

Critical Care after Lung Transplantation

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Since the first successful lung transplantation in 1983, there have been many advances in the field. Nevertheless, the latest data from the International Society for Heart and Lung Transplantation revealed that the risk of death from transplantation is 9%. Various aspects of postoperative management, including mechanical ventilation, could affect intensive care unit stay, hospital stay, and immediate postoperative morbidity and mortality. Complications such as reperfusion injury, graft rejection, infection, and dehiscence of anastomosis increase fatal adverse side effects immediately after surgery. In this article, we review the possible immediate complications after lung transplantation and summarize current knowledge on prevention and treatment.

Key Words: critical care; immunosuppression; lung transplantation; postoperative care; postoperative complications; preventive care; transplant rejection; transplantation immunology

INTRODUCTION

Immediate postoperative management of lung transplant recipients consists of ventilator support and weaning, sedation and pain control, meticulous fluid management, close hemodynamic monitoring, primary graft dysfunction (PGD) or other organ dysfunction, such as acute kidney injury or heart failure. Lung transplantation is a major operation, and various technical surgical complications may occur in the early postoperative period. In order to ease a patient's return to normal daily life after lung transplantation, rehabilitation and education should be added to the postoperative care plan. However, here we will only cover the immediate postoperative complications and the strategies for the prevention of various complications.

IMMEDIATE POSTOPERATIVE MANAGEMENT OF LUNG TRANSPLANTATION

Medical Complications

Primary graft dysfunction

PGD after lung transplantation represents the multifactorial injury of the transplanted lung that occurs within first 72 hours after transplantation. PGD is the preferred term and is sometimes referred to as "ischemia-reperfusion injury," "early graft dysfunction," and "reimplanta-

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Table 1. The 2016 International Society for Heart and Lung Transplantation definition of PGD

Grade ^a	Pulmonary edema on chest X-ray	PaO ₂ /FiO ₂ ratio
PGD grade 0	No	Any
PGD grade 1	Yes	>300
PGD grade 2	Yes	200–300
PGD grade 3	Yes	<200

PGD: primary graft dysfunction; PaO₂: partial pressure of arterial oxygen; FiO₂: fraction of inspired oxygen.

^aPatients with no evidence of pulmonary edema on chest X-ray are considered grade 0. The grade of severity was categorized according to the PaO₂/FiO₂ ratio.

tion edema.” Hypoxia occurring within the first 72 hours after lung transplantation and diffuse opaque radiographic appearances of unknown cause are called PGD. A typical histologic finding is diffuse alveolar damage. The definition proposed by the International Society for Heart and Lung Transplantation (ISHLT) in 2016 is shown in Table 1 [1].

The severity of PGD is evaluated based on the oxygenated artery fraction (PaO₂/FiO₂ ratio, PF ratio), and if there is no diffuse pulmonary edema on chest X-ray, all PF ratios are considered to be grade 0. The PF ratio is ideally measured at a positive end-expiratory pressure (PEEP) of 5 cm H₂O at FiO₂ of 1.0 and may need correction at elevated altitudes. All measurements of PGD are performed four times, and reperfusion time of the second lung (T0), 24 hours, 48 hours, and 72 hours (T24, T48, T72). The PGD score at 72 hours may be the most important time-point for predicting survival [2]. In terms of treatment and prognosis, most patients who maintain normal pulmonary artery pressure, usually of PGD grade 2 or lower, could improve with conventional therapy, such as a protective lung ventilation strategy and conservative fluid management. Inhaled nitric oxide (iNO) may be used in patients with severe PGD (grade 3) whose oxygenation is not improving, despite conservative treatment and the maintenance of pulmonary arterial hypertension, although the effect of iNO has not yet been proven [3,4]. However, there is no evidence that the use of iNO prevents PGD [5]. For severe PGD patients not responding to iNO and general treatment, it is advisable to initiate extracorporeal membrane oxygenation (ECMO) within 24 hours of severe PGD, and most patients will improve with venovenous ECMO [6–8]. Prognosis is poor when retransplantation for PGD, and most transplantation centers try to avoid retransplantation [9,10]. PGD is considered a risk factor for chronic lung allograft dysfunction (CLAD), reoperation rate, longer ventilator application, longer intensive care unit (ICU) stay, and higher rate of renal replacement therapy; in principle, it is

KEY MESSAGES

- We review the possible immediate complications after lung transplantation.
- We summarize current knowledge on prevention and treatment of possible immediate complications after lung transplantation.

best to prevent PGD rather than to treat it [11–15]. The selection of adequate donor lungs and optimization of preservation, storage, and intraoperative efforts to reduce ischemia-reperfusion injury is the best strategy to prevent PGD.

