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Chapter

Perioperative Care for Lung Transplant Recipients: A Multidisciplinary Approach

Stacey H. Brann, Steven S. Geier, Olga Timofeeva,
Norihisa Shigemura, Francis Cordova and Yoshiya Toyoda

Abstract

Lung transplantation has evolved as the gold standard for selective patients with end-stage lung disease since the first clinical lung transplant was performed in 1983 in the United States. Over the last few decades, lung transplantation volume has increased worldwide with steadily improving outcomes; however, access to lung transplantation remains limited due to the critical shortage of donor organs. Factors that have contributed to improved outcomes include a multidisciplinary management approach supported by advancements in surgical and anesthetic techniques, nursing and critical care, immunosuppressive therapy, transplant immunobiology, and the perioperative use of extracorporeal membrane oxygenation (ECMO) and ex vivo lung perfusion (EVLP). Excellent outcomes have been achieved in selective patients with high-risk comorbidities such as age over 65 years, concomitant severe coronary artery disease (CAD), and preexisting sensitization with donor-specific antibodies (DSAs). Such comorbidities are no longer considered absolute contraindications to lung transplantation. This chapter provides an overview of perioperative care of lung transplant recipients with focus on a multidisciplinary approach and highlights management strategies for patients with concomitant severe coronary artery disease and end-stage lung disease as well as those with preexisting sensitization with DSAs.

Keywords: perioperative care, lung transplantation, multidisciplinary management

1. Introduction

Lung transplantation has evolved as the gold standard for select patients with end-stage lung disease since the first clinical lung transplant was performed in 1983 in the United States. Over the last few decades, worldwide lung transplantation volume has steadily increased to approximately 4000 cases annually with progressive improvements in long-term survival. Perioperative management of lung transplant recipients is a highly complex endeavor. Crucial components include mechanical ventilation and weaning strategies, fluid management, and immunosuppression including induction therapy, management of rejection, perioperative antibiotics, antimicrobial prophylaxis, chest tube management, nutritional support, discharge planning, and education.

Optimal early outcomes are dependent on a well-coordinated, multidisciplinary approach. Factors that have contributed to improved outcomes include advancements in perioperative critical care, surgical and anesthetic techniques, improved

immunosuppression and understanding of transplant immunobiology, stringent post-transplant surveillance for infection, rejection, and the perioperative use of extracorporeal membrane oxygenation (ECMO) [1] used to bridge decompensating patients to lung transplantation and ex vivo lung perfusion (EVLP) to facilitate optimization and transplantation of marginal donor lungs with outcomes considered equivalent to those from lungs transplanted using standard criteria [2, 3]. Given the aging population, older patients with a higher comorbid burden are being referred for lung transplant evaluation. In the United States, national registry data reveal a progressively increasing number of lung transplant recipients over age 70 years [4]. Advanced CAD is one such comorbidity that is no longer considered an absolute contraindication to lung transplantation. Excellent early outcomes have been reported with concomitant coronary artery bypass grafting (CABG) and lung transplantation [5]. However, the optimal treatment strategy for patients with concomitant advanced CAD and end-stage lung disease remains controversial, requires complex decision-making, and is evolving [6].

Highly sensitized transplant candidates, i.e., those with a high titer of preexisting HLA donor-specific antibodies (DSA), present unique challenges requiring specialized perioperative management. Antibody-mediated rejection (AMR) remains a problem without a reliable treatment in the care of lung transplant patients. AMR is usually mediated by anti-HLA DSA, and both pretransplant and posttransplant DSAs in lung transplant recipients are associated with acute rejection, chronic allograft dysfunction, and decreased survival [7, 8]. Patients transplanted with pretransplant DSAs are at a higher risk of hyperacute/accelerated acute ABMR, chronic rejection, and allograft loss across all solid organs [9]. Although several desensitization protocols have been reported for lung transplant candidates, the guidelines for protocol selection as well as criteria for successful response to treatment remain unclear [10–12].

In this chapter, an overview of general perioperative management of the lung transplant recipient is presented, including specific management strategies for concomitant advanced CAD and end-stage lung disease and perioperative management of the highly sensitized patient are presented.

