidal volume: ≤ 6 ml/kg, predicted body weight (donor)
- Inspiratory plateau pressure: < 25 cm H_2O
- PEEP: adjust according to ARDS network table*
- Respiratory rate: < 35 breaths/min

If Pao_2/Fio_2 < 150

- Consider neuromuscular blockade
- Consider inhaled NO

If Pao_2/Fio_2 < 100

- Consider ECMO

Hemodynamics

Continuous multimodal hemodynamic monitoring (Swan–Ganz catheter) and careful fluid management to achieve adequate end-organ perfusion while avoiding lung reperfusion injury

- Mean arterial pressure: 65–75 mmHg
- Cardiac index: 2.2–2.5 l · min^{-1} · m^{-2}
- Central venous pressure: ≤ 7 mmHg
- Wedge pressure or left atrial pressure: ≤ 10 mmHg
- Diuresis > 0.5 ml · kg^{-1} · h^{-1}

Nutritional intake and gastrointestinal management

Maintain a caloric intake of 25–30 kcal/kg; if indirect calorimetry is not available, maintain normal glucose blood level (45–65% of total calories), lipid: 20–35% of total calories, protein: 1.3–2.5 g · kg^{-1} · day^{-1}

Micronutrients and electrolytes intake: maintain normal sodium, potassium, and magnesium levels; supplemental calcium and vitamins A, C, and D

- Early enteral nutrition to prevent muscle mass loss
- Use of nonpharmacologic (sleeping with 30-degree bed position) and pharmacologic interventions (proton pump inhibitors and prokinetics) to prevent and manage gastroesophageal reflux

Early abdominal computed tomography with iv contrast in presence of even minor clinical suspicion of abdominal complications

Immunosuppression

Maintenance therapy: triple-drug therapy including calcineurin inhibitors, cell-cycle inhibitors, and steroids

Induction therapy: in patients at risk of renal dysfunction (consider basiliximab)

Antimicrobials

Antibiotics: empiric broad-spectrum antibiotic prophylaxis for 72 h, awaiting final results of donor and recipient bronchoalveolar lavage cultures

Consider multidrug resistance coverage

Treatment of confirmed infections with tailored therapy

Antivirals: cytomegalovirus prophylaxis (according to donor/recipient status)

Pneumocystis jirovecii prophylaxis

Antifungals: consider prophylaxis in colonized recipients

Treatment of confirmed fungal infection

Prevention of neurologic dysfunction

- Adequate pain control
- Early mobilization to prevent ICU-acquired weakness
- Early delirium screening and treatment
- Sleep hygiene
- Benzodiazepines-free sedation
- Hyperammonemia screening and source control
- Posterior reversible encephalopathy syndrome prevention

* Values:

Fio_2	0.3	0.4	0.5	0.6–0.7	0.8–1
PEEP	5	5–8	8–10	10–12	12–14

ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; Fio_2, inspired oxygen fraction; ICU, intensive care unit; iv, intravenous; PEEP, positive end-expiratory pressure; Spo_2, oxygen saturation measured by pulse oximetry.

ventilation settings result in adequate gas exchange (pH greater than 7.25, Pao_2/Fio_2 greater than 200 mmHg) and the risk of primary graft dysfunction is low, mechanical ventilation and sedation are rapidly weaned. As soon as spontaneous breathing is established, if the mechanical ventilation and hemodynamic targets are maintained (table 2), a spontaneous breathing trial (continuous positive airway pressure 5 cm H_2O for 30 min) is performed to assess for extubation readiness. In single lung transplantation recipients, the difference in compliance between the graft and the native lung warrants additional considerations. In single lung transplantation with fibrotic disease, tidal volumes of 4 to 6 ml/kg donor predicted body weight should be used to reduce the risk of overdistension of the more compliant allograft. In single lung transplantation with obstructive disease, maximizing the expiratory time reduces the risk of dynamic hyperinflation of the native lung.[16]

In noncomplicated patients, weaning from sedation and mechanical ventilation is usually completed within 72 h and extubation performed in the ICU. The median duration of mechanical ventilation after lung transplantation is 2 to 3 days.[15,22] In hemodynamically stable patients with Pao_2/Fio_2 greater than 300 mmHg, early extubation in the operating room has been described as feasible.[23] In patients with a high risk of severe primary graft dysfunction[5] or inadequate gas exchange, sedation and mechanical ventilation are usually intentionally weaned in a slower fashion (over 3 to 5 days). When weaning from mechanical ventilation becomes challenging and is prolonged to longer than 1 week, early tracheostomy is considered.[24,25] However, high-grade evidence is not available on this topic, and further studies are needed to address the optimal timing for tracheostomy in lung transplantation recipients.

The use of noninvasive ventilation in lung transplantation recipients has been proposed for the management of postoperative respiratory complications.[26] However, a high grade of evidence on its benefits is absent in this selected population, and concerns exist about continuous positive airways pressure potentially increasing the risk of aspiration and impeding adequate airways clearance. Recently, high-flow nasal cannulas have been increasingly used as humidified oxygen delivery devices early after extubation.[27] Early mobilization and chest physiotherapy are very important parts of the postoperative care plan to facilitate bronchial hygiene and avoid lung atelectasis, which are challenging issues in lung transplantation recipients due to the lack of lung innervation and bronchial circulation. Frequent bronchoscopies, chest percussion combined with postural drainage, and a high frequency chest wall oscillation may have an important role when the patient is unable to clear secretions.[28] The use of cough assist is discouraged due to the high risk of injury to the healing bronchial anastomosis.

In case of severe primary graft dysfunction (bilateral lung infiltrates and Pao_2/Fio_2 less than 200 mmHg) or other acute respiratory complications, including infections, rejection, and anastomotic leaks, the duration of mechanical ventilation is variably increased, and the use of protective mechanical ventilation becomes crucial[16] (table 2). Driving pressure higher than 14 cm H_2O, calculated as the difference between airway plateau pressure and total PEEP, has been shown to be strongly associated with mortality in patients with ARDS, and can hence be used as marker of the severity of lung injury and risk of ventilator-induced lung injury.[20] High PEEP (greater than 12 to 14 cm H_2O) is generally avoided for its potential negative effects on the bronchial healing and alveolar overdistension. Assisted spontaneous breathing could be prudently pursued while maintaining moderate sedation as it may have several advantages, such as avoiding deconditioning, delirium, and diaphragmatic dysfunction. However, protective mechanical ventilation targets need to be maintained, and targets of excessive inspiratory effort should be carefully evaluated at the bedside to avoid self-inflicted lung injury.[29] These may include inspiratory plateau pressure less than 25 cm H_2O, driving pressure 14 cm H_2O or less,[30] and airway occlusion pressure of the first 100 ms 4 cm H_2O or less, a validated index of respiratory drive in patients with acute respiratory failure.[31] Repeated bronchoscopies may be required to rule out anastomotic airway complications, such as dehiscence, necrosis, stenosis, among others, which are associated with increased morbidity and mortality. The management can be extremely challenging and vary depending on several factors, including the type, cause, and severity.[32]

When the severity of primary graft dysfunction increases (Pao_2/Fio_2 less than 150 mmHg) and persists for several hours, protective mechanical ventilation and sedation are continued, and rescue treatments (table 2), such as prone positioning, the administration of neuromuscular blockade, and inhaled NO, are considered.[33] Since endogenous NO levels are reduced after lung reperfusion, routine post–lung transplantation administration inhaled NO has been previously proposed to optimize ventilation/perfusion mismatch, but in a controlled randomized trial did not prevent primary graft dysfunction.[34] Thus, although there is no rationale for the routine administration of inhaled NO, it can be used to treat selected cases of severe primary graft dysfunction where both gas exchange and vascular resistance are impaired.[6] The application of prone positioning has also been described as a rescue treatment to improve oxygenation in 22 lung transplantation recipients with refractory hypoxemia.[35] This is challenging to do in an acute postoperative patient, and further investigations are required to support its use in severe primary graft dysfunction.

Very severe graft dysfunction with Pao_2/Fio_2 less than 100 mmHg despite optimal ventilation settings, or respiratory acidosis associated with high ventilator pressures requirements (plateau pressure greater than 30 cm H_2O, PEEP greater than 12 to 14 cm H_2O) may require extracorporeal membrane

oxygenation (ECMO) support. The use of ECMO in post–lung transplantation acute respiratory failure has increased in the last 10 yr, facilitated by improved ease of use and safety. Several case series[22,36] reported that recipients with refractory primary graft dysfunction requiring ECMO who survived the critical first 3 months after lung transplantation experienced long-term survival similar to that reported in patients not supported with ECMO. These data support the use of ECMO for the management of refractory primary graft dysfunction, particularly to prevent additional ventilator-induced lung injury and oxygen toxicity to the already injured graft. In addition, observational data suggest that early consideration of ECMO may result in better outcome than its deployment in advanced refractory conditions.[37] Furthermore, recently the prophylactic use of ECMO during the early postoperative period in recipients with a high risk of primary graft dysfunction or impaired graft function at the end of implantation has been reported as a very promising strategy.[38] The best ECMO configuration to manage refractory primary graft dysfunction remains controversial.[6] Peripheral veno-arterial ECMO has been proposed since it provides both adequate respiratory and hemodynamic support. Importantly, veno-arterial ECMO effectively offloads the pulmonary flow, allowing for more protective lung perfusion,[22,39,40] which nonetheless needs to be maintained to a certain extent, to provide some nutritive blood flow and to clear the edema. This is managed by monitoring end-tidal carbon dioxide, which is proportional to pulmonary blood flow, and pulmonary arterial pulse pressure tracing with the Swan–Ganz catheter. Veno-arterial ECMO has, however, been associated with more complications (bleeding, cerebrovascular- and cannulation-related, and the "Arlequin" or north–south syndrome in peripheral veno-arterial ECMO due to differential hypoxia in recipients with poor lung function and adequate cardiac output) than veno-venous ECMO.[41] The use of veno-venous ECMO allows for effective control of gas exchange and remarkably reduces mechanical stress to the graft. However, with veno-venous ECMO, the amount of pulmonary perfusion, and thus the risk of reperfusion injury, remains less affected, although the reduction of ventilation pressures and the correction of blood gases and pH tend to decrease pulmonary artery pressures and improve cardiac (right ventricle) function. During both veno-arterial and veno-venous ECMO, there are no specific evidence-based guidelines to recommend optimal mechanical ventilation settings; however, the main goal is to reduce all the potential causes of ventilator-induced lung injury, such as high tidal volume, high F_{IO_2}, and high respiratory rate.[42,43] Weaning from veno-venous ECMO is performed when the graft function is improved (*i.e.*, gas exchange and respiratory system compliance) and the patient tolerates protective mechanical ventilation parameters. Similarly, weaning from veno-arterial ECMO is considered when the cardiac function has sufficiently recovered to maintain adequate cardiac output and organ perfusion with modest doses of inotropes.[40]