Acute rejection

Acute rejection in lung transplantation is still a problem despite aggressive immunosuppressive regimens. Acute rejection is relatively common, especially in the first post-transplant year. International registry data have reported the percentage of acute rejection as approximately 28% [16] and Korean registry data have reported approximately 21% [17]. The problems of acute rejection include not only early graft loss and mortality but also initiation of CLAD.

Clinical manifestations tend to be nonspecific, including cough with or without sputum, dyspnea, mild fever, malaise, or pleural effusion without definite evidence of infection or other causes [18]. Suspicion of acute rejection is important because there are no specific diagnostic tools. Chest X-ray or high-resolution computed tomography (CT) findings are also nonspecific, consisting of bilateral ground glass opacities of lower lobe predominance, interlobular septal thickening without consolidation, atelectasis, or cardiomegaly [19,20].

Acute rejection can be categorized in acute cellular rejection (ACR) and acute antibody-mediated rejection (AMR). The findings of perivascular and peribronchial lymphocytic infiltration in transbronchial biopsy confirm ACR. Prompt management of ACR is important, and treatment generally consists of a 3-day, high-dose, intravenous administration of methylprednisolone with optimizing immunosuppression [18]. AMR is related to antibodies in lung allografts, and this concept evolved as concept of CLAD. The lack of standardized data available for the establishment of diagnostic criteria and proper treatments for AMR have been the greatest difficulties. Therefore, ISHLT published a consensus document on pulmonary AMR which showed that measurable allograft dysfunction and the presence of circulating donor-specific antibodies and positive C4d peritubular capillary staining should be considered diagnostic of AMR [21,22]. Treatment options

for AMR include intravenous immunoglobulin, plasmapheresis, or anti-CD 20 monoclonal antibodies; however, the treatment of AMR is still challenging [18]. The response to treatment of AMR can be complete, partial, stabilized or there may be no response to treatment [22].

Postoperative infection

Infectious complications represent one of the most important causes of adverse outcomes in lung transplantation. Compared with other solid organ transplants, reasons for the high susceptibility to infection unique to lung transplantation are the continuous and direct exposure of the lung to environmental pathogens, denervation of the allograft—which destroys host defense mechanisms, such as the cough reflex—and the transmission of infection from the donor lung [23].

Surgical Complications

Postoperative hemorrhage

Postoperative hemorrhage was once one of the most common complications (Figure 1). In the early lung transplantation program, hemorrhage was a common complication, requiring about 25% of reoperation patients after cardiopulmonary bypass, en bloc bilateral lung transplantation. However, posterolateral thoracotomy for single lung transplantation and clamshell incision for bilateral lung transplantation have been effective in securing vision and reducing bleeding. In addition, ECMO for intraoperative hemodynamic support, instead of the conventional cardiopulmonary bypass, reduced

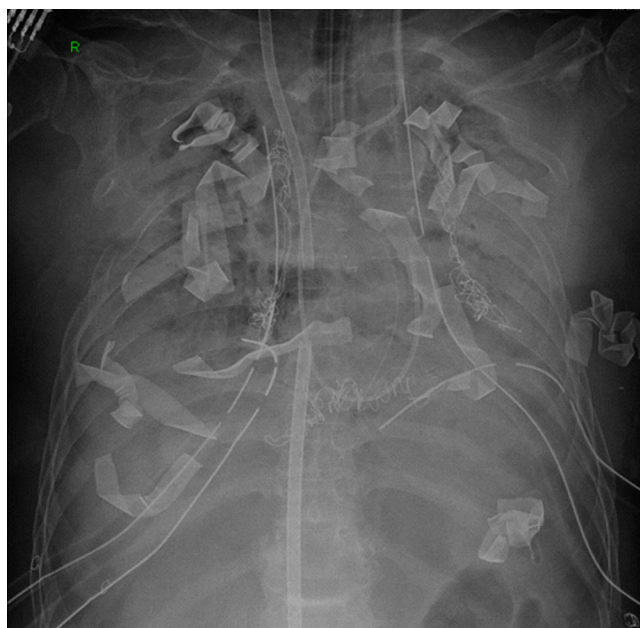


Figure 1. Gauzes were packed to control postoperative bleeding.

the amount of intraoperative and postoperative bleeding by decreasing the dose of heparin [24,25].