2. A management algorithm for concomitant severe CAD in end-stage lung disease

As mentioned above, the optimal treatment strategy for high-risk patients with advanced CAD and end-stage lung disease remains controversial, requires complex decision-making, and is evolving. The author [SHB] presents an algorithm for management of these high-risk patients (**Figure 1**). Severe CAD is defined as an angiographically significant lesion (>70% stenosis) in at least one of the main coronary artery branches and/or when clinical or physiologic criteria demonstrate significant coronary flow limitation. An experienced interventional cardiologist and two cardiac surgeons jointly review the CAD severity of these patients upon referral for lung transplantation evaluation. Individualized treatment options are then formulated using the presented algorithm. For example, patients who become clinically unstable are hospitalized and urgently evaluated and are either listed for concomitant lung transplantation and CABG or CABG versus PCI, if deemed feasible, followed by lung transplantation depending on relative disease severity. If PCI prior to lung transplantation is deemed necessary, coronary lesion complexity and coronary stent characteristics determine the duration of dual antiplatelet therapy (DAPT) required to prevent in-stent restenosis. In general, more complex lesions require a longer duration of DAPT. Recommended DAPT duration by stent type is as follows: (i) Bare metal stent (ideal for patients anticipated to have a short wait list time)- one (1) month; (ii) Synergy stent- three (3) months; and (iii) typical second generation
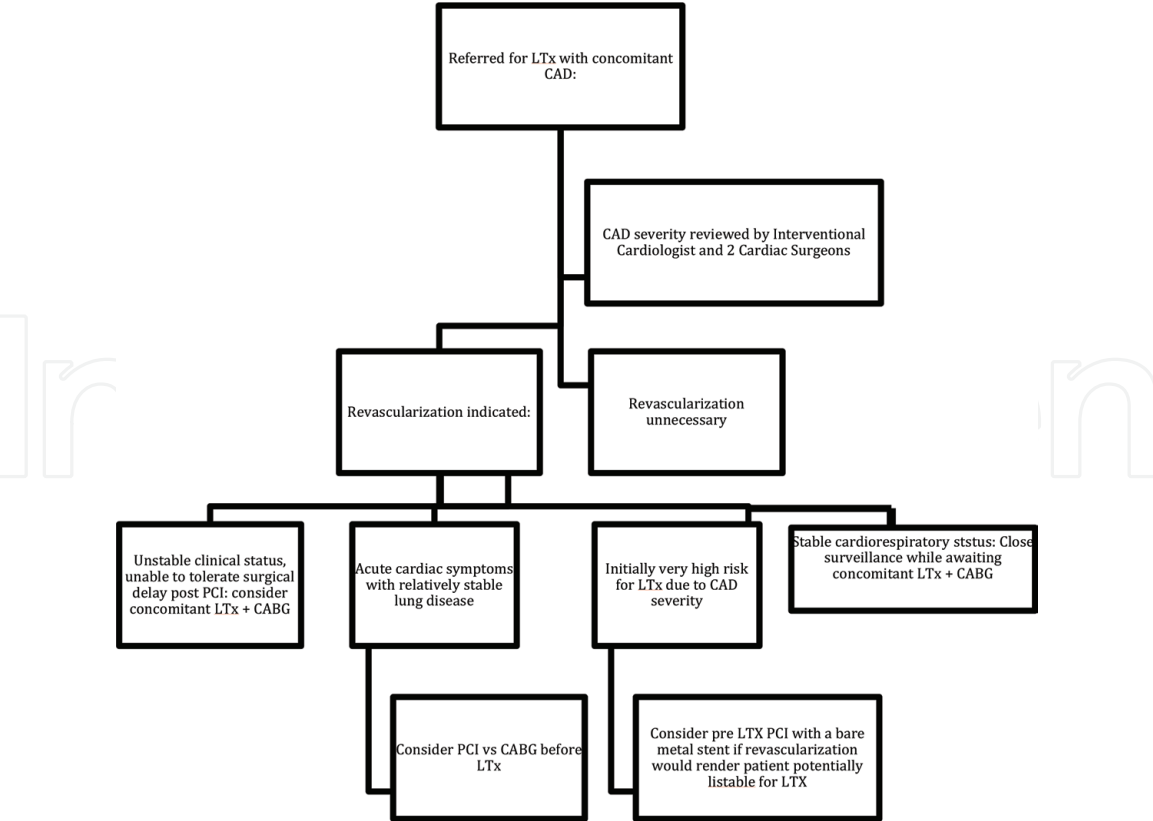
Figure 1.
Algorithm for management of patients with concomitant severe CAD and end-stage lung disease. LTX, lung transplant; PCI, percutaneous coronary intervention.

drug eluting stent- six (6) months. However, should lung transplantation become necessary before completion of DAPT, we proceed to lung transplantation albeit at a higher risk of perioperative bleeding. Close follow-up by the cardiologist and pulmonologist is maintained regardless of the treatment option.

3. Perioperative care of the lung transplant recipient

3.1 Intraoperative management

Preemptive management strategies that include meticulous and continuous cardiorespiratory monitoring, prompt initiation of vasoactive pharmacotherapy, volume administration, and institution of extracorporeal support are of critical importance during specific phases of intraoperative care. During these intraoperative phases of care (described below), there is a high risk of hemodynamic instability, lung derecruitment, worsening ventilation/perfusion mismatch, and alveolar hypoventilation leading to hypoxemia and hypercarbia in varying degrees of severity. The goals of perioperative ventilator support in lung transplantation rely on providing adequate minute ventilation while preventing oxygen toxicity, barotrauma, and volutrauma.

Specific problems that may occur during various intraoperative phases, and the recommended management strategies, are highlighted below:

3.1.1 Induction of anesthesia

Specific problems: acute RV decompensation due to (i) volume overload, (ii) decreased right ventricular (RV) preload and low cardiac output especially in the hypovolemic patient caused by increased intrathoracic pressure on

commencement of positive pressure ventilation, (iii) Trendelenburg positioning, and (iv) medication-induced hypercarbia, hypoxia, and systemic hypotension leading to an acute exacerbation of preexisting pulmonary hypertension (PHTN) or severe new-onset PHTN.

Management strategies:

i. Invasive arterial blood pressure monitoring is required as hemodynamics can deteriorate rapidly in these patients.

ii. Temperature monitoring is mandatory as hypothermia exaggerates pulmonary vascular resistance (PVR) [13]. Core temperature can be measured with the pulmonary artery catheter.

iii. Following induction, orotracheal intubation options for selective lung ventilation include a double-lumen endotracheal tube or a single-lumen tube with a bronchial blocker, if a double-lumen tube cannot be passed successfully. The appropriate intubation strategy depends on laterality in cases of single-lung transplantation and surgical technique in particular whether the procedure will be performed using cardiopulmonary bypass (CPB) support. The intubation strategy should be discussed with the surgical team prior to induction.

iv. Initial ventilator parameters are adjusted according to the arterial blood gas (ABG) to maintain low arterial CO_2 tension and prevent hypoxemia. Suggested parameters include tidal volume 6–7 cc/kg body weight, a positive end-expiratory pressure (PEEP) of 5 cm H_2O, respiratory rate 14/min, inspired oxygen concentration (FiO_2) to maintain arterial oxygen saturation above 95%, and inspiration to expiration ratio (I:E) of 1:2 to prevent auto-PEEP especially in COPD patients.

v. Volume resuscitation is achieved with leukocyte-depleted packed red blood cells if the hemoglobin is <10 g/dL or colloid (albumin 5%) rather than crystalloid if the hemoglobin is >10 g/dL. Blood transfusion is minimized to due to the risk of allosensitization.

vi. Sedative agents should be administered with caution before induction as even minor respiratory depression may lead to increased PVR and acute RV decompensation.

vii. Pulmonary artery (PA) pressure monitoring via either a Swan-Ganz catheter or transesophageal echocardiography (TEE) is employed to guide anesthetic management, especially in high-risk patients.

viii. TEE monitoring is routinely performed (unless contraindicated) in all patients at the authors' institution to evaluate ventricular filling, ventricular function, and patent foramen ovale (PFO) status and to ensure correct Swan-Ganz catheter tip position in the main PA to prevent inadvertent catheter entrapment on clamping either branch PA. The probe is placed under the guidance of the attending anesthesiologist.

ix. Hemodynamic goals include avoidance of hypotension, bradycardia/tachycardia and exacerbation of PHTN. Heart rate and mean arterial pressure (MAP) goals are 60–100/min and 70–75 mmHg, respectively. An epinephrine infusion (2–4 μm/min) should be prepared and started in those patients with a preoperative history of, or evident, pulmonary hypertension or RV dysfunction. Baseline physiological assessment includes an ABG, a mixed

venous blood gas (SvO_2) from the PA port of the Swan-Ganz catheter, and measurement of a thermodilution cardiac output.

x. Inhaled pulmonary vasodilator therapy, e.g., inhaled nitric oxide (INO) at 20 ppm, is used for all lung transplants at the authors' institution and is started following intubation.

xi. The surgical team as well as the perfusionist should be present in the room during anesthetic induction and be prepared to rapidly institute resuscitative measures that include emergent extracorporeal life support, such as peripheral veno-venous ECMO, veno-arterial ECMO, or CPB.