Management of Fluids and Hemodynamics

The assessment of the heart–lung interactions is a fundamental and challenging aspect of the lung transplantation postoperative phase, which may be further complicated by hemodynamic instability (or shock) due to bleeding, hypovolemia, sepsis, pump failure, or pulmonary embolism. A Swan–Ganz catheter is an essential part of the standard of care in the largest lung transplantation centers[44] in this phase for accurate monitoring and management of cardiac preload (central venous pressure, wedge pressure), systemic and pulmonary arterial pressure, systemic and pulmonary vascular resistance, cardiac output, and mixed venous oxygen saturation (table 2; fig. 2). The initial goal is to maintain adequate end-organ perfusion, which is monitored by measuring lactate, urine output, and mixed venous oxygen saturation, with the lowest possible cardiac output to reduce the risk of exacerbating lung edema induced by reperfusion injury. Usually, at ICU admission, lung transplantation recipients require careful fluid management to achieve euvolemia.[45] Lung perfusion is then judiciously increased, allowing cardiac output to progressively reach its expected normal target, usually just by weaning sedation, while the graft function (gas exchange, lung compliance) is carefully monitored. The rapidity of this process depends on the graft function and the risk of developing primary graft dysfunction.[46] If the increase in lung perfusion results in gas exchange worsening, the weaning process is conducted at a slower pace. Postoperative bleeding may prevent the maintenance of an adequate cardiac output and thus should be properly addressed. Several risk factors are associated with postoperative bleeding, including the recipient diagnosis (cystic fibrosis, pleural adhesions, redo transplantation, among others), the intraoperative procedural techniques (cardiopulmonary bypass *vs.* ECMO), and pre-existing or acquired coagulopathies. Use of coagulation factors, antifibrinolytic agents, and point-of-care transfusion strategies may potentially reduce postoperative bleeding and the risk of blood products–related alloimmunization.[47,48] In uncomplicated recipients with excellent lung function, weaning from artificial life support and sedation may occur in a time frame of minutes to hours. In recipients with initially poor graft function or very high risk of primary graft dysfunction, such as those with primary pulmonary hypertension, the weaning process is carried out more slowly over a period of a few days.

The application of a dedicated protocol including the maintenance of specific hemodynamic targets (central venous pressure 7 mmHg or less, mean arterial pressure 65 to 75 mmHg, and a cardiac index 2.2 to 2.5 $l \cdot min^{-1} \cdot m^{-2}$) and the use of a standardized lung protective ventilation strategy have been shown in other centers to be associated with reduced severity of primary graft dysfunction.[46] In addition, it has been shown that the use of a fluid restrictive strategy (central venous pressure 7 mmHg or less) was not associated with increased use of vasopressors or a

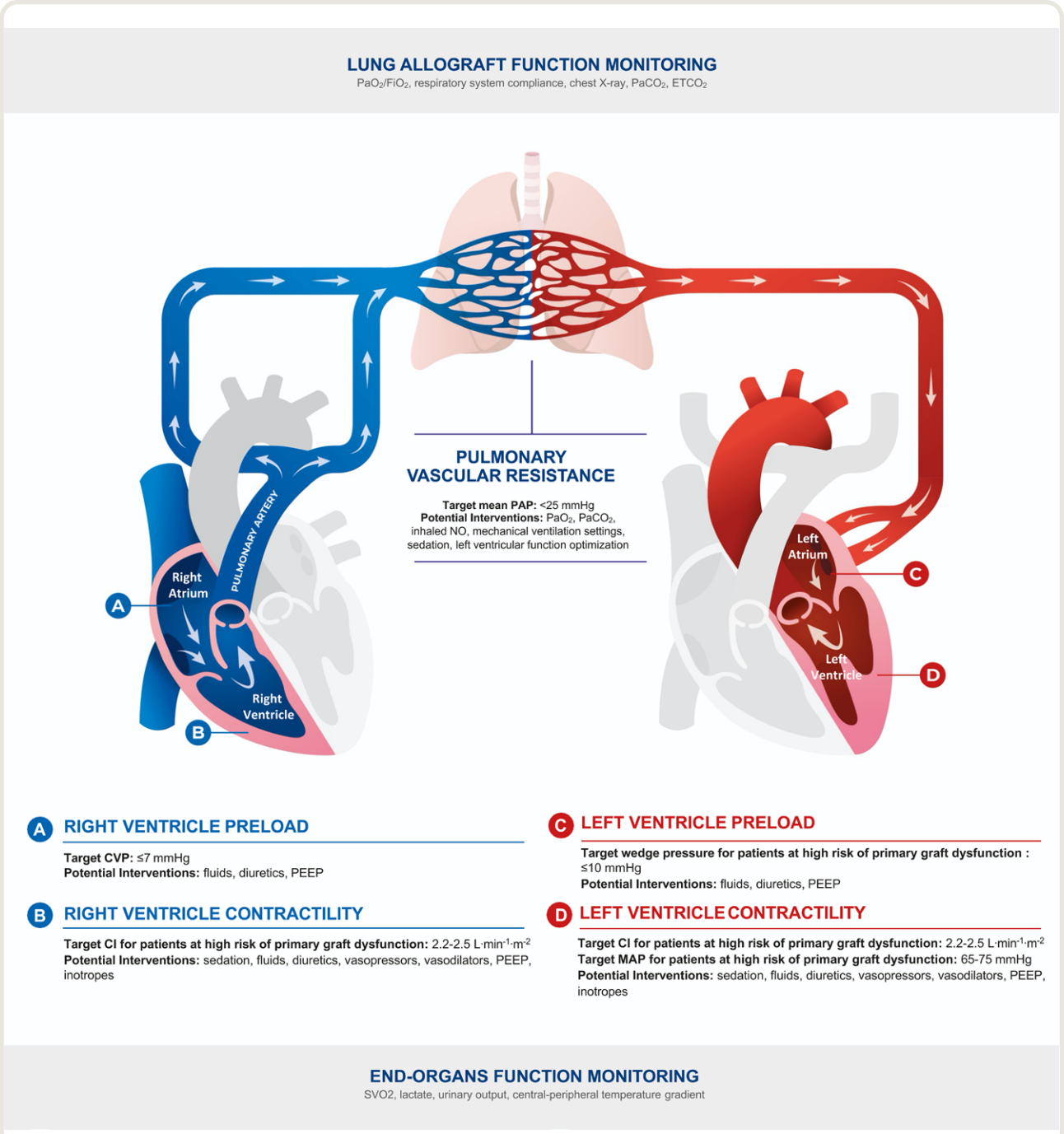

Fig. 2. Physiologic variables, monitoring targets, and potential interventions to manage function, interaction, and perfusion of the heart, lung, and end-organs of lung transplant recipients in the postoperative intensive care unit. CVP, central venous pressure; $ETco_2$, end-tidal carbon dioxide; Fio_2, inspired oxygen fraction; MAP, mean systemic arterial pressure; PAP, pulmonary arterial pressure; PEEP, positive end-expiratory pressure; Svo_2, mixed venous oxygen saturation.

deterioration of renal function,[49] which is often present in the postoperative period (up to 52.5%).[50] Postoperative kidney injury is mainly secondary to pre-renal causes with the concomitant use of nephrotoxic immunosuppressive, antibiotic, and other drugs, and not infrequently requires renal replacement therapy.

The use of other types of hemodynamic monitoring based on transpulmonary thermodilution has been described when the use of the Swan–Ganz catheter is not feasible.[51] These devices show promise in the setting of lung transplantation in that they can provide a measurement of the extravascular lung water index.[51] Continuous

left atrial pressure monitoring is a valuable alternative to the wedge pressure measurement, especially in children or in patients receiving lung transplantation for severe pulmonary hypertension.[39,40] In these patients, the risk of severe primary graft dysfunction is considerably higher.[5] Two possible mechanisms may explain this form of primary graft dysfunction: endothelial injury due to shear-stress forces applied by a "well-trained" right ventricle, or a transient form of diastolic dysfunction of the left ventricle, which becomes incapable of acutely managing a normal preload in the early postoperative period.[40] To specifically address these issues and allow progressive controlled loading of the left ventricle, the systematic prophylactic use of early "awake" veno-arterial ECMO, with rapid extubation and liberation from mechanical ventilation after cannulation, has been described for the postoperative management of recipients with severe pulmonary hypertension.[38–40,52,53] In our and other centers, veno-arterial ECMO is generally used as a rescue therapy for refractory cardiogenic shock or in recipients with pulmonary hypertension developing marked pulmonary edema postoperatively. Importantly, the veno-arterial ECMO support should be instituted early, as soon as the trend toward persistent deterioration is recognized.