Large airway complications

Airway complications are major causes that deteriorate the clinical outcomes of recipients. There are several factors involved in large airway complications that occur after lung transplantation, such as interruption of bronchial circulation, airway colonization and infection, and immune responses to airways. Bronchial stenosis is the most frequent airway complication and is usually seen within 2 to 9 months after transplant, with an incidence of between 1.6% and 32% [26]. It is mostly observed at the surgical anastomosis and, on occasion, can occur distally. The right side is more frequently affected. Bronchial stenosis may be asymptomatic or show symptoms of declining expiratory flows, dyspnea, cough, or pneumonia. Stenosis is diagnosed by visual inspection with serial flexible bronchoscopy. Chest CT is useful for characterizing stenosis. Several interventions, including ballooning, inserting stents, and surgical brachioplasty have been used to improve symptoms [27,28]. Bronchial necrosis and dehiscence is a rare complication with an incidence of between 1% and 10% and is associated with high morbidity and mortality, often secondary to sepsis. Necrosis starts at the mucosa and is visible by flexible bronchoscopy. Necrosis without dehiscence may be managed by conservative care, with antimicrobials and keeping fully expanded lung. Dehiscence starts with signs of pneumomediastinum, subcutaneous emphysema, pneumothorax, and new onset of air leakage (Figure 2). A self-expanding metal stent can be applied to stimulate granulation tissue and serve as a scaffold for healing [29]. However, in case of failure, surgical repair or pneumonectomy should be considered. Exophytic granulation tissue narrowing the airway lumen by 25% or more may cause respiratory symptoms. Concurrent infection with aspergillus may increase granulation [30]. Although recurrence is common, debridement or brachytherapy have been effective in relieving symptoms.

Vascular anastomotic complications

Vascular anastomotic complications occur in 1.75% of patients after lung transplantation [31]. Pulmonary artery and atrium anastomosis both can be involved. Donor-recipient size mismatch, the anastomotic technique, twisting or thrombosis may cause these problems. Complications involving the pulmonary artery are more common (Figure 3). Poor orientation of the pulmonary artery and narrowing or kinking due to excessive length may cause these complications. Vascular com-