3.1.2 Preincision

Management strategies:

i. If the decision is made to use CPB or ECMO, a 70 mg/kg IV bolus of aminocaproic acid followed by an IV infusion at 30 mg/kg/h is given to minimize fibrinolysis.

ii. The induction immunotherapy protocols are detailed in Section 3.4.1 and Appendices (**Table 1**).

iii. Perioperative antibiotics: protocol details are provided in Section 3.5 below.

iv. For patients with a recent (<7 days) history of Coumadin administration, an IV infusion of vitamin K 10 mg diluted in 100 mL of normal saline is administered over 15 min.

Protocol for all patients except CMV mismatch, HBV/HCV/HIV infection, or history of malignancy
A. Induction (intraoperative): begin induction when final decision is made by the surgeons to accept the lungs
1. Premedication (30 min prior to alemtuzumab)
i. Methylprednisolone (Solu-Medrol): 1 g IV
ii. Acetaminophen (Tylenol): 650 mg PO/feeding tube
iii. Diphenhydramine (Benadryl): 50 mg IV
iv. Famotidine (Pepcid): 20 mg IV
2. Alemtuzumab (Campath) 30 mg IV over 2 h
3. Methylprednisolone (Solu-Medrol): additional dose of 250 mg IV prior to reperfusion of each lung
B. Postoperative Immunosuppression (Campath):
POD#1
1. Prednisone 5 mg orally or feeding tube daily; 10 mg if on chronic prednisone therapy preoperatively
2. Standard tacrolimus and mycophenolate mofetil/MMF (Cellcept) schedule

Table 1.
Induction therapy: Alemtuzumab (Campath).

3.1.3 Preimplantation

Management strategies:

i. An early trial of one-lung ventilation is advisable to see if acceptable gas exchange (pO_2, pCO_2, pH) and cardiac function can be maintained.

ii. To minimize a combustion hazard while using electrocautery:

- The FiO_2 should be minimized as tolerated during lung and bronchial dissection.

- On isolation of the lung for explantation, the appropriate lumen of the double-lumen endotracheal tube is suctioned with a flexible suction catheter to entrain room air when the bronchus is divided.

iii. If a vasoconstrictor infusion is needed to maintain blood pressure, options include vasopressin 0.01–0.04 units/min (institutional preference), norepinephrine 2–30 mcg/min, and phenylephrine 50–300 mcg/min, titrated to effect.

iv. Inotropic support may be provided either with IV infusions of epinephrine 2–10 mcg/min or milrinone 0.1–0.5 mcg/kg/min (renally dosed as appropriate), titrated to achieve a normal cardiac output and index.

v. Immediately prior to reperfusion of each transplanted lung, the surgeon will request an additional bolus of methylprednisolone 250 mg IV.

vi. In preparation for reperfusion, the hemodynamic status should be optimized in anticipation of volume loss to the transplanted organ and peripheral vasodilation resulting from washout of vasoactive substances when the allograft is unclamped.

3.1.4 Postimplantation to lung allograft reperfusion/reexpansion

Specific problems: systemic vasodilatation and hypotension, reperfusion pulmonary edema (increased vascular permeability and loss of lymphatic drainage), and hyperacute rejection.

Management strategies:

i. On completion of the vascular anastomoses, a controlled reperfusion maneuver is performed by gradually releasing the pulmonary artery clamp to prevent the development of allograft reperfusion pulmonary edema.

ii. Initial re-expansion of the donor lung is achieved with a sustained Valsalva maneuver to 30 cm H_2O, and interruptions to ventilation should be minimized thereafter.

iii. The ventilation strategy immediately posttransplant is intended to minimize injury to the donor lung from either mechanical factors or oxygen free radicals: typical settings will be FiO_2 0.40, PEEP 10 cm H_2O, rate 20/min, and TV 6 mL/kg (donor weight).

iv. Peripheral pulse oximeters are frequently inaccurate around the time of reperfusion, and the SvO_2 may be used as an indirect measure of adequate oxygen exchange.

v. If oxygenation is inadequate, FiO_2 may be increased in a stepwise fashion up to 0.60 while communicating these changes with the surgeon.

vi. If graft performance is initially inadequate, consideration should be given to temporarily support gas exchange with ECMO rather than use a sustained high FiO_2.

vii. Five minutes after reperfusion, an ABG should be checked.

viii. After reperfusion, the TEE should be used to assess for LV and RV function, the presence of air in the left heart, and evidence of stenosis at the pulmonary vein anastomoses.

ix. A thermodilution cardiac output should be measured and recorded following reperfusion and after chest closure.

x. A cardiac index of 2.2–2.5 is ideal—higher rates of pulmonary blood flow may increase the risk of significant pulmonary edema. Specific hemodynamic optimization strategies are detailed in Section 3.1.3 above.

xi. Because of the adverse effects on donor lung function, the requirement for blood products should be agreed upon between the attending anesthesiologist and surgeon.

xii. The double-lumen ETT tube will need to be changed to a single-lumen ETT at the end of the case to facilitate flexible bronchoscopy for anastomosis surveillance and tracheobronchial toilet. The FiO_2 should be increased transiently to 1.0 before this procedure.

3.1.5 Chest closure

Specific problems: restrictive chest cavity dynamics caused by:

i. Direct lung allograft compression leading to acute allograft dysfunction manifested by decreased compliance, derecruitment, and ventilation-perfusion mismatch. Etiologies include excessive donor-recipient size mismatching, noncompliant "frozen" pleural cavity associated with pulmonary fibrosis, severe pleural thickening and/or calcification, asymmetric chest cavities, severe kyphoscoliosis, and diaphragmatic elevation.

ii. Direct cardiac compression resulting in a cardiac tamponade physiology.