The postoperative period of the lung transplantation patient can also be complicated by other cardiac events, such as pericarditis, supraventricular tachyarrhythmias,[54,55] and pulmonary venous anastomotic–related dysfunction or torsion, inducing pulmonary edema.[56] In particular, atrial fibrillation is reported with a variable incidence between 20 and 39%.[55] Although in some studies it has been associated with increased hospital stay and hospital mortality, its actual impact on the outcome is unclear.[54,55,57] The most common risk factors for postoperative atrial fibrillation in lung transplantation include electrolyte imbalance, gas exchange abnormalities, pain, fluid overload, vasopressors and inotropes, airway issues, and pericardial effusion. In the great majority of lung transplantation recipients, atrial fibrillation is a transitory event, as almost all patients are discharged in sinus rhythm.[58] The management of perioperative atrial fibrillation follows the American Association for Thoracic Surgery (Beverly, Massachusetts) guidelines.[59] In particular, adequate levels of plasma electrolytes (K^+, Mg^{++}, Ca^{++}) are maintained while applying a rate control strategy with antiarrhythmic drugs as a first-line approach in hemodynamically stable patients. Electrical cardioversion is reserved for unstable patients or those refractory to medical therapy. Anticoagulation is generally started if atrial fibrillation persists, continuously or intermittently, for longer than 48 h, and there are no concerns for surgical bleeding. In lung transplantation recipeints, antiarrhythmic agents should be cautiously chosen due to the possible interactions with the immunosuppressive drugs, based on heart function and comorbidities. β Blockers are first-line choices in hemodynamically stable patients. In several centers, amiodarone is used only in very selected cases due to its associated idiosyncratic risk of inducing lung injury,[57,60] and usually replaced by sotalol as a class III antiarrhythmic.

Prevention and Management of Neurologic Complications

Postoperative neurologic complications including delirium, stroke, posterior reversible encephalopathy syndrome, immunosuppressive drug–induced encephalopathy, seizures, phrenic and recurrent laryngeal nerve injury, and ICU-acquired weakness affect almost half of the lung transplantation recipients in some reports and are associated with worse outcomes.[61–63] Although the biologic mechanisms responsible for neurologic complications in lung transplantation are all not fully understood, important insights can be gained from knowledge of the preoperative recipient clinical status (*e.g.*, chronic hypoxia and hypercapnia, atherosclerotic disease, systemic hypertension, heart rhythm disturbances, diabetes, among others) and perioperative risk factors (*e.g.*, cardiopulmonary bypass or ECMO, intraoperative hypotension, bleeding, severe primary graft dysfunction).[64]

Delirium represents one of the most frequent (40%) neurologic complications after lung transplantation.[62,65] Diagnosis and management of delirium follow the evidence-based clinical practice guidelines of the Society of Critical Care Medicine (Mount Prospect, Illinois) and rely on a multidisciplinary approach including critical care physicians, nurses, respiratory/physical therapists, occupational therapists, nutritionists, and psychiatrists.[66] Delirium prevention, early detection (Confusion Assessment Method for the ICU or the Intensive Care Delirium Screening Checklist) and management with nonpharmacologic (sleep hygiene, early mobilization) and pharmacologic interventions (benzodiazepine-free sedation) are associated with improved patient outcomes.[65,66] Adequate pain control is of key importance to prevent delirium; to facilitate early mobilization, reducing the risk of muscle mass loss and ICU-acquired weakness; and to expedite weaning from mechanical ventilation.[67] A multipharmacologic approach (opioids, acetaminophen, gabapentin, ketamine) is the most commonly applied strategy. In other centers, the additional use of neuraxial catheters (epidural) or other types of neural blocks (paravertebral or erector spine plane block) have been proposed to reduce the dose of opioids.[68] The use of dexmedetomidine, which has sedative and analgesic properties, has been also considered for the postoperative management of lung transplantation recipients.[69]

Acute encephalopathy and in particular posterior reversible encephalopathy syndrome,[70] characterized by syndromes including confusion, tremors, seizures, depression, and coma, represents the second most frequent (25%) neurologic complication.[61,64] Importantly, immunosuppressive agents are recognized as potential contributors to the development of toxic central nervous system impairment.[71] In these cases, temporary withholding of calcineurin inhibitors

and substituting them with basiliximab, with strict therapeutic drug monitoring, can reverse the neurologic condition.[72]

Phrenic nerve injury by stretching or direct surgical injury may occur after lung transplantation.[73] Diagnosis is often clinical (paradox breathing pattern during weaning from mechanical ventilation or early extubation failure in absence of primary graft dysfunction) and confirmed by fluoroscopic examination of the diaphragm function. Phrenic nerve injury may prolong weaning from mechanical ventilation and ICU stay. Phrenic nerve reconstruction and diaphragm pacing may be considered to support functional recovery.[74]

Hyperammonemic encephalopathy is a rare but often fatal complication in lung transplantation (1 to 4%).[75–77] It is a medical emergency, as the delay of its management results in potential irreversible neurologic injury. The rapid elevation of serum ammonia can cause nonspecific neurologic abnormalities and, if uncontrolled, cerebral edema, coma, and brain death. Evidence suggests that the cause is donor-derived ureaplasma species lung infection.[78] As early detection and management are key to preventing devastating neurologic injury, in our center, plasma ammonia concentration is routinely monitored daily for at least the first 2 weeks postoperatively. When the ammonia plasma concentration is higher than 100 μmol/l (normal, 72 μmol/l or less), hemodialysis is urgently started, and antimicrobial therapy targeting ureaplasma species with a combination of moxifloxacin and doxycycline is initiated.

Ischemic or hemorrhagic cerebral vascular complications represent the third most frequent complication (4 to 10%)[61,63,64] and carry a high morbidity and mortality (15%).[61] Infective neurologic complications, including brain abscess, viral encephalitis, and cryptococcal meningitis, are possible, but are extremely rare in the immediate postoperative phase.[79] However, these should be considered in patients with prolonged immunosuppression before transplantation.

Current Trends and Future Insights on Immunosuppressive Therapies

Acute rejection affects more than 50% of the recipients in the first year after transplantation, and it has been found to be a significant risk factor for the subsequent development of chronic lung allograft dysfunction.[80] Its diagnosis is challenging, especially in the early days after the lung transplantation. Primary graft dysfunction, lung infections, and fluid overload can be difficult to differentiate from acute rejection in the early postoperative phase. In these cases, bronchoscopy to rule out infection is usually performed before commencing empirical medical therapy for infection or rejection.[81,82] Transbronchial biopsies can also be considered to confirm the diagnosis of rejection or infection; however, caution should be used in ventilated patients for the high risk of bleeding (greater than 20%) and pneumothorax (6 to 10%).[83]

Although the immunosuppressive drug regimens have not changed significantly over recent years, the understanding of how to optimize immunosuppression has improved.[84] The immediate posttransplant immunosuppressive regimen should be tailored according to the center-specific protocols, but also specifically to the lung transplantation recipient. It may consist of induction therapy (basiliximab, antithymocyte globulin, and alemtuzumab being the most common) and triple-drug immunosuppression with a calcineurin inhibitor (cyclosporine A or tacrolimus), a cell-cycle inhibitor (azathioprine or mycophenolate mofetil/mycophenolic acid), and a corticosteroid. Nonetheless, some centers have used lower immunosuppression after alemtuzumab induction.[85]

There remains significant heterogeneity in use of induction agents, with around 50% of centers not using induction.[86] In registry analyses, improved survival was reported for patients receiving induction,[87,88] and retrospective cohort analyses suggested alemtuzumab to be more effective in preventing acute rejection.[85,89] However, robust randomized trials comparing different induction regimens are lacking, and there is no generalized consensus on the right approach to induction therapy.

There is considerable evidence to suggest that pretransplant sensitization of the recipient to donor human leukocyte antigens increases mortality after lung transplantation if no specific therapies are given.[90] Many centers would therefore avoid transplanting across a positive virtual crossmatch, especially if the actual flow crossmatch is positive. Aggressive multimodal desensitization protocols have been used to manage these cases, with controversial results.[91] Use of intraoperative and perioperative plasmapheresis followed by intravenous immunoglobulin therapy and antithymocyte globulin has been reported to result in equivalent allograft and chronic lung allograft dysfunction–free survival between sensitized and unsensitized lung transplantation patients.[90]

In patients with underlying renal disease, older patients, and patients with a complicated lung transplantation surgery, the risk of early kidney injury is high. In these patients, early basiliximab therapy can be considered to enable a delayed start of nephrotoxic calcineurin inhibitors.[92] Basiliximab is removed by plasmapheresis, and this should be taken into account when administering it. Some programs advocate basiliximab induction routinely to reduce the risk of renal complications.[72]

Antimicrobial Therapy

Infections are the most frequent complications in lung transplantation recipients (up to 42% within 3 months).[93,94] The risk factors for postoperative infections are classified into issues related to the donor, the recipient pretransplant, and the recipient posttransplant (table 3). Early and adequate broad-spectrum empirical antibiotic prophylaxis (table 2) remains the mainstay approach in the immediate

72-h postoperative period while awaiting the final results of the donor and recipient bronchoalveolar lavage cultures.[95,96] Inadequate antimicrobial management has been associated with significant increased mortality.[93] However, optimal duration of antimicrobial prophylaxis remains unknown, and prophylactic regimens of 48 h to 7 days have been reported.[97] Note that perioperative antimicrobial management in lung transplantation recipients includes usual surgical site infection prophylaxis, but also broader spectrum antibiotics to address any information available related to the colonization and/or infection of the donor lung and the recipient.