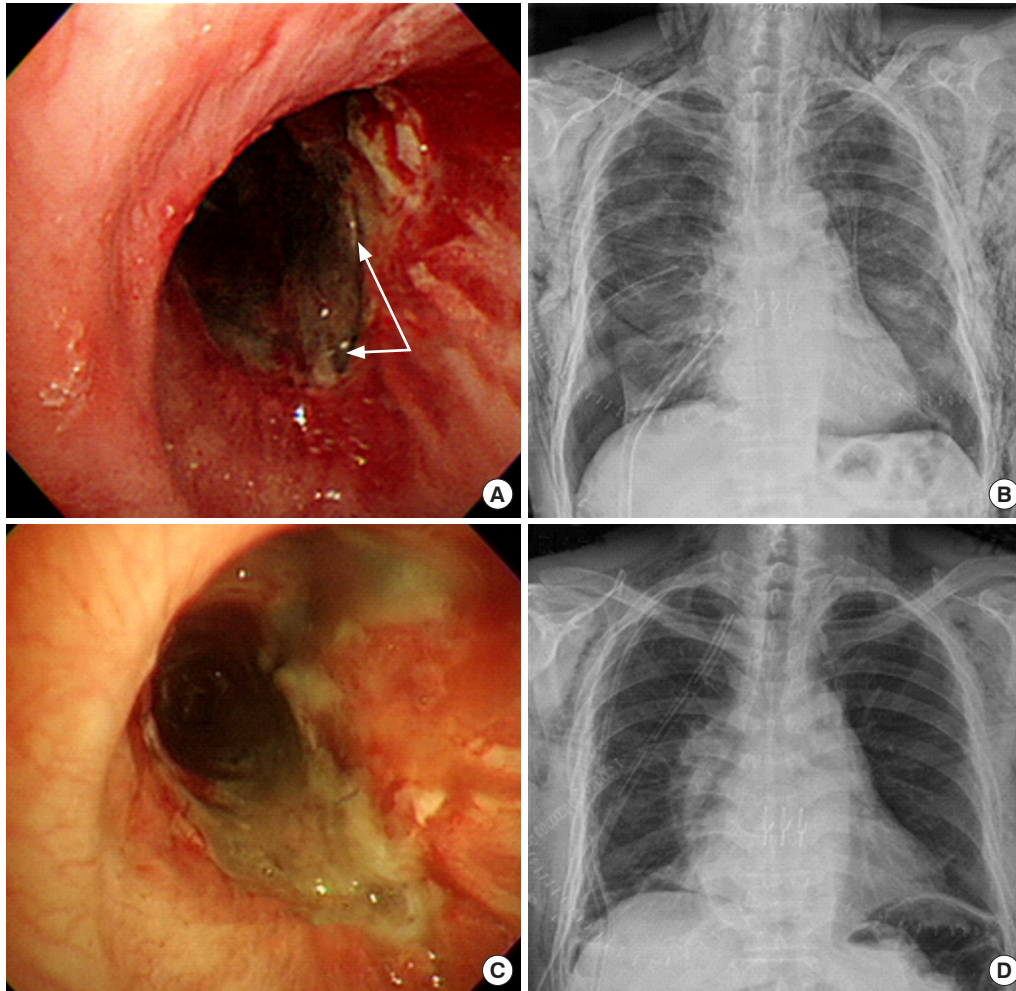


Figure 2. Bronchopleural fistula (BPF). (A) Fiberoptic bronchoscopy (FOB) finding of BPF (arrows). (B) Suddenly developed pneumothorax and subcutaneous emphysema on chest X-ray. (C) FOB finding showing repaired BPF with omental flap. (D) Chest X-ray after BPF repair with omental flap.

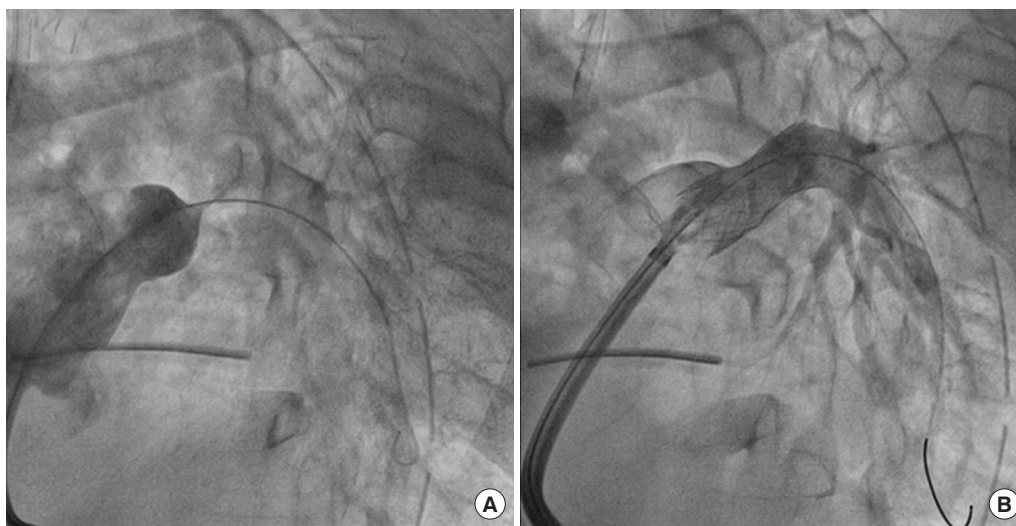


Figure 3. Pulmonary artery stenosis. (A) Pulmonary angiography shows nearly total obstruction (kinking) of left main pulmonary artery. (B) A stent was inserted on left main pulmonary artery and left pulmonary flow was restored.

plications should be suspected when the patient shows unexplained hypoxemia or pulmonary edema. Chest CT or perfusion scan should be considered. If diagnosed, surgical revision or intervention, including stenting or ballooning, can be applied. For the early detection of vascular complications in the operating room, transesophageal echocardiography is useful.