Management strategies include:

• Immediately reopening the chest

• Ventilator adjustments to prevent barotrauma, i.e., transient reductions in TV and/or PEEP

• Volume administration to optimize preload

• Leaving the intercostal space open with closure of only the muscular, subcutaneous tissue and skin layers or lung volume reduction followed by attempted reclosure.

3.1.6 Disruption to positive pressure ventilation

This can occur during (i) ventilator disconnection prior to patient bed to bed transfer, (ii) switching to a single-lumen endotracheal tube to facilitate postprocedure bronchoscopy, (iii) airway dislodgement, and (iv) manual ventilation while

the patient is being transported. Gentle Valsalva maneuvers to 30 cm H_2O are performed immediately after any disruptions to positive pressure ventilation.

3.1.7 The use of pulmonary vasodilator therapy

The use of pulmonary vasodilator therapy with INO or epoprostenol (Flolan) is indicated for: (i) hypoxemia during single-lung ventilation, (ii) refractory hypoxemia in severe primary graft dysfunction (PGD), (iii) to prevent/mitigate exacerbations in PHTN and subsequent cardiorespiratory perturbations during induction and pulmonary artery clamping and thus potentially avoiding the institution of CPB [14].

3.2 Intensive care unit management

Initial postoperative care for all lung transplant recipients is provided on the intensive care unit. Interventions specific to the care of the lung transplant patient will include, but are not limited to, the following:

i. *Ventilator management*: The goal is to provide adequate minute ventilation while preventing oxygen toxicity, barotrauma, and volutrauma. As such, ventilatory parameters are individualized and adjusted to achieve these goals. The aim is early extubation as soon as is clinically feasible. Recommended ventilatory parameters are detailed in Section 3.1.4 above. In particular, the goal is the use the lowest FiO_2 to maintain arterial oxygen saturations greater than 91% and a tidal volume based on donor height (where possible) to prevent/minimize PGD [15, 16].

ii. *INO weaning protocol*: In single-lung transplants for pulmonary fibrosis, the author [SB] recommends weaning INO first (if used) within the first 6–12 h followed by oxygen and PEEP weaning, as tolerated. In single-lung transplants for COPD, the PEEP is weaned first (to prevent compression of the less compliant lung allograft by the hyperinflated native lung) followed by INO (within 6–12 h) and oxygen weaning, as tolerated. After double-lung transplants, the goal is to wean INO within 24 h. Following extubation, the patient will be instructed in the use of the incentive spirometer and the flutter valve. Early mobilization out of bed to chair is instituted.

iii. *Hemodynamic management and fluid administration protocol*: Due to the propensity of lung allografts to develop pulmonary edema (altered tissue hydrostatic forces, endothelial dysfunction, destruction of lymphatic drainage channels), the goals are to maintain adequate cardiac output; avoid high cardiac output states; wean inotropes rapidly when no longer clinically indicated; use colloid (albumin 5%) rather than crystalloid for volume replacement; medication infusions are concentrated to reduce volume loading; maintain hemoglobin at 10 g/dL with leukocyte-depleted packed red blood cells, CVP 10–12 mmHg, and MAP 65–75 mmHg; and adjust appropriately for urine output above 0.5 mL/kg body weight, SvO_2 > 65%, and lactate <2 mmol/L. Additional blood products are given per clinical need (FFP, cryoprecipitate, and platelets).

• A cardiac index of 2.2–2.5 is ideal—to minimize the risk of significant pulmonary edema. Specific hemodynamic optimization strategies are detailed in Section 3.1.3 above. Serial lactate levels and SvO_2 are measured every 6 h or as needed depending on clinical status.

- Once clinically stable and not on high-dose pressors, aggressive diuresis as dictated by the patient's clinical status and radiographic findings is initiated with Lasix 20–40 mg IV every 8 h or a Lasix infusion 0.5–4 mg/min, titrated to achieve a negative intake/output balance (500 mL to 1 L) over the initial 24 h.

iv. Postoperative pain and sedation management: Important goals include use of the lowest effective dose and timely weaning of opioids such as fentanyl infusion 0.5–1.5 mcg/kg/h or 50–100 mcg IV boluses every 1–2 h (use renal dosing where applicable), sedatives such as Precedex 0.2–1.4 mcg/kg/h, and anxiolytics such as Versed 0.02–0.1 mg/kg/h to prevent respiratory depression, hypotension, oversedation, and delayed extubation.

v. *Flexible bronchoscopy* is performed on all patients prior to extubation to facilitate tracheobronchial toilet and to evaluate the integrity of the airways.

vi. *Chest tube removal* is started in POD#1 once criteria are met (no air leak, total serosanguineous drainage <200 mL/24 h, and/or <20 mL/h for the three consecutive hours prior to planned removal). Our institutional protocol involves removal of the posterior-dependent chest tube first, conversion of the anterior and middle chest tubes to H_2O seal, and removal of the anterior and last the middle chest tube when the patient has been ambulant to minimize residual pleural effusion collections.

vii. *Nutritional support*: While oral intake of all medications and nutrition is preferred, the patient will undergo a swallowing assessment 24–48 h following extubation and a nutritional assessment within 48 h after admission to the ICU. Until oral intake is established, for patients deemed at high risk of aspiration, a postpyloric naso-enteric feeding tube is placed immediately on extubation. In low-risk patients, orogastric tube feeds are started shortly after arrival to the ICU absent contraindications that include known severe gastroesophageal reflux disease, gastric distension, esophageal dysmotility syndromes, and high pressor requirements. The dietitian will make individualized recommendations for the patient's nutritional needs and will follow the patient throughout the hospitalization and make recommendations to the team accordingly. Gastroenterology consultation will be initiated as warranted by the patient's condition.

viii. *DVT prophylaxis* will be initiated per hospital protocol (subcutaneous heparin 5000 units every 8 h). Weekly surveillance upper and lower extremity Doppler studies are performed.

ix. *Physical therapy consultation* will be completed within 48 h of transplantation; early mobility is the goal.