Pneumonia is the most common type of bacterial infection after transplantation (incidence up to 44%),[93] and *Pseudomonas aeruginosa* is the most common cause, followed by *Staphylococcus aureus*.[94] The early pneumonia in the lung transplantation patient is more often related to the recipient ICU nosocomial flora than the donor ICU flora. Pneumonia is associated with several risk factors, including exposure of the graft to the external environment through the airway, aspiration, interruption of graft innervation potentially impairing adequate coughing and mucociliary clearance, transitory postoperative interruption of lymphatic drainage, and anastomotic complications.[93] Transmission of infections from donor lungs (donor-associated pneumonia), or from the native lung in single lung transplantation, prolonged mechanical ventilation (ventilator-associated pneumonia), bacterial airway colonization,[82] and primary graft dysfunction and rejection[81] further increase the diagnostic and therapeutic complexity. Once the diagnosis of pneumonia is confirmed, tailored antimicrobial therapy is continued for a total duration of 10 to 14 days course guided by clinical response. A considerable challenge derives from multidrug-resistant microorganisms, which are frequently isolated, especially in recipients with cystic fibrosis and in those with previous antimicrobial exposure.[96] In these cases, knowledge of the recipient pretransplant cultures helps in selecting appropriate antimicrobial therapy. Airway colonization with opportunistic microorganisms (*e.g.*, *Burkholderia cepacia* complex and *Mycobacterium abscessus*) or multidrug-resistant bacteria (*e.g.*, pseudomonas aeruginosa) may compromise long-term lung transplantation survival.[98–101] In particular, isolation of the *Burkholderia cenocepacia* species has been reported to have a very a high risk of postoperative mortality in cystic fibrosis recipients, and, with the exception of our and few other lung transplantation programs, it is considered a contraindication to lung transplantation in many centers.[98] Colonization with *M. abscessus*, in contrast, is associated with a low incidence of recurrent infection after lung transplantation and good outcomes when an aggressive management and surveillance strategy is applied.[102]

Cytomegalovirus infection is the most prevalent viral infection in lung transplantation recipients and requires adequate prophylaxis starting from the immediate postoperative ICU admission, although it is rarely a severe clinical issue in the immediate postoperative phase.[93,103] Lung transplantation recipients who are cytomegalovirus negative (R–) and receive cytomegalovirus-positive donor lungs (D+) have the highest risk of developing severe life-threatening disease. Median time from lung transplantation to the onset of cytomegalovirus infection has significantly increased after the widespread use of prophylaxis for 6 to 12 months.[93] Consensus guidelines on the management of cytomegalovirus in solid-organ transplantation suggest for lung transplantation recipients the use of intravenous ganciclovir followed by oral valganciclovir in D+/R– mismatch patients for a total of 9 months, 6 months of the same prophylaxis in D–/R+ and D+/R+ patients, and acyclovir for 3 months in D–/R– patients. Cytomegalovirus treatment is suggested when the viral load exceeds a specific threshold which is variable in each laboratory (500 copies/ml in D+/R– and 1,000 copies/ml in the rest).[103]

Candida and *Aspergillus* species are often isolated as colonizing organisms in the lung transplantation recipients' bronchoalveolar lavage. Some centers prescribe empiric antifungal prophylaxis in the early postoperative course.[104,105]

Table 3. Donor and Recipient Preoperative and Postoperative Infective Risk Factors

Donor Factors	Recipient Factors: Preoperative	Recipient Factors: Postoperative
• Bacterial or fungal allograft colonization • Allograft latent infection (toxoplasma, cytomegalovirus, other viruses, endemic mycosis, tuberculosis)	• Age • Diabetes • Hypogammaglobulinemia • Renal failure • No immunity against cytomegalovirus, toxoplasmosis, rubeola virus, varicella zoster virus • Latent infection tuberculosis, cytomegalovirus, herpes simplex virus, varicella zoster virus, Epstein–Barr virus, endemic mycosis • Colonization with multidrug-resistant microorganisms • Immunosuppressive therapy • Rejection • Environmental exposure (gardener, animals, caves, travel) • Native lung colonization	• Allograft injury (ischemia, preservation, reperfusion) • Complexity and length of surgery • Postsurgical care (mechanical ventilation, intravenous catheters, drains, bladder catheter, extracorporeal membrane oxygenation) • Transfusion • Intensive care stay

The efficacy of this approach is questionable, especially when performed with inhaled amphothericin B. In alignment with the recommendation of the International Society of Heart and Lung Transplantation, antifungal prophylaxis should not be routinely instituted.[93,105] Nonetheless, invasive fungal infections in lung transplantation have been associated with high morbidity and mortality,[106,107] and most often caused by *Aspergillus* (72.7%), rather than non-*Aspergillus* species (27.3%; *e.g.*, *Scedosporium*, mucormycosis, Zygomycetes).[108] Reported risk factors include fungal colonization, idiopathic pulmonary fibrosis, older age, increased body mass index, airway ischemia, single lung transplantation, severity of recipient clinical condition, and major construction projects around the hospital center.[106] The diagnosis of invasive aspergillosis in lung transplantation is challenging due to the lack of specific clinical and radiological signs and low sensitivity of culture-based diagnostic methods. Serum galactomannan, proposed as surrogate marker for invasive aspergillosis, carries low sensitivity in lung transplantation, whereas galactomannan in the bronchoalveolar lavage has low specificity.[93] Voriconazole is the recommended first-line therapy for suspected invasive aspergillosis, while echinocandin, liposomal amphotericin B, isavuconazole, or posaconazole are alternatives.[93,105,109]

Pneumocystis jirovecii (table 2) can cause severe pneumonia in lung transplantation recipients. Thus, prophylaxis with trimethoprim–sulfamethoxazole is commonly instituted immediately after lung transplantation.[93] No consensus exists about the adequate duration of this prophylactic treatment. In our center, we have adopted lifelong prophylaxis.[93]

Bloodstream infections are also severe complications in lung transplantation recipients (incidence approximately 25%) and are associated with graft failure and increased mortality (25% for bacteremia, up to 50% for candidemia).[93,106,110] Pneumonia is the most common source of these infections and indwelling vascular catheters the second. Empiric treatment of *Candida* bloodstream infection is provided with echinocandin or, in case of resistance, with liposomal amphotericin B.[107] Tailored therapy according to antifungal sensitivity when available is prescribed for 14 days from the first negative blood culture after removal of contaminated central lines. Longer duration is recommended in case of more serious infections, such as endocarditis or endophtalmitis.[93]

Empyema, surgical wound infection, mediastinitis, and pericarditis are other infective complications occurring after lung transplantation with a considerable effect on mortality.[111] In general, any drainable source of sepsis is aggressively dealt with by percutaneous or surgical approach.

Nutritional Support and Management of Abdominal Complications

The nutritional support of the lung transplantation recipient differs according to the primary disease and the transplant-related complications.[112] Nonetheless, currently no studies have evaluated the specific nutritional requirements of lung transplantation recipients and their impact on outcomes.[112] Similar to patients receiving other solid organ transplants or other major surgery, the total daily calorie intake requirement during the early postoperative phase is 25 to 35 kcal/kg (table 2). Oral feeding is generally restarted after extubation and in the absence of complications (*i.e.*, dysphagia, recurrent aspiration); in all the other cases requiring prolonged mechanical ventilation and ICU stay, starting early enteral nutrition is a clinical priority.[112] Lung transplantation recipients with cystic fibrosis deserve specific considerations due to the frequently associated pancreatic insufficiency and malabsorption of dietary fats, proteins, carbohydrates, and fat-soluble vitamins.[113] Enteral nutrition with elemental or semielemental feed formulations are provided to these patients, in association with pancreatic enzymes.[114,115]

Oropharyngeal dysphagia is a frequent complication after lung transplantation (54% of the patients screened), especially in frail patients after prolonged intubation and in those with recurrent laryngeal nerve injury resulting in vocal fold paralysis. Both dysphagia and vocal fold paralysis may increase the risk of aspiration. Assessment and treatment by speech-language pathologists is recommended to minimize these risks. Recent data suggest that clinical bedside examination is not often sensitive and fails to identify patients with deep laryngeal penetration and silent aspirations; therefore, when the patient is able to resume oral intake, instrumental testing including modified barium swallow and fiberoptic endoscopic evaluation of swallowing should be performed. This approach has been shown to improve the immediate and short-term outcome after lung transplantation.[116,117]

Gastroesophageal reflux is another very common complication after lung transplantation and has been associated with altered thoracic mechanics, postoperative vagal nerve dysfunction, immunosuppressive treatment, or the primary disease (*e.g.*, scleroderma). Its management with positioning of the patient (head of bed elevated 30 degrees), proton pump inhibitors, and prokinetic agents is critical since gastroesophageal reflux has been associated with the development of chronic lung allograft dysfunction.[118]

Other gastrointestinal complications may also occur after lung transplantation.[119] The immunosuppressive regimen can reduce the intestinal transit time and blunt the abdominal symptoms, which should thus not be underestimated.[120] In the presence of any clinical suspicion of gastrointestinal complications, early imaging (abdominal computed tomography, with iv contrast if the renal function is not compromised) and prompt consultation with the surgical team should be considered. Approximately 20% of these complications require surgical intervention. Early surgical intervention is preferred over conservative or

expectant observation in these complex patients, where systemic immunosuppression tends to mask key clinical findings related to intra-abdominal catastrophes. Patients with abdominal complications occurring in the first week after lung transplantation requiring surgery have higher mortality compared with patients who had late surgical abdominal complications. The most frequent causes of early post–lung transplantation abdominal surgery are bowel ischemia and bowel perforation.[121] The right colon is the most frequently involved by ischemia. In contrast, the most common late indications for surgery are perforations of the descending colon due to inflamed diverticulitis. It is worth mentioning that β-1-antitrypsin–deficiency lung transplantation recipients have been reported to have an increased incidence of early postoperative gastrointestinal complications.