Postoperative Management

Monitoring

Postoperative monitoring in ICUs is on a continuum with intraoperative monitoring. Monitoring in the ICU is essential for the diagnosis of the clinical condition of a patient that can change rapidly and for the planning of future treatment. Like most other centers, our center continues to use pulmonary arterial catheter, electrocardiogram, pulse oximetry, manometer, and transthoracic echocardiography immediately after surgery. Unlike the operating room, postoperative patients in the ICU undergo application of an invasive monitoring device for a few days after surgery. As such, medical staff should be very cautious about the chance of infection associated with invasive monitoring devices. Furthermore, intensivists should always be careful that side effects, such as catheter removal, do not occur, because the patients move, unlike patients during surgery.

Mechanical ventilation care and ventilator weaning

Major respiratory complications (e.g., atelectasis, pneumonia, or respiratory failure) were consistently reported in 15% to 40% of patients within the first 3 days after thoracic surgery [32,33]. The onset of these complications may be associated with a unique pattern of recovery of pulmonary function after open thoracotomy, which presents with an initial 72-hour postoperative delay not seen in other major surgery. Previous studies have shown that active pain control, such as thoracic epidural, may improve postoperative respiratory function [32]. The goal of immediate ventilatory care is to reduce respiratory acidosis and maintain adequate oxygenation. We do not routinely monitor end-tidal CO₂ but apply it, if necessary. Patients are usually kept on mechanical ventilation on the day of surgery for monitoring because of the risk of reperfusion injury. Chest X-ray and arterial blood gas analysis are performed at least twice a day to observe the initial changes closely. There is no evidence for which mode is the best for postoperative ventilator setting, but controlled ventilation is preferred to prevent barotrauma on the bronchial anastomosis site and to limit the plateau pressure below 35 mmHg [34]. All recipients

are ventilated using a lung-protective ventilation strategy, regardless of the nature of the primary disease (emphysema, pulmonary hypertension or interstitial lung disease) or the type of transplantation (bilateral versus single). Protective mechanical ventilation includes PEEP and low tidal volume (6 to 8 mL/ideal body weight) with permissive hypercapnia. There are no large-scale randomized trials of lung-protective ventilation strategies for patients undergoing lung transplantation. PGD within 72 hours after lung transplantation is similar to acute respiratory distress syndrome (ARDS) clinically and histologically, and lung-protective ventilation strategies are known to be beneficial to ARDS patients. Therefore, most physicians apply a lung-protective ventilation strategy to lung recipients. In a recent multinational survey-based study, most respondents in 18 countries reported using lung-protective ventilation strategies in lung recipients. Low tidal volumes were frequently chosen based on recipient characteristics. On the other hand, the characteristics of donors are not often considered [35].

The PEEP level is selected according to the presence or absence of bronchial fistula [36]. In the presence of bronchial fistula, ZEEP (zero end expiratory pressure) is used, and in recipients without bronchial fistula, different levels of PEEP are applied. PEEP should be set to maximize alveolar recruitment while avoiding over-distention. If the patient is hemodynamically stable and oxygenation is improved adequately (SpO₂ >90%, while receiving a FiO₂ <0.5 and PEEP <5 cmH₂O), mechanical ventilator weaning should be attempted as soon as possible. A 1-hour t-tube challenge test is a convenient and economical way to assess the possibility of weaning success and to predict potential complications associated with spontaneous breathing trials.

Sedation and pain control

In the latest guidelines for sedation in the ICU, benzodiazepine is no longer recommended as a sole sedative, but it is not known which sedative other than benzodiazepine is the best [37]. Similarly, there is no evidence on which combination of sedatives and analgesics has the best prognosis in patients undergoing lung transplantation. According to a recent multicenter survey, more than half of respondents answered that propofol in combination with opiates were preferred over other combinations, such as opiates with intermittent benzodiazepine. However, approximately 40% reported that there is no official drug policy on sedation and analgesia for the transplanted patient [38]. Recently, the use of dexmedetomidine, a selective alpha agonist, has been increasing in ICUs. In many

previous studies, it was found that dexmedetomidine can reduce the incidence of postoperative delirium for adult cardiac and non-cardiac surgical patients [39]. In our center, the use of dexmedetomidine during spontaneous breathing trials is increasing in lung-transplanted patients. Dexmedetomidine produces less respiratory depression than other sedatives and has antianxiety effects and small analgesic effects in addition to its sedative properties, so it can be used safely even after extubation.