3.2.1 Primary graft dysfunction

PGD is an acute manifestation of ischemia-reperfusion injury associated with multiple risk factors (donor-derived and related to procurement/preservation and reperfusion) with a peak incidence within the first 72 h after lung transplantation [17, 18]. The severity of PGD is graded based on the presence or absence of diffuse opacities on chest radiograph and the ratio of arterial oxygen pressure to inspired oxygen concentration, i.e., the PaO_2/FiO_2 ratio. The severity ranges from

grade 0 (absent radiographic infiltrates, any PaO_2/FiO_2 ratio, extubated patient with/without supplemental oxygen) to grade 3 (radiographic infiltrates present bilaterally or, if single-lung transplant—absent in the native lung, PaO_2/FiO_2 ratio <200, mechanical ventilation with FiO_2 >50% for 48 h, requirement for extra-corporeal life support). Severe PGD negatively impacts short-term outcome after lung transplantation (30-day mortality up to 50%) and is also associated with the development of chronic allograft dysfunction, i.e., bronchiolitis obliterans syndrome [15, 19, 20]. Management of PGD is predominantly supportive, i.e., cardiorespiratory support including lung protective ventilation, inhaled pulmonary vasodilator therapy, fluid and transfusion restriction, diuretic therapy, and extracorporeal life support for refractory hypoxemia with/without hemodynamic instability [21, 22].

3.2.2 The role of extracorporeal support: ECMO versus CPB in lung transplantation

In the United States, the rate of CPB use during lung transplantation varies widely. CPB provides hemodynamic stability with the heart in a decompressed state, which affords technical advantages by reducing right heart distension and vascular wall tension/shear stress, especially in the presence of moderate pulmonary hypertension. This facilitates nontraumatic vascular clamping and the performance of tension-free anastomoses. However, several studies have reported worse early postoperative outcomes as compared to off-pump lung transplantation [23, 24]. ECMO as an alternative to CPB provides certain advantages: reduced heparin requirements, reduced systemic inflammatory response, and coagulopathy resulting in less bleeding and lower transfusion requirements. Additionally, ECMO can be continued into the early postoperative period to facilitate allograft recovery while optimizing cardiorespiratory support.

3.3 Immunologic assessment of the lung transplant recipient

To decrease the immunologic AMR risk posttransplant, high-titer pretransplant DSAs that result in positive complement-dependent cytotoxicity (CDC) crossmatch and cause hyperacute rejection should be effectively avoided or preemptively treated based on acceptable risk defined by the transplant center. However, antibody avoidance results in longer waiting times and death on waiting list. At TUH, about 13% of waitlisted patients have CPRA > 80% (11 out of 83 active patients), but only about 3.5% of transplanted patients have CPRA > 80% (12 out of 345 patients transplanted between 2016 and 2017), showing a disparity in transplantation rates for highly sensitized patients (**Figure 2**). In thoracic transplantation, the use of the virtual crossmatch without a prospective serologic crossmatch became the standard practice. In virtual crossmatch, compatibility between donor and recipient is predicted by comparing the recipient's HLA-specific antibodies with the HLA antigens of the prospective donor. The primary method for antibody identification is the solid-phase single-antigen bead (SAB) assay that provides information about antibody specificities and their relative strengths based on mean fluorescence intensity (MFI) readout. **Figure 3** shows examples of positive and negative virtual crossmatches performed using SAB results that allow evaluation of compatibility between the donor and the recipient. However, there are several limitations to accurate virtual crossmatching based on SAB assay alone, including (1) that SAB assay is prone to detection of the so-called naturally occurring antibodies against denatured/cryptic antigens and that (2) it is not clearly understood at what MFI threshold DSA should be considered as clinically relevant [25].
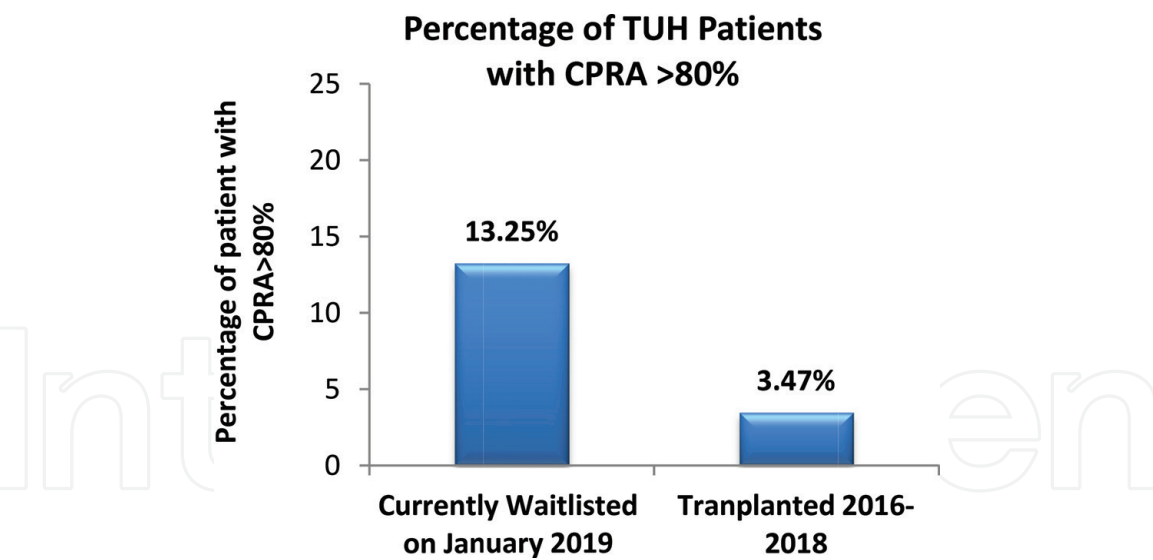
Figure 2.
Only 4% of transplanted patients (12/296) have CPRA > 80%, while 13% (11/83) patients on the waitlist have CPRA >80%.
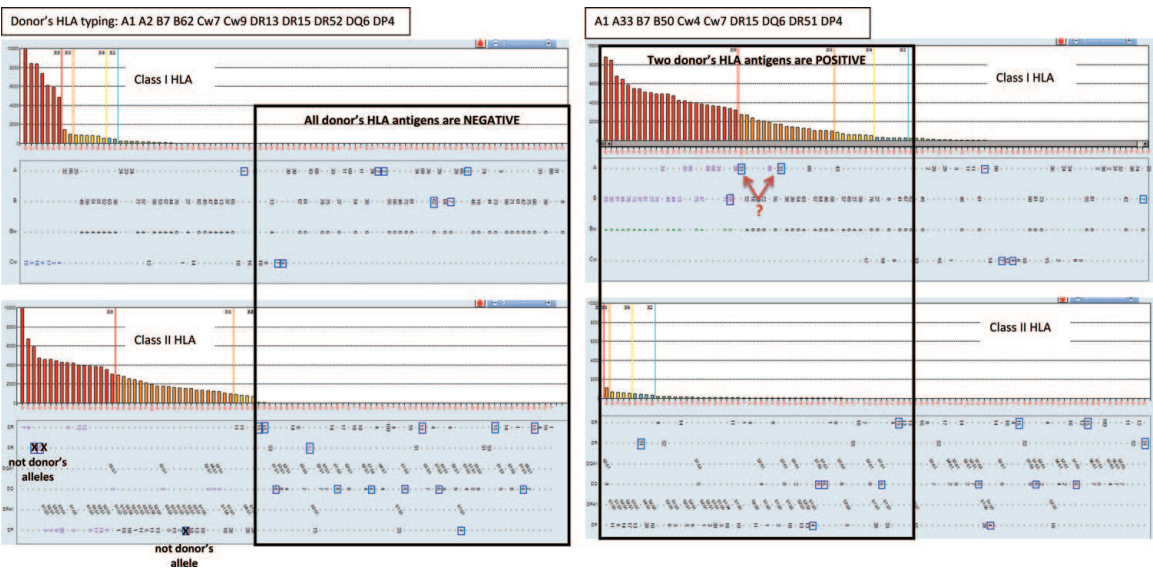