Minor abdominal complications (vomiting, constipation, diarrhea, and dyspepsia) are generally more frequent and can be treated with laxatives or prokinetics. To prevent distal intestinal obstruction syndrome in cystic fibrosis patients, polyethylene-glycol electrolyte solutions or N-acetylcysteine are administered enterally as soon as enteral feeding is started and continued until the patient has a first bowel movement.[121]

Conclusions

The postoperative management of the lung transplantation recipient in the ICU is complex and can critically affect the ultimate outcome. The perioperative management can hence be optimally delivered only by the integrated care provided by a multidisciplinary dedicated team with specific expertise in lung transplantation, including intensivists, thoracic surgeons, pneumologists, infectious disease specialists, nurses, clinical pharmacists, physiotherapists, social workers, and psychologists. The increasing number of lung transplantations worldwide is saving more lives than ever of patients with end-stage lung disease. The increasing age and complexity of the recipients and the still considerable lack of knowledge in this field warrant continued research and clinical trials to further improve the care of these patients and their short- and long-term outcomes.

Search Strategy and Selection Criteria

References for this review were identified through searches of OVID Medline and PubMed from January 2009 to December 2019, using the terms "lung transplantation," "critical care management," "intensive care management," "postoperative management," and "postoperative complications." Only articles published in the English language were included. We selected predominantly articles from the past 10 yr, although we did not exclude earlier reports, especially if they were highly cited articles or unique or high-quality clinical trials. We also searched the reference lists of articles identified by this search strategy and selected the most relevant.

Acknowledgments

The authors are thankful to Velia Marta Antonini, M.Sc. (Cardiovascular Perfusion, Azienda Unità Sanitaria Locale Romagna, Department of Biomedical, Metabolic and Neural Sciences, University of Modena & Reggio Emilia, Modena, Italy), for assistance in illustration and figure editing.

Research Support

Support was provided solely from institutional and/or departmental sources.

Competing Interests

Dr. Keshavjee and Dr. Cypel are cofounders of Perfusix Canada (Toronto, Ontario, Canada), cofounders of XOR Labs Toronto (Toronto, Ontario, Canada), and consultants for Lung Bioengineering and United Therapeutics (Silver Spring, Maryland). Dr. Ferguson reports personal fees from Xenios (Heilbronn, Germany) and Baxter (Alliston, Ontario, Canada). Dr. Tikkanen is a consultant for and reports funding from Boehringer-Ingelheim (Burlington, Ontario, Canada). Dr. Husain is a consultant for TFF Pharmaceuticals (Austin, Texas), IBT-Med (Stockholm, Sweden), Takeda (Tokyo, Japan), and Gilead (Foster City, California). The other authors declare no competing interests.

Correspondence

Address correspondence to Dr. Del Sorbo: Toronto General Hospital, 585 University Avenue, PMB 11-122, Toronto, Ontario, Canada M5G 2N2. lorenzo.delsorbo@uhn.ca.

References

1. Yusen RD, Edwards LB, Dipchand AI, Goldfarb SB, Kucheryavaya AY, Levvey BJ, Lund LH, Meiser B, Rossano JW, Stehlik J; International Society for Heart and Lung Transplantation: The Registry of the International Society for Heart and Lung Transplantation: Thirty-third adult lung and heart-lung transplant report-2016; Focus theme: Primary diagnostic indications for transplant. J Heart Lung Transplant 2016; 35:1170–84
2. Snell GI, Yusen RD, Weill D, Strueber M, Garrity E, Reed A, Pelaez A, Whelan TP, Perch M, Bag R, Budev M, Corris PA, Crespo MM, Witt C, Cantu E, Christie JD: Report of the ISHLT Working Group on Primary Lung Graft Dysfunction, part I: Definition and grading-A 2016 Consensus Group statement of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2017; 36:1097–103

3. Ehrsam JP, Benden C, Seifert B, Opitz I, Schneiter D, Weder W, Inci I: Lung transplantation in the elderly: Influence of age, comorbidities, underlying disease, and extended criteria donor lungs. J Thorac Cardiovasc Surg 2017; 154:2135–41
4. Diamond JM, Arcasoy S, Kennedy CC, Eberlein M, Singer JP, Patterson GM, Edelman JD, Dhillon G, Pena T, Kawut SM, Lee JC, Girgis R, Dark J, Thabut G: Report of the International Society for Heart and Lung Transplantation Working Group on Primary Lung Graft Dysfunction, part II: Epidemiology, risk factors, and outcomes-A 2016 Consensus Group statement of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2017; 36:1104–13
5. Diamond JM, Lee JC, Kawut SM, Shah RJ, Localio AR, Bellamy SL, Lederer DJ, Cantu E, Kohl BA, Lama VN, Bhorade SM, Crespo M, Demissie E, Sonett J, Wille K, Orens J, Shah AS, Weinacker A, Arcasoy S, Shah PD, Wilkes DS, Ware LB, Palmer SM, Christie JD; Lung Transplant Outcomes Group: Clinical risk factors for primary graft dysfunction after lung transplantation. Am J Respir Crit Care Med 2013; 187:527–34
6. Van Raemdonck D, Hartwig MG, Hertz MI, Davis RD, Cypel M, Hayes D Jr, Ivulich S, Kukreja J, Lease ED, Loor G, Mercier O, Paoletti L, Parmar J, Rampolla R, Wille K, Walia R, Keshavjee S: Report of the ISHLT Working Group on primary lung graft dysfunction part IV: Prevention and treatment: A 2016 Consensus Group statement of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2017; 36:1121–36
7. Krutsinger D, Reed RM, Blevins A, Puri V, De Oliveira NC, Zych B, Bolukbas S, Van Raemdonck D, Snell GI, Eberlein M: Lung transplantation from donation after cardiocirculatory death: A systematic review and meta-analysis. J Heart Lung Transplant 2015; 34:675–84
8. Munshi L, Keshavjee S, Cypel M: Donor management and lung preservation for lung transplantation. Lancet Respir Med 2013; 1:318–28
9. Eberlein M, Reed RM, Bolukbas S, Diamond JM, Wille KM, Orens JB, Brower RG, Christie JD; Lung Transplant Outcomes Group: Lung size mismatch and primary graft dysfunction after bilateral lung transplantation. J Heart Lung Transplant 2015; 34:233–40
10. Slutsky AS, Ranieri VM: Ventilator-induced lung injury. N Engl J Med 2013; 369:2126–36
11. de Perrot M, Imai Y, Volgyesi GA, Waddell TK, Liu M, Mullen JB, McRae K, Zhang H, Slutsky AS, Ranieri VM, Keshavjee S: Effect of ventilator-induced lung injury on the development of reperfusion injury in a rat lung transplant model. J Thorac Cardiovasc Surg 2002; 124:1137–44
12. King CS, Valentine V, Cattamanchi A, Franco-Palacios D, Shlobin OA, Brown AW, Singh R, Bogar L, Nathan SD: Early postoperative management after lung transplantation: Results of an international survey. Clin Transplant 2017; 31:1–7
13. Dezube R, Arnaoutakis GJ, Reed RM, Bolukbas S, Shah AS, Orens JB, Brower RG, Eberlein M: The effect of lung-size mismatch on mechanical ventilation tidal volumes after bilateral lung transplantation. Interact Cardiovasc Thorac Surg 2013; 16:275–81
14. Yonan NA, el-Gamel A, Egan J, Kakadellis J, Rahman A, Deiraniya AK: Single lung transplantation for emphysema: Predictors for native lung hyperinflation. J Heart Lung Transplant 1998; 17:192–201
15. Beer A, Reed RM, Bölükbas S, Budev M, Chaux G, Zamora MR, Snell G, Orens JB, Klesney-Tait JA, Schmidt GA, Brower RG, Eberlein M: Mechanical ventilation after lung transplantation. An international survey of practices and preferences. Ann Am Thorac Soc 2014; 11:546–53
16. Barnes L, Reed RM, Parekh KR, Bhama JK, Pena T, Rajagopal S, Schmidt GA, Klesney-Tait JA, Eberlein M: Mechanical ventilation for the lung transplant recipient. Curr Pulmonol Rep 2015; 4:88–96
17. Del Sorbo L, Goligher EC, McAuley DF, Rubenfeld GD, Brochard LJ, Gattinoni L, Slutsky AS, Fan E: Mechanical ventilation in adults with acute respiratory distress syndrome. Summary of the Experimental Evidence for the Clinical Practice Guideline. Ann Am Thorac Soc 2017; 14(suppl 4):261–70
18. Fan E, Del Sorbo L, Goligher EC, Hodgson CL, Munshi L, Walkey AJ, Adhikari NKJ, Amato MBP, Branson R, Brower RG, Ferguson ND, Gajic O, Gattinoni L, Hess D, Mancebo J, Meade MO, McAuley DF, Pesenti A, Ranieri VM, Rubenfeld GD, Rubin E, Seckel M, Slutsky AS, Talmor D, Thompson BT, Wunsch H, Uleryk E, Brozek J, Brochard LJ; American Thoracic Society, European Society of Intensive Care Medicine, and Society of Critical Care Medicine: An official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline: Mechanical ventilation in adult patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 2017; 195:1253–63
19. Acute Respiratory Distress Syndrome Network, Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000; 342:1301–8
20. Amato MB, Meade MO, Slutsky AS, Brochard L, Costa EL, Schoenfeld DA, Stewart TE, Briel M, Talmor D, Mercat A, Richard JC, Carvalho CR, Brower RG: Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med 2015; 372:747–55
21. Barbateskovic M, Schjørring OL, Russo Krauss S, Jakobsen JC, Meyhoff CS, Dahl RM, Rasmussen BS, Perner A, Wetterslev J: Higher versus lower fraction of