Postoperative dysrhythmia

Cardiovascular adverse events, including myocardial infarction and dysrhythmia, are frequent in the immediate postoperative period. Atrial fibrillation has been found in about 40% of recipients and generally responds well to conventional treatments, such as calcium channel blockers, beta blockers and amiodarone. The elderly patients, and the presence of idiopathic pulmonary fibrosis, known coronary disease, enlarged left atrium, and the use of postoperative vasopressors increase the risk of postoperative atrial fibrillation [40]. In our institution, transesophageal echocardiography is performed in patients with postoperative cardiovascular adverse events or preoperative cardiac comorbidities before ventilator weaning. Antithrombotic agents are not routinely used because of the risk of bleeding immediately after surgery, but they may be used with caution when dysregulated arrhythmia persists.

Fluid management

Fluid management may influence the degree of lung dysfunction. After lung transplantation, ischemia-reperfusion injury increases pulmonary vascular permeability and decreases lymphatic drainage, resulting in some degree of pulmonary edema [41]. To decrease the postoperative pulmonary vascular burden, we perform intravenous fluid therapy very restrictively and cautiously, to maintain adequate urine output (0.5 to 1 ml/kg/hr or more), oxygen saturation level ($SpO_2 > 95\%$ or more) and mean blood pressure (65 mmHg or more) [42]. Dynamic parameters, such as pulmonary capillary wedge or central venous pressure, have traditionally been used to assess adequate fluid balance in the immediate postoperative patients. Recently, various minimally invasive hemodynamic monitoring devices, including pulse pressure/stroke volume variation [43], esophageal doppler [44], and extravascular lung water measurement [45], were evaluated for optimizing perioperative fluid therapy for major surgery. One thing that is clear is that excessive fluid resuscitation or inotropic support resulting in a hyperdynamic right ventricle and the exacerbation

of lung reperfusion injury should be avoided [46].

Immunosuppressant use and monitoring

Immunosuppressants are important for the prevention of graft rejection. Immunosuppressants can be classified as “induction” and “maintenance.” The purpose of induction therapy is to reinforce early immunosuppression and to allow for a less toxic maintenance immunosuppressant going forward [47]. However, induction therapy is still controversial in patients undergoing lung transplantation, and registry data shows that induction therapy is used in approximately 60% of transplantation centers [16]. Polyclonal antithymocyte globulin, interleukin-2R antagonists or alemtuzumab can be used for induction therapy [16].

The use of maintenance immunosuppressants in lung transplantation generally involves a three-drug regimen and the exact composition can vary by transplantation center. The three-drug regimen includes a calcineurin inhibitor (CNI; tacrolimus or cyclosporine), a corticosteroid and a nucleotide blocking agent (mycophenolate mofetil or azathioprine). Recently, the use of a combination of tacrolimus, corticosteroid, and mycophenolate has been increasing [16].

In lung transplantation, higher maintenance immunosuppression is needed because lung tissues have an apparently higher immunogenicity. Therefore, therapeutic drug monitoring (TDM) is important for treatment individualization and TDM for CNI is always needed in lung transplantation. The target blood concentration for the CNI can be different depending on the center. Moreover, minimizing the variability of blood levels is also needed adding to the maintaining the high mean CNI level for reducing the risk of allograft rejection [48]. Variability in blood concentration can be related to non-adherence with drug guideline, interacting medications (such as some types of anti-fungal agents or rifampin), differences in the cytochrome P450 enzyme system, changes in the fat content of meals and changes in gastrointestinal motility [48,49].

Infection control: immunization

Candidates for lung transplantation should have their vaccines updated as early as possible before transplantation, because antibody responses to vaccines are decreased during organ failure, and are significantly reduced after transplantation by mycophenolate mofetil treatment and advanced age. The optimal timing to begin posttransplant vaccination is 6 months after transplantation but should be individualized for each patient. Lung transplantation candidates without hepatitis A or B antibodies are vaccinated prior to transplantation. Before

lung transplantation, a 13-valent protein-conjugated pneumococcal vaccine is used for priming, followed 8 weeks later by a 23-valent polysaccharide vaccine. Candidates that have not received the tetanus, diphtheria, pertussis (Tdap) vaccine or are unaware of their Tdap vaccine status are administered the Tdap vaccine and a tetanus-diphtheria booster every 10 years. All lung transplantation candidates and recipients are advised to receive annual influenza vaccinations.