Figure 3.
Examples of negative (A) and positive (B) virtual crossmatches using results of single-antigen bead assay.

The precise role of naturally occurring antibodies is not well understood yet, but several studies suggest that such antibodies do not have clinical significance [26–29]. Usually antibodies against cryptic epitope do not result in positive flow cytometric or CDC crossmatches and do not impact clinical posttransplant outcomes. Several reports demonstrated that some antibodies detected in SAB assays may be directed against cryptic epitopes on recombinant HLA proteins created by missing peptides and/or b2-macroglobulin [30]. Other studies estimate that about 20–30% of waitlisted patients have antibodies against denatured antigens [28]. The naturally occurring antibodies can easily be recognized by negative reactions in cell-based crossmatch testing, but thoracic programs rarely have a luxury of performing a prospective crossmatch. Therefore, when/if not recognized as antibodies against denatured antigens, these specificities can deny an organ transplant based on virtual crossmatch. Starting in October 2016, our center began modifying our existing HLA testing protocols to better identify patients with and without pretransplant DSA by using multiple assay platforms, including FlowPRA Screen, phenotypic beads, and the well-established single-antigen beads. We studied 58 consecutive

VXM performed during July–December 2016 for lung candidates with CPRA>10%. Twenty-eight patients had no DSAs or had acceptably weak DSAs; they proceeded to transplant based VXM. All retrospective flow crossmatches were negative. The other 30 patients had positive VXM due to one or more moderate to strong DSAs, and the organ offers were refused. We found that 7 out of 30 (23.3%) VXM were called unacceptably positive due to the presence of antibody against denatured antigens [31]. Among these seven patients, three patients had antibodies against class I denatured antigens (2500–3500 MFI), and four patients had antibodies against class II denatured antigens (2000–14,000 MFI). We also found that by using LSPRA (Phenotypic Bead) and FlowPRA Screen assays along with SAB, we can preemptively recognize antibodies against denatured antigens not to deny organ offers unnecessarily. Instead of performing VXM using only SAB results, we now confirm that donor's antigens are positive by other assays as well (**Figure 3A**). Whenever antibody is detected only by SAB assay, it is considered to be directed against a cryptic epitope and, therefore, to be clinically irrelevant and not able to cause positive flow cytometry crossmatch (**Figure 4A**). DSAs detected by both SAB and phenotypic bead assays are considered as antibody against native HLA antigens (**Figure 4B**). The "true" DSAs undergo evaluation for strength as described below. Using this strategy we successfully transplanted five out of seven patients who were denied offers during July–December 2016 period. Since January 2017, all transplant candidates undergo antibody testing by SAB and LSPRA/FlowPRA Screen assays, so the presence of antibodies against cryptic epitopes can be easily recognized at the time of donor evaluation. This strategy results in reducing the number of unacceptable antigens and reduces percentage
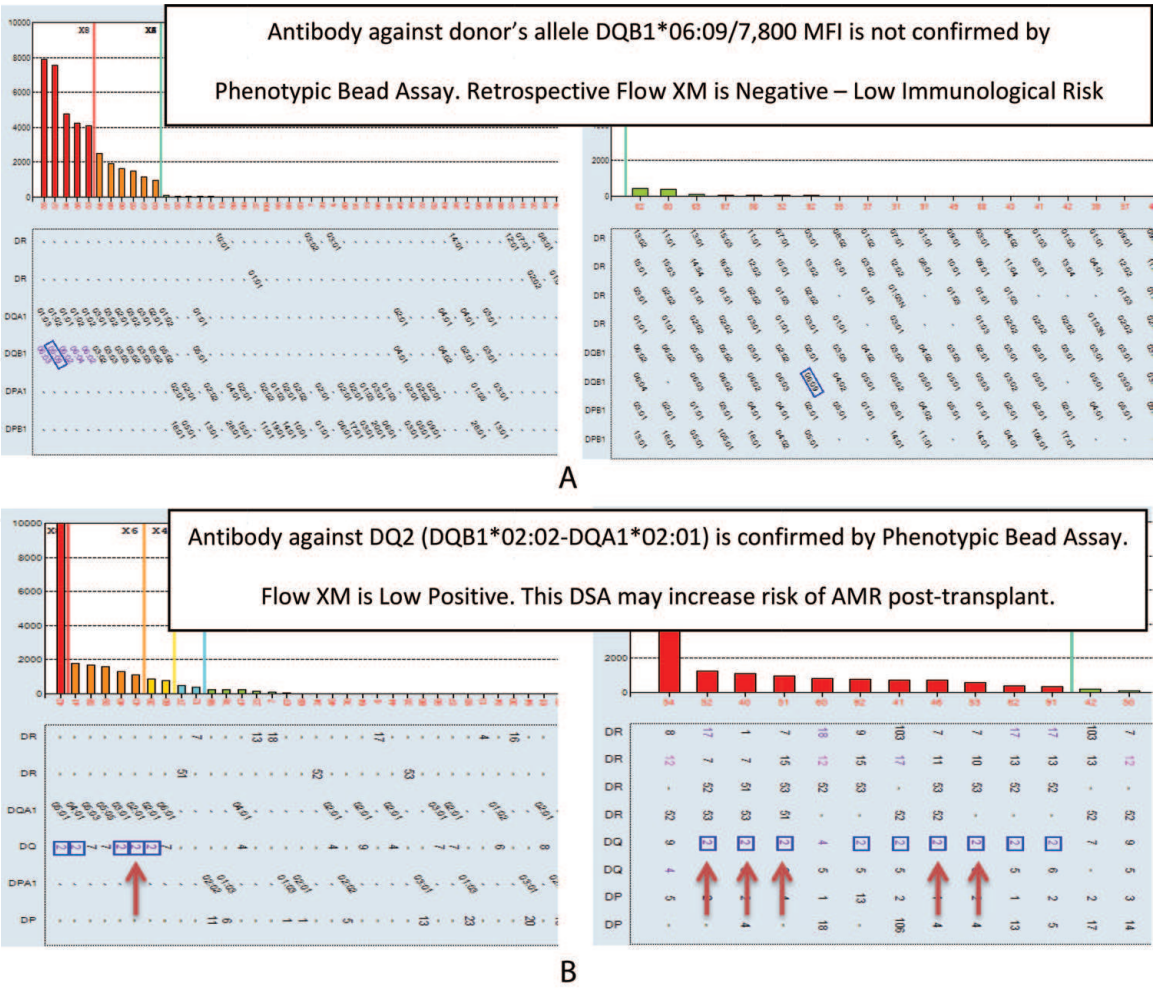