inspired oxygen or targets of arterial oxygenation for adults admitted to the intensive care unit. Cochrane Database Syst Rev 2019; 11:CD012631
22. Bellier J, Lhommet P, Bonnette P, Puyo P, Le Guen M, Roux A, Parquin F, Chapelier A, Sage E; Foch Lung Transplantation Group: Extracorporeal membrane oxygenation for grade 3 primary graft dysfunction after lung transplantation: Long-term outcomes. Clin Transplant 2019; 33:e13480
23. Felten ML, Moyer JD, Dreyfus JF, Marandon JY, Sage E, Roux A, Parquin F, Cerf C, Zuber B, Le Guen M, Fischler M; Foch Lung Transplant Group: Immediate postoperative extubation in bilateral lung transplantation: Predictive factors and outcomes. Br J Anaesth 2016; 116:847–54
24. Feltracco P, Milevoj M, Alberti V, Carollo C, Michieletto E, Rea F, Loy M, Marulli G, Ori C: Early tracheostomy following lung transplantation. Transplant Proc 2011; 43:1151–5
25. Miyoshi R, Chen-Yoshikawa TF, Hamaji M, Kawaguchi A, Kayawake H, Hijiya K, Motoyama H, Aoyama A, Date H: Effect of early tracheostomy on clinical outcomes in critically ill lung transplant recipients. Gen Thorac Cardiovasc Surg 2018; 66:529–36
26. Rocco M, Conti G, Antonelli M, Bufi M, Costa MG, Alampi D, Ruberto F, Stazi GV, Pietropaoli P: Noninvasive pressure support ventilation in patients with acute respiratory failure after bilateral lung transplantation. Intensive Care Med 2001; 27:1622–6
27. Chaudhuri D, Granton D, Wang DX, Burns KEA, Helviz Y, Einav S, Trivedi V, Mauri T, Ricard JD, Mancebo J, Frat JP, Jog S, Hernandez G, Maggiore SM, Mbuagbaw L, Hodgson CL, Jaber S, Goligher EC, Brochard L, Rochwerg B: High-flow nasal cannula in the immediate postoperative period: A systematic review and meta-analysis. Chest 2020; 158:1934–46
28. Langer D: Rehabilitation in patients before and after lung transplantation. Respiration 2015; 89:353–62
29. Brochard L, Slutsky A, Pesenti A: Mechanical ventilation to minimize progression of lung injury in acute respiratory failure. Am J Respir Crit Care Med 2017; 195:438–42
30. Bellani G, Grassi A, Sosio S, Gatti S, Kavanagh BP, Pesenti A, Foti G: Driving pressure is associated with outcome during assisted ventilation in acute respiratory distress syndrome. Anesthesiology 2019; 131:594–604
31. Telias I, Junhasavasdikul D, Rittayamai N, Piquilloud L, Chen L, Ferguson ND, Goligher EC, Brochard L: Airway occlusion pressure as an estimate of respiratory drive and inspiratory effort during assisted ventilation. Am J Respir Crit Care Med 2020; 201:1086–98
32. Crespo MM, McCarthy DP, Hopkins PM, Clark SC, Budev M, Bermudez CA, Benden C, Eghtesady P, Lease ED, Leard L, D'Cunha J, Wigfield CH, Cypel M, Diamond JM, Yun JJ, Yarmus L, Machuzak M, Klepetko W, Verleden G, Hoetzenecker K, Dellgren G, Mulligan M: ISHLT consensus statement on adult and pediatric airway complications after lung transplantation: Definitions, grading system, and therapeutics. J Heart Lung Transplant 2018; 37:548–63
33. Fan E, Brodie D, Slutsky AS: Acute respiratory distress syndrome: Advances in diagnosis and treatment. JAMA 2018; 319:698–710
34. Meade MO, Granton JT, Matte-Martyn A, McRae K, Weaver B, Cripps P, Keshavjee SH; Toronto Lung Transplant Program: A randomized trial of inhaled nitric oxide to prevent ischemia-reperfusion injury after lung transplantation. Am J Respir Crit Care Med 2003; 167:1483–9
35. Riera J, Maldonado C, Mazo C, Martínez M, Baldirà J, Lagunes L, Augustin S, Roman A, Due M, Rello J, Levine DJ: Prone positioning as a bridge to recovery from refractory hypoxaemia following lung transplantation. Interact Cardiovasc Thorac Surg 2017; 25:292–6
36. Bermudez CA, Adusumilli PS, McCurry KR, Zaldonis D, Crespo MM, Pilewski JM, Toyoda Y: Extracorporeal membrane oxygenation for primary graft dysfunction after lung transplantation: Long-term survival. Ann Thorac Surg 2009; 87:854–60
37. Wigfield CH, Lindsey JD, Steffens TG, Edwards NM, Love RB: Early institution of extracorporeal membrane oxygenation for primary graft dysfunction after lung transplantation improves outcome. J Heart Lung Transplant 2007; 26:331–8
38. Hoetzenecker K, Schwarz S, Muckenhuber M, Benazzo A, Frommlet F, Schweiger T, Bata O, Jaksch P, Ahmadi N, Muraközy G, Prosch H, Hager H, Roth G, Lang G, Taghavi S, Klepetko W: Intraoperative extracorporeal membrane oxygenation and the possibility of postoperative prolongation improve survival in bilateral lung transplantation. J Thorac Cardiovasc Surg 2018; 155:2193–2206.e3
39. Moser B, Jaksch P, Taghavi S, Muraközy G, Lang G, Hager H, Krenn C, Roth G, Faybik P, Bacher A, Aigner C, Matilla JR, Hoetzenecker K, Hacker P, Lang I, Klepetko W: Lung transplantation for idiopathic pulmonary arterial hypertension on intraoperative and postoperatively prolonged extracorporeal membrane oxygenation provides optimally controlled reperfusion and excellent outcome. Eur J Cardiothorac Surg 2018; 53:178–85
40. Tudorache I, Sommer W, Kühn C, Wiesner O, Hadem J, Fühner T, Ius F, Avsar M, Schwerk N, Böthig D, Gottlieb J, Welte T, Bara C, Haverich A, Hoeper MM, Warnecke G: Lung transplantation for severe pulmonary hypertension–awake extracorporeal membrane oxygenation for postoperative left ventricular remodelling. Transplantation 2015; 99:451–8
41. Hartwig MG, Appel JZ III, Cantu E III, Simsir S, Lin SS, Hsieh CC, Walczak R, Palmer SM, Davis RD Jr: Improved results treating lung allograft failure with