Infection control: prophylactic strategies for postoperative infections

For the prevention of postoperative infections, antibacterial, antifungal, and antiviral prophylaxis is administered. Intraoperative antibiotic prophylaxis includes cefepime for Gram-negative coverage, and vancomycin or teicoplanin for Gram-positive coverage. The cefepime and vancomycin or teicoplanin are typically discontinued or de-escalated after 5 days, once all intraoperative cultures are finalized as negative.

Regardless of the cytomegalovirus (CMV) serostatus of recipients and donors, intravenous ganciclovir is given for antiviral prophylaxis at a dosage of 5 mg/kg every 24 hours after lung transplantation. If the recipient can tolerate oral intake, he or she is transitioned to valganciclovir at a dose of 900 mg orally daily. The total duration of antiviral prophylaxis is 6 months, but in patients who are CMV IgG negative with a CMV immunoglobulin G-positive donor, CMV prophylaxis is considered for lifetime as tolerated. Ganciclovir and valganciclovir dosing is adjusted based on renal function.

Fungal infections, especially by *Aspergillus* species, are very common. One frequent site of infection is the bronchial anastomosis. For this reason, most centers recommend some form of fungal prophylaxis at least during the first 3 months after the transplant [50]. Antifungal prophylaxis varies from center to center. Azole antifungals or inhaled formulations of amphotericin B are used, depending on the situation. We use itraconazole for antifungal prophylaxis during the 6 months after transplant.

In solid organ transplant recipients, *Pneumocystis jirovecii* infection is associated with a high mortality rate, despite an adapted treatment [51,52]. Therefore, *P. jirovecii* prophylaxis is commonly instituted after all solid organ transplants. There are different guidelines addressing *P. jirovecii* prophylaxis after solid organ transplants and there is no universal consensus on the optimal duration of prophylaxis. The American Society of Transplantation recommends a general prophylaxis for 6–12 months after solid organ transplants. Lifelong prophylaxis is recommended for patients after lung or small-bowel

transplantation, chronic CMV infection, and in all patients with a history of prior *P. jirovecii* infection [53]. In our center, lifelong trimethoprim/sulfamethoxazole (80/400 mg or 160/800 mg) is administered to prevent *P. jirovecii* infection after lung transplantation.

Venous thromboembolism prevention

Lung transplant recipients are at increased risk for postoperative venous thromboembolism (VTE: deep vein thrombosis and pulmonary embolism) [54,55]. Most patients are treated with low-dose subcutaneous unfractionated heparin and intermittent pneumatic compression [56], but patients with a history of previous VTE may require more intensive therapy [57]. In general, VTE prevention continues until hospital discharge.

Surveillance bronchoscopy

The role of surveillance bronchoscopy for regular biopsy in asymptomatic patients receiving lung transplants is still controversial and the strategy depends on the center. Schedules of surveillance bronchoscopy are different; however, monthly biopsies are performed in the immediate postoperation period and the interval is increased after 3 months in many centers. There are some reports that the incidence of asymptomatic ACR is up to 25% [58]; therefore, some centers maintain strategies for surveillance bronchoscopy.

CONCLUSIONS

The immediate postoperative period is critical for the management of patients undergoing lung transplantation. PGD, acute rejection, and postoperative infection should be carefully monitored. In addition, it is important to understand that postoperative hemorrhage, large airway complications, and vascular anastomotic complications may occur due to the complexity of the lung transplant procedure itself. Therefore, intraoperative hemodynamic monitoring should be continued in the ICU after surgery. Moreover, based on hemodynamic parameters, meticulous fluid management and mechanical ventilation should be performed. The application and maintenance of immunosuppressants in patients with lung transplantation vary from center to center, but the combination of tacrolimus, corticosteroids, and mycophenolate has increased recently. Controlling the plasma levels of immunosuppressants is very important for reducing allograft rejection. Patients undergoing lung transplantation who are at high risk for infection should be preoperatively vaccinated and given prophylactic antibiotics after surgery. The risk of

PTE is higher than in patients after other major surgery, and VTE prevention should be continued during hospitalization. The postoperative critical care management after lung transplantation is very complicated; therefore, a careful approach is important. For these reasons, a multidisciplinary approach is needed, and proper critical care management after lung transplantation is essential to improve outcomes.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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