Figure 4.
Accuracy of virtual crossmatch can be improved by performing SAB alone with screening assays.

of CPRA (the percent of incompatible donors). Our data on relevance of antibodies against cryptic epitopes correlate well with several recent studies, including meta-analysis of 13 cohorts of lung recipients (total 3039 patients) showed that only DSAs that were detected by both SAB and screening assays were associated with CLAD (HR = 2.02, 95% CI = 1.37–2.97, P < 0.001). When DSAs were detected by SAB alone, the association with CLAD was no longer significant [32]. Overall, our experience is that use of SAB assay by itself may unnecessarily deny an organ offer due to the false-positive reactions and that use of screening assays improves the accuracy of virtual crossmatches and provides additional opportunities for sensitized patients.

Another important consideration is how to determine a threshold level below which DSA is clinically irrelevant or manageable perioperatively. Mean fluorescence intensity units somewhat indicate the quantity of antibody binding, when serum is pretreated with EDTA to inactivate complement and remove prozone-like inhibition in SAB assay. It is important to note that when untreated serum is used, the correlation between MFI and antibody quantity is very poor [33]. MFI values cannot be reliably measured above 20,000 MFI due to saturation effect, and intercenter studies suggest that the positive cutoff for DSA should be ~1500 MFI [33]. At TUH, antibodies <3000 are considered as weak and can be crossed without perioperative treatment, while antibodies >10,000 strong in general considered as strong and present unacceptably high risk. For patients with CPRA < 50%, UA are listed in UNET based on 3000 MFI cutoff. However, for patients with CPRA >50%, the immunologic management strategy differs depending on the urgency for transplant and the strength of antibody specificities.

Data from our center show that it is possible to reduce HLA antibody levels temporarily using various protocols, including high dose of IVIG plus Rituxan or five plasma exchanges with or without bortezomib (Velcade) followed by high dose of IVIG. However, if not transplanted during that "window of opportunity," the patient's antibodies invariably rebound and sometimes to the levels even higher than prior to initiation of desensitization. Even for patients with high LAS, who receive a priority during allocation, it is not easy to predict when a "compatible" donor may become available. Instead of implementing desensitization while patients are waiting for the offers, the Toronto Lung Transplant Program has developed a perioperative desensitization protocol-guiding organ allocation and maintenance immunotherapy [34]. At TUH, Toronto's protocol is implemented with some modifications. Highly sensitized patients with antibodies >3000 MFI are additionally tested at 1:16 serum dilution. Antibodies that become <3000 MFI at 1:16 are usually not listed as unacceptable antigens (UA) in UNET, while antibodies >3000 MFI at 1:16 are generally listed as UA. Our center experience is that antibodies <3000 MFI would result in borderline or low-positive flow cytometry crossmatch and can be managed postoperatively as needed. Therefore, if antibody decreases to <3000 at 1:16 dilution, it will result only at most in low-positive flow crossmatch after a single plasma exchange. This additional step allows us to avoid a prospective crossmatch for rapidly declining patients with high CPRA and to accept an offer based on VXM. The treatment usually continues posttransplant with additional 4–5 plasma-exchange sessions, followed by high dose of IVIG and Rituxan as needed. The perioperative desensitization is implemented at the time of transplant decision-making, which reduces unnecessary treatments and the risk of complications for patients who did not proceed to transplant.

3.4 Immunosuppressive therapy

3.4.1 Induction therapy

Induction therapy is determined at the time of listing and is modified for the patient as medically indicated. Induction therapy is administered in the operating room by the

anesthesiologist. Exceptions to the standard therapy are documented in the patient's medical record. Alemtuzumab (Campath) is the first-line induction therapy (**Table 1**). Basiliximab (Simulect) is given to patients with cytomegalovirus (CMV) mismatch, Hepatitis B virus (HBV)/HCV/HIV infection, and/or a history of malignancy (**Table 2**).

3.4.2 Postoperative immunosuppression

i. Postoperative immunosuppression is a combination therapy including a calcineurin-inhibitor therapy (CIT), steroids, and antimetabolite therapy. The postoperative immunosuppression administration and dosing guidelines are found in **Tables 1**–**3**.

ii. Tacrolimus is the first-line CIT and is initiated on the first postoperative day (POD) #1 via the sublingual route of administration. Initiation of tacrolimus may be held at the discretion of the lung transplant surgeon and/or transplant pulmonologist if the patient is not hemodynamically stable, aggressive diuresis is required, or there is evidence of renal complications. Oral medication will be administered when the patient has been cleared for oral intake. The intravenous route of administration is not preferred.

iii. Postoperative steroid therapy begins on POD #1 and the dosing is based on the specified induction therapy for the patient.

iv. Mycophenolate mofetil (Cellcept) is the first-line antimetabolite and begins on POD #1 if the platelet count is greater than 40,000 and rising and the lymphocyte count is greater than 10. The dose is reevaluated daily for titration to goal of 750 mg Q12 h.

v. For patients receiving basiliximab (Simulect) based induction, an additional dose of basiliximab (Simulect) is administered on POD #4.