venovenous extracorporeal membrane oxygenation. Ann Thorac Surg 2005; 80:1872–9; discussion 1879–80
42. Del Sorbo L, Goffi A, Goligher E, Fan E, Slutsky AS: Setting mechanical ventilation in ARDS patients during VV-ECMO: Where are we? Minerva Anestesiol 2015; 81:1369–76
43. Abrams D, Schmidt M, Pham T, Beitler JR, Fan E, Goligher EC, McNamee JJ, Patroniti N, Wilcox ME, Combes A, Ferguson ND, McAuley DF, Pesenti A, Quintel M, Fraser J, Hodgson CL, Hough CL, Mercat A, Mueller T, Pellegrino V, Ranieri VM, Rowan K, Shekar K, Brochard L, Brodie D: Mechanical ventilation for acute respiratory distress syndrome during extracorporeal life support. Research and practice. Am J Respir Crit Care Med 2020; 201:514–25
44. Snell G, Klepetko W: Perioperative lung transplant management, Lung Transplantation, European Respiratory Society Monograph, vol. 26. Edited by Boe J, Estenne M, Weder W. Lausanne, European Respiratory Society Publications, 2003, pp 130–42
45. Malbrain MLNG, Langer T, Annane D, Gattinoni L, Elbers P, Hahn RG, De Laet I, Minini A, Wong A, Ince C, Muckart D, Mythen M, Caironi P, Van Regenmortel N: Intravenous fluid therapy in the perioperative and critical care setting: Executive summary of the International Fluid Academy (IFA). Ann Intensive Care 2020; 10:64
46. Currey J, Pilcher DV, Davies A, Scheinkestel C, Botti M, Bailey M, Snell G: Implementation of a management guideline aimed at minimizing the severity of primary graft dysfunction after lung transplant. J Thorac Cardiovasc Surg 2010; 139:154–61
47. Smith I, Pearse BL, Faulke DJ, Naidoo R, Nicotra L, Hopkins P, Ryan EG: Targeted bleeding management reduces the requirements for blood component therapy in lung transplant recipients. J Cardiothorac Vasc Anesth 2017; 31:426–33
48. Pena JJ, Bottiger BA, Miltiades AN: Perioperative management of bleeding and transfusion for lung transplantation. Semin Cardiothorac Vasc Anesth 2020; 24:74–83
49. Pilcher DV, Scheinkestel CD, Snell GI, Davey-Quinn A, Bailey MJ, Williams TJ: High central venous pressure is associated with prolonged mechanical ventilation and increased mortality after lung transplantation. J Thorac Cardiovasc Surg 2005; 129:912–8
50. Lertjitbanjong P, Thongprayoon C, Cheungpasitporn W, O'Corragain OA, Srivali N, Bathini T, Watthanasuntorn K, Aeddula NR, Salim SA, Ungprasert P, Gillaspie EA, Wijarnpreecha K, Mao MA, Kaewput W: Acute kidney injury after lung transplantation: A systematic review and meta-analysis. J Clin Med 2019; 8:E1713
51. Della Rocca G, Costa MG, Coccia C, Pompei L, Di Marco P, Vilardi V, Pietropaoli P: Cardiac output monitoring: Aortic transpulmonary thermodilution and pulse contour analysis agree with standard thermodilution methods in patients undergoing lung transplantation. Can J Anaesth 2003; 50:707–11
52. Sabashnikov A, Mohite PN, Zeriouh M, Zych B, García-Sáez D, Maier J, Weymann A, Fatullayev J, Mahesh B, Popov AF, Stock U, De Robertis F, Bahrami T, Wahlers T, Carby M, Simon AR, Reed A: The role of extracorporeal life support in the management with severe idiopathic pulmonary artery hypertension undergoing lung transplantation: Are those patients referred too late? J Thorac Dis 2019; 11(suppl 6):929–37
53. Hoeper MM, Benza RL, Corris P, de Perrot M, Fadel E, Keogh AM, Kuhn C, Savale L, Klepetko W: Intensive care, right ventricular support and lung transplantation in patients with pulmonary hypertension. Eur Respir J 2019; 53:1–12
54. Waldron NH, Klinger RY, Hartwig MG, Snyder LD, Daubert JP, Mathew JP: Adverse outcomes associated with postoperative atrial arrhythmias after lung transplantation: A meta-analysis and systematic review of the literature. Clin Transplant 2017; 31:1–10
55. Garcia S, Canoniero M, Sattiraju S, Chen LY, Adkisson W, Hertz M, Benditt DG: Atrial fibrillation after lung transplantation: Incidence, predictors and long-term implications. J Atr Fibrillation 2011; 4:363
56. Kumar N, Essandoh M, Bhatt A, Whitson BA, Sawyer TR, Flores A, Awad H, Dimitrova G, Gorelik L, Bhandary S, Perez WJ, Iyer MH, Stein E, Fiorini K, Turner K, Saklayen S, Hussain N: Pulmonary cuff dysfunction after lung transplant surgery: A systematic review of the evidence and analysis of its clinical implications. J Heart Lung Transplant 2019; 38:530–44
57. Orrego CM, Cordero-Reyes AM, Estep JD, Seethamraju H, Scheinin S, Loebe M, Torre-Amione G: Atrial arrhythmias after lung transplant: Underlying mechanisms, risk factors, and prognosis. J Heart Lung Transplant 2014; 33:734–40
58. Mason DP, Marsh DH, Alster JM, Murthy SC, McNeill AM, Budev MM, Mehta AC, Pettersson GB, Blackstone EH: Atrial fibrillation after lung transplantation: Timing, risk factors, and treatment. Ann Thorac Surg 2007; 84:1878–84
59. Frendl G, Sodickson AC, Chung MK, Waldo AL, Gersh BJ, Tisdale JE, Calkins H, Aranki S, Kaneko T, Cassivi S, Smith SC Jr, Darbar D, Wee JO, Waddell TK, Amar D, Adler D; American Association of Thoracic Surgery: 2014 AATS guidelines for the prevention and management of perioperative atrial fibrillation and flutter for thoracic surgical procedures. Executive summary. J Thorac Cardiovasc Surg 2014; 148:772–91
60. Isiadinso I, Meshkov AB, Gaughan J, Sandhu P, Lim S, Cordova F, Criner G: Atrial arrhythmias after lung and heart-lung transplant: Effects on short-term mortality and the influence of amiodarone. J Heart Lung Transplant 2011; 30:37–44

61. Mateen FJ, Dierkhising RA, Rabinstein AA, Van De Beek D, Wijdicks EFM: Neurological complications following adult lung transplantation. Am J Transplant 2010; 10:908–14
62. Smith PJ, Blumenthal JA, Hoffman BM, Davis RD, Palmer SM: Postoperative cognitive dysfunction and mortality following lung transplantation. Am J Transplant 2018; 18:696–703
63. Zivković SA, Jumaa M, Barisić N, McCurry K: Neurologic complications following lung transplantation. J Neurol Sci 2009; 280:90–3
64. Shigemura N, Sclabassi RJ, Bhama JK, Gries CJ, Crespo MM, Johnson B, Pilewski JM, Bermudez CA: Early major neurologic complications after lung transplantation: Incidence, risk factors, and outcome. Transplantation 2013; 95:866–71
65. Sher Y, Mooney J, Dhillon G, Lee R, Maldonado JR: Delirium after lung transplantation: Association with recipient characteristics, hospital resource utilization, and mortality. Clin Transplant 2017; 31:10.1111/ctr.12966
66. Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJC, Pandharipande PP, Watson PL, Weinhouse GL, Nunnally ME, Rochwerg B, Balas MC, van den Boogaard M, Bosma KJ, Brummel NE, Chanques G, Denehy L, Drouot X, Fraser GL, Harris JE, Joffe AM, Kho ME, Kress JP, Lanphere JA, McKinley S, Neufeld KJ, Pisani MA, Payen JF, Pun BT, Puntillo KA, Riker RR, Robinson BRH, Shehabi Y, Szumita PM, Winkelman C, Centofanti JE, Price C, Nikayin S, Misak CJ, Flood PD, Kiedrowski K, Alhazzani W: Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. Crit Care Med 2018; 46:e825–73
67. Wickerson L, Rozenberg D, Janaudis-Ferreira T, Deliva R, Lo V, Beauchamp G, Helm D, Gottesman C, Mendes P, Vieira L, Herridge M, Singer LG, Mathur S: Physical rehabilitation for lung transplant candidates and recipients: An evidence-informed clinical approach. World J Transplant 2016; 6:517–31
68. Kelava M, Anthony D, Elsharkawy H: Continuous erector spinae block for postoperative analgesia after thoracotomy in a lung transplant recipient. J Cardiothorac Vasc Anesth 2018; 32:e9–11
69. Schlichter RA: Dexmedetomidine is an excellent agent for sedation status-post lung transplant. J Clin Anesth 2010; 22:1–2
70. Chen S, Hu J, Xu L, Brandon D, Yu J, Zhang J: Posterior reversible encephalopathy syndrome after transplantation: A review. Mol Neurobiol 2016; 53:6897–909
71. Wigfield CH, Love RB: Clinical neurology in lung transplantation. Handb Clin Neurol 2014; 121:1237–43
72. Högerle BA, Kohli N, Habibi-Parker K, Lyster H, Reed A, Carby M, Zeriouh M, Weymann A, Simon AR, Sabashnikov A, Popov AF, Soresi S: Challenging immunosuppression treatment in lung transplant recipients with kidney failure. Transpl Immunol 2016; 35:18–22
73. LoMauro A, Righi I, Privitera E, Vergari M, Nigro M, Aliverti A, Frykholm P, Tarsia P, Morlacchi L, Nosotti M, Palleschi A: The impaired diaphragmatic function after bilateral lung transplantation: A multifactorial longitudinal study. J Heart Lung Transplant 2020; 39:795–804
74. Kaufman MR, Bauer T, Onders RP, Brown DP, Chang EI, Rossi K, Elkwood AI, Paulin E, Jarrahy R: Treatment for bilateral diaphragmatic dysfunction using phrenic nerve reconstruction and diaphragm pacemakers. Interact Cardiovasc Thorac Surg 2021; 32:753–60
75. Anwar S, Gupta D, Ashraf MA, Khalid SA, Rizvi SM, Miller BW, Brennan DC: Symptomatic hyperammonemia after lung transplantation: Lessons learnt. Hemodial Int 2014; 18:185–91
76. Lichtenstein GR, Yang YX, Nunes FA, Lewis JD, Tuchman M, Tino G, Kaiser LR, Palevsky HI, Kotloff RM, Furth EE, Bavaria JE, Stecker MM, Kaplan P, Berry GT: Fatal hyperammonemia after orthotopic lung transplantation. Ann Intern Med 2000; 132:283–7
77. Chen C, Bain KB, Iuppa JA, Yusen RD, Byers DE, Patterson GA, Trulock EP, Hachem RR, Witt CA: Hyperammonemia syndrome after lung transplantation: A single center experience. Transplantation 2016; 100:678–84
78. Bharat A, Cunningham SA, Scott Budinger GR, Kreisel D, DeWet CJ, Gelman AE, Waites K, Crabb D, Xiao L, Bhorade S, Ambalavanan N, Dilling DF, Lowery EM, Astor T, Hachem R, Krupnick AS, DeCamp MM, Ison MG, Patel R: Disseminated ureaplasma infection as a cause of fatal hyperammonemia in humans. Sci Transl Med 2015; 7:284re3
79. George IA, Santos CAQ, Olsen MA, Powderly WG: Epidemiology of cryptococcosis and cryptococcal meningitis in a large retrospective cohort of patients after solid organ transplantation. Open Forum Infect Dis 2017; 4:ofx004
80. Ailawadi G, Smith PW, Oka T, Wang H, Kozower BD, Daniel TM, Kron IL, Jones DR: Effects of induction immunosuppression regimen on acute rejection, bronchiolitis obliterans, and survival after lung transplantation. J Thorac Cardiovasc Surg 2008; 135:594–602
81. Parulekar AD, Kao CC: Detection, classification, and management of rejection after lung transplantation. J Thorac Dis 2019; 11(suppl 14):1732–9
82. Mazo C, Pont T, Ballesteros MA, López E, Rellán L, Robles JC, Rello J: Pneumonia *versus* graft dysfunction as the cause of acute respiratory failure after lung transplant: A 4-year multicentre prospective study in 153 adults requiring intensive care admission. Eur Respir J 2019; 54:1801512
83. Loor K, Culebras M, Sansano I, Álvarez A, Berastegui C, de Gracia J: Optimization of transbronchial cryobiopsy