Protocol for patients with CMV mismatch HBV/HCV/HIV infection, or history of malignancy		
A. Induction (intraoperative): begin induction when final decision is made by the surgeons to accept the lungs		
1. Basiliximab (Simulect) 20 mg IV and methylprednisolone (Solu-Medrol) 1 g IV at the start of the procedure		
2. Methylprednisolone (Solu-Medrol): additional dose of 250 mg IV prior to reperfusion of each lung		
B. Postoperative immunosuppression (Simulect)		
1. POD #1 Steroid taper		
Begin with methylprednisolone (Solu-Medrol) IV and switch to prednisone when tolerating PO		
POD	Prednisone (mg)	Methylprednisolone (mg)
1	50 daily	20 Q 12 h
2	40 daily	32 daily
3	30 daily	24 daily
4–14	20 daily	16 daily
15	15 daily	12 daily Taper dose to 0.1 mg/kg/day by 3 months
2. Standard tacrolimus (Prograf) and MMF (Cellcept) schedule		
POD #4 Basiliximab (Simulect) 20 mg IV		

Table 2.
Induction therapy: Basiliximab (Simulect).

POD#1
1. Tacrolimus (Prograf) 0.5 mg orally or sublingual Q 12 h (target 10–12): IV route is to be avoided. Begin when patient is hemodynamically stable and aggressive diuresis is not required. For split doses, the higher dose is scheduled for the evening
2. MMF (Cellcept) 250 mg orally or feeding tube Q 12 h: dose if lymphocyte count greater than or equal to 10 and/or platelet count greater than or equal to 40 K (oral dose = IV dose). Reevaluate daily for titration to goal of 750 mg Q 12 h
Prograf dose on the day of discharge from initial transplant admission is required to be greater than or equal to 6

Table 3.
Postoperative immunosuppression: all patients.

3.4.3 Maintenance and monitoring of immunosuppressant levels

Daily tacrolimus level measurements are taken. The target tacrolimus level is 10–15 ng/dl with a goal level of 12. In general, once the tacrolimus level is within this range, trough levels will be measured every Monday, Wednesday, and Friday or prior to the administration of the fourth dose. The target level is maintained throughout the first six (6) months posttransplantation.

Tacrolimus may be switched to cyclosporine if clinically warranted. Cyclosporine is maintained at a target level of 350–400 ng/ml. When the patient is able to take medications orally, the parenteral cyclosporine medication is changed to Neoral given every 12 h. The target level is maintained throughout the first 6 months posttransplantation. Cyclosporine trough levels are monitored in the same manner as described above for tacrolimus levels.

In the immediate postoperative period, daily monitoring of complete blood count, platelet count, liver function data, electrolytes, magnesium, calcium, phosphorus, and creatinine is performed. Frequency of blood draws is modified based on the patient's clinical condition. A baseline immune cell function level is obtained preoperatively, 1 week postoperatively, and prior to lung biopsies.

3.5 Perioperative antibiotic therapy

3.5.1 Intraoperative phase

Antibiotics are given in the operating room 1 h or less before incision and include vancomycin 1 g IV and cefepime 2 g IV (if allergic to penicillin, substitute ciprofloxacin 400 mg IV). Metronidazole (Flagyl) 500 mg IV is used only for patients with a history of prior *Clostridium difficile* infection.

3.5.2 Immediate postoperative phase

Postoperatively, the patient is given vancomycin 15 mg/kg IV every 12 h for 3 days (patients with a creatinine clearance of less than 50 will require renal dosing of vancomycin) and cefepime 2 g IV every 12 h for 3 days to begin 12 h after the dose given in the operating room. Ciprofloxacin 400 mg IV every 8 h for 3 days is substituted for patients with a penicillin allergy. Metronidazole (Flagyl) 500 mg IV is used only for patients with history of prior *Clostridium difficile* infection. Antibiotic therapy is adjusted by the team based on donor culture/gram stains and allergy history.

The Transplant Infectious Disease physician is consulted on all postoperative transplant patients.

3.6 Antimicrobial prophylaxis

3.6.1 Antifungal prophylaxis

Patients are ordered antifungal prophylaxis on admission to the ICU. Voriconazole (Vfend) is the first-line agent. Amphotericin B lipid complex (Abelcet) will be ordered for patients with intolerance to voriconazole (Vfend).

3.6.2 PCP prophylaxis

The patient is ordered Bactrim DS one (I) tab Monday, Wednesday, and Friday when the patient is discharged following transplant. Atovaquone (Mepron) 750 mg every 12 h is substituted or monthly inhaled pentamidine for patients with a sulfa allergy. PCP prophylaxis is given throughout the patient's posttransplant course.

3.6.3 CMV prophylaxis

Cytomegalovirus (CMV) prophylaxis is initiated on the POD# 1 based on the donor and recipient CMV status. CMV infection following the completion of the prophylaxis is treated at the induction dose for 3 weeks then decreased to the maintenance dose. Duration of therapy is determined in consultation with the Transplant Infectious Disease physician.

4. Conclusions

Lung transplantation has evolved as the gold standard for selective patients with end-stage lung disease but remains limited by a critical donor shortage. Perioperative management of lung transplant recipients is a highly complex endeavor. National registry data reveal progressively improving early as well as long-term survival. Optimal perioperative outcomes are dependent on preemptive, well-coordinated, and multidisciplinary management strategies. Certain high-risk patient subsets with end-stage lung disease such as highly sensitized patients, and those with concomitant severe CAD present unique challenges requiring specialized perioperative management.

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Conflict of interest

There are no conflicts of interest.

Author details

Stacey H. Brann*, Steven S. Geier, Olga Timofeeva, Norihisa Shigemura,
Francis Cordova and Yoshiya Toyoda
Temple University Hospital, Philadelphia, USA

*Address all correspondence to: stacey.brann@tuhs.temple.edu

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