in lung transplant recipients. Ann Thorac Surg 2019; 108:1052–8
84. Ivulich S, Westall G, Dooley M, Snell G: The evolution of lung transplant immunosuppression. Drugs 2018; 78:965–82
85. Benazzo A, Schwarz S, Muckenhuber M, Schweiger T, Muraközy G, Moser B, Sigüenza JM, Lang G, Taghavi S, Klepetko W, Hoetzenecker K, Jaksch P, Lambers C: Alemtuzumab induction combined with reduced maintenance immunosuppression is associated with improved outcomes after lung transplantation: A single centre experience. PLoS One 2019; 14:e0210443
86. Christie JD, Edwards LB, Kucheryavaya AY, Benden C, Dipchand AI, Dobbels F, Kirk R, Rahmel AO, Stehlik J, Hertz MI; International Society of Heart and Lung Transplantation: The Registry of the International Society for Heart and Lung Transplantation: 29th adult lung and heart-lung transplant report-2012. J Heart Lung Transplant 2012; 31:1073–86
87. Whitson BA, Lehman A, Wehr A, Hayes D Jr, Kirkby S, Pope-Harman A, Kilic A, Higgins RS: To induce or not to induce: A 21st century evaluation of lung transplant immunosuppression's effect on survival. Clin Transplant 2014; 28:450–61
88. Furuya Y, Jayarajan SN, Taghavi S, Cordova FC, Patel N, Shiose A, Leotta E, Criner GJ, Guy TS, Wheatley GH, Kaiser LR, Toyoda Y: The impact of alemtuzumab and basiliximab induction on patient survival and time to bronchiolitis obliterans syndrome in double lung transplantation recipients. Am J Transplant 2016; 16:2334–41
89. Whited LK, Latran MJ, Hashmi ZA, Wang IW, Wozniak TC, Duncan MD, Roe DW, Baz MA, Hage CA: Evaluation of alemtuzumab *versus* basiliximab induction: A retrospective cohort study in lung transplant recipients. Transplantation 2015; 99:2190–5
90. Tinckam KJ, Keshavjee S, Chaparro C, Barth D, Azad S, Binnie M, Chow CW, de Perrot M, Pierre AF, Waddell TK, Yasufuku K, Cypel M, Singer LG: Survival in sensitized lung transplant recipients with perioperative desensitization. Am J Transplant 2015; 15:417–26
91. Snyder LD, Gray AL, Reynolds JM, Arepally GM, Bedoya A, Hartwig MG, Davis RD, Lopes KE, Wegner WE, Chen DF, Palmer SM: Antibody desensitization therapy in highly sensitized lung transplant candidates. Am J Transplant 2014; 14:849–56
92. Scheffert JL, Raza K: Immunosuppression in lung transplantation. J Thorac Dis 2014; 6:1039–53
93. Alsaeed M, Husain S: Infections in heart and lung transplant recipients. Crit Care Clin 2019; 35:75–93
94. Burguete SR, Maselli DJ, Fernandez JF, Levine SM: Lung transplant infection. Respirology 2013; 18:22–38
95. Coiffard B, Prud'Homme E, Hraiech S, Cassir N, Le Pavec J, Kessler R, Meloni F, Leone M, Thomas PA, Reynaud-Gaubert M, Papazian L: Worldwide clinical practices in perioperative antibiotic therapy for lung transplantation. BMC Pulm Med 2020; 20:109
96. Clajus C, Blasi F, Welte T, Greer M, Fuehner T, Mantero M: Therapeutic approach to respiratory infections in lung transplantation. Pulm Pharmacol Ther 2015; 32:149–54
97. Soave R: Prophylaxis strategies for solid-organ transplantation. Clin Infect Dis 2001; 33(suppl 1):S26–31
98. De Soyza A, Meachery G, Hester KL, Nicholson A, Parry G, Tocewicz K, Pillay T, Clark S, Lordan JL, Schueler S, Fisher AJ, Dark JH, Gould FK, Corris PA: Lung transplantation for patients with cystic fibrosis and *Burkholderia cepacia* complex infection: A single-center experience. J Heart Lung Transplant 2010; 29:1395–404
99. Hamad Y, Pilewski JM, Morrell M, D'Cunha J, Kwak EJ: Outcomes in lung transplant recipients with *Mycobacterium abscessus* infection: A 15-year experience from a large tertiary care center. Transplant Proc 2019; 51:2035–42
100. Shaw LP, Doyle RM, Kavaliunaite E, Spencer H, Balloux F, Dixon G, Harris KA: Children with cystic fibrosis are infected with multiple subpopulations of *Mycobacterium abscessus* with different antimicrobial resistance profiles. Clin Infect Dis 2019; 69:1678–86
101. Kavaliunaite E, Harris KA, Aurora P, Dixon G, Shingadia D, Muthialu N, Spencer H: Outcome according to subspecies following lung transplantation in cystic fibrosis pediatric patients infected with *Mycobacterium abscessus*. Transpl Infect Dis 2020; 22:e13274
102. Perez AA, Singer JP, Schwartz BS, Chin-Hong P, Shah RJ, Kleinhenz ME, Gao Y, Venado A, Leard LE, Golden JA, Kukreja J, Greenland JR, Hays SR: Management and clinical outcomes after lung transplantation in patients with pre-transplant *Mycobacterium abscessus* infection: A single center experience. Transpl Infect Dis 2019; 21:e13084
103. Razonable RR, Humar A: Cytomegalovirus in solid organ transplant recipients-Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant 2019; 33:e13512
104. Leal S, Sacanell J, Riera J, Masclans JR, Rello J: Early postoperative management of lung transplantation. Minerva Anestesiol 2014; 80:1234–45
105. Husain S, Sole A, Alexander BD, Aslam S, Avery R, Benden C, Billaud EM, Chambers D, Danziger-Isakov L, Fedson S, Gould K, Gregson A, Grossi P, Hadjiliadis D, Hopkins P, Luong ML, Marriott DJE, Monforte V, Muñoz P, Pasqualotto AC, Roman A, Silveira FP, Teuteberg J, Weigt S, Zaas AK, Zuckerman A, Morrissey O: The 2015 International Society for Heart and Lung Transplantation guidelines for the management of fungal infections in mechanical circulatory support and cardiothoracic organ

transplant recipients: Executive summary. J Heart Lung Transplant 2016; 35:261–82
106. Clark NM, Weigt SS, Fishbein MC, Kubak B, Belperio JA, Lynch JP III: Fungal infections complicating lung transplantation. Semin Respir Crit Care Med 2018; 39:227–54
107. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, Reboli AC, Schuster MG, Vazquez JA, Walsh TJ, Zaoutis TE, Sobel JD: Clinical practice guideline for the management of candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis 2016; 62:e1–50
108. Doligalski CT, Benedict K, Cleveland AA, Park B, Derado G, Pappas PG, Baddley JW, Zaas DW, Harris MT, Alexander BD: Epidemiology of invasive mold infections in lung transplant recipients. Am J Transplant 2014; 14:1328–33
109. Husain S, Camargo JF: Invasive *Aspergillosis* in solid-organ transplant recipients: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant 2019; 33:e13544
110. Palmer SM, Alexander BD, Sanders LL, Edwards LJ, Reller LB, Davis RD, Tapson VF: Significance of blood stream infection after lung transplantation: Analysis in 176 consecutive patients. Transplantation 2000; 69:2360–6
111. Shields RK, Clancy CJ, Minces LR, Shigemura N, Kwak EJ, Silveira FP, Abdel-Massih RC, Bhama JK, Bermudez CA, Pilewski JM, Crespo M, Toyoda Y, Nguyen MH: Epidemiology and outcomes of deep surgical site infections following lung transplantation. Am J Transplant 2013; 13:2137–45
112. Jomphe V, Lands LC, Mailhot G: Nutritional requirements of lung transplant recipients: Challenges and considerations. Nutrients 2018; 10:E790
113. Ratchford TL, Teckman JH, Patel DR: Gastrointestinal pathophysiology and nutrition in cystic fibrosis. Expert Rev Gastroenterol Hepatol 2018; 12:853–62
114. Erskine JM, Lingard C, Sontag M: Update on enteral nutrition support for cystic fibrosis. Nutr Clin Pract 2007; 22:223–32
115. Turck D, Braegger CP, Colombo C, Declercq D, Morton A, Pancheva R, Robberecht E, Stern M, Strandvik B, Wolfe S, Schneider SM, Wilschanski M: ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children, and adults with cystic fibrosis. Clin Nutr 2016; 35:557–77
116. Baumann B, Byers S, Wasserman-Wincko T, Smith L, Hathaway B, Bhama J, Shigemura N, Hayanga JWA, D'Cunha J, Johnson JT: Postoperative swallowing assessment after lung transplantation. Ann Thorac Surg 2017; 104:308–12
117. Black RJ, Bogaardt H, McCabe P, Glanville AR, MacDonald P, Madill C: Clinical predictors for oropharyngeal dysphagia and laryngeal dysfunction after lung and heart transplantation. Int J Lang Commun Disord 2019; 54:894–901
118. Castor JM, Wood RK, Muir AJ, Palmer SM, Shimpi RA: Gastroesophageal reflux and altered motility in lung transplant rejection. Neurogastroenterol Motil 2010; 22:841–50
119. Miller CB, Malaisrie SC, Patel J, Garrity E, Vigneswaran WT, Gamelli RL: Intraabdominal complications after lung transplantation. J Am Coll Surg 2006; 203:653–60
120. Golda T, Kreisler E, Mercader C, Frago R, Trenti L, Biondo S: Emergency surgery for perforated diverticulitis in the immunosuppressed patient. Colorectal Dis 2014; 16:723–31
121. Sulser P, Lehmann K, Schuurmans MM, Weder W, Inci I: Early and late abdominal surgeries after lung transplantation: Incidence and outcome. Interact Cardiovasc Thorac Surg 2018; 27:727–32