



Care of the Postoperative Pulmonary Resection Patient

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John Kuckelman and Daniel G. Cuadrado

Indications for Admission to the ICU

Indication for Surgery

Lung cancer remains the predominate indication for pulmonary resection. Estimates from the American Cancer Society in the United States for 2017 report that 220,500 new cases of lung cancer will be diagnosed. Of these, only 10–15% present with disease that is potentially surgically curable. The same risk factors for the development of lung cancer place these patients at risk for other comorbid diseases such as coronary artery disease (CAD) and chronic obstructive pulmonary disease (COPD).

Anatomic pulmonary resection remains the gold standard treatment in medically operable patients with early-stage malignancies. Based on the NCCN guidelines, determination of resectability, surgical staging, and resection should be performed by a board-certified thoracic surgeon with patients undergoing a multidisciplinary evaluation.

Current recommendations guiding the preoperative evaluation of patients for pulmonary resection along with improved minimally invasive techniques will expand the number of patients that are offered pulmonary resection for non-small cell lung cancer (NSCLC) [1]. We can expect the number of patients who would have once been deemed physiologically inoperable to decrease. By increasing the number of early-stage diagnosis with low-dose CT scan (LDCT) lung cancer screening programs, we can expect an increasing population of higher-risk surgical candidates [2].

J. Kuckelman
Department of Surgery, Madigan Army Medical Center, Joint Base Lewis-McChord, Tacoma, WA, USA

D. G. Cuadrado (✉)
General and Thoracic Surgery, Department of Surgery, Madigan Army Medical Center, Tacoma, WA, USA
e-mail: daniel.g.cuadrado.mil@mail.mil

Admission Criteria: Planned Versus Unplanned

Routine postoperative admission to the ICU has been suggested for patients over the age of 70, ASA > II and preexisting fibrotic lung disease [3]. In general, ICU admission should be reserved for postoperative organ failure, high-risk patients, and complex surgical resections. Around 6.3–18% of patients undergoing pulmonary resection will require unplanned admission to intensive care postoperatively [4–7]. Table 20.1 lists the criteria for considering planned admission to intensive care.

Examination of the Society of Thoracic Surgeons (STS) database and other large series demonstrate that the perioperative mortality rate for all resections is around 2–4% [8, 9]. Independent predictors of mortality include pneumonectomy, bilobectomy, ASA, renal dysfunction, induction therapy, steroids, age, and urgent procedures [8]. Pneumonectomy in particular carries an inhospital and 90-day mortality rate of upward of 10% [8–10].

Patients undergoing diagnostic lung biopsy for interstitial lung disease represent a unique population deserving additional attention. A recent review of around 12,000 patients undergoing lung biopsy in the United States shows that these patients have a mortality of 1.7% for elective procedures [11]. This increases dramatically for nonelective procedures up to 16% [12].

Postoperative complications remain the main reason for admission to the ICU. Complications requiring reoperation are uncommon occurring in around 4% of cases. Bleeding represents the majority of these cases and is most often associated with technical issues or preoperative anticoagulants [13].

More than half of patients requiring salvage intensive care postoperatively require some degree of respiratory support. Those requiring mechanical ventilation, renal replacement therapy, or both have mortality rates upward of 70% [14].

Cardiopulmonary bypass is a well-established adjunct in allowing for extended thoracic resections [15, 16]. Extracorporeal membrane oxygenation (ECMO) as a means of salvage from cardiopulmonary failure may be an option in select institutions; however, long-term data in this population are lacking [17–19].

Table 20.1 Factors for consideration of planned postoperative admission to intensive care

Patient factors	Physiologic factors	Procedural factors
Pulmonary fibrosis	PPO FEV1/DLCO <30%	Pneumonectomy
Induction chemoradiotherapy	VO ₂ max <15 ml/kg/min	Carinal resection
Elevated ASA/poor performance status	Preoperative PaCO ₂ >50 mmHg	Extended resection with cardiopulmonary bypass
Urgent/emergent surgery		Lung transplant
BMI > 40		

Functional Status

The preoperative physiologic assessment of patients being considered for pulmonary resection is performed using a systematic approach. As noted in the clinical practice guidelines published in *Chest* in 2013, age alone is not a factor, and it is recommended that all patients with resectable disease be evaluated for surgery [1].

The forced expiratory volume in 1 second (FEV1) and diffusing capacity for carbon monoxide (DLCO) are obtained during standard pulmonary function tests (PFTs) and provide a good noninvasive initial assessment. The predicted postoperative (PPO) FEV1 and DLCO can be calculated taking into account the number of bronchopulmonary segments to be resected. In patients in which PPO FEV1 and PPO DLCO are >60% predicted, no further testing is required prior to resection [1].

Low-technology exercise tests, such as the stair climb (>12 m), can be utilized in cases where either PPO FEV1 or DLCO is >30 but <60% predicted. Formal exercise testing with cardiopulmonary exercise testing (CPET) and a calculation of maximal oxygen consumption (VO₂ max) is reserved for patients with PPO FEV1/DLCO <30% predicted. A VO₂max <10 ml/kg/min or 35% predicted is a contraindication to major resection as it is associated with a high rate of mortality [1].

Patients with a preexisting cardiac disease, symptoms consistent with angina, heart failure, or the inability to climb two flights of stairs should receive a formal cardiology evaluation. As recommended in the *Chest* guidelines, smoking cessation, cardiac evaluation, and preoperative pulmonary rehabilitation are ways to mitigate poor outcomes in high-risk candidates.

Procedural Considerations

Surgical complexity varies greatly, and the resection needed depends on tumor size, adjacent organ involvement, prior ipsilateral operations, and proximity to the hilar vessels. The surgical approach may range from thoracotomy (posterolateral, axillary, muscle sparing), sternotomy, video-assisted thoracoscopic surgery (VATS), and robotic video-assisted thoracoscopic surgery (RVATS).

A recent review of the National Cancer Database examined patients undergoing surgery for stage I–IIIA NSCLC. During the 2-year time period from 2010 to 2012, 62,000 lobectomies were performed. The vast majority were performed via thoracotomy (73%) followed by VATS (21%) and robotic (6%) [20]. Other than a 1-day reduction in hospital stay, VATS and robotic lobectomy are equivalent in terms of morbidity, mortality, and long-term oncologic outcomes [21].

For patients undergoing anatomic lobectomy, segmentectomy, or non-anatomic resection, the rate of morbidity and mortality is low [8]. When comparing VATS to open lobectomy, patient undergoing VATS have a mortality and pulmonary morbidity rate of 2.5–26.2% compared to 7.8–45.5% with thoracotomy [22]. In patients with predicted postoperative FEV1 or DLCO <40%, mortality and complication rates are reduced by more than half with VATS over an open approach [23].

Extensive resections such as pneumonectomy or extrapleural pneumonectomy have higher rates of morbidity and mortality [8–10]. Sleeve resections are performed as a parenchymal sparing approach in anatomically favorable tumors but require bronchial anastomosis. Although more technically complex, sleeve resection offers better early- and long-term survival in large part due to preservation of lung function [12].

Neoadjuvant Therapy

Patients with locally advanced, but resectable, disease can be considered for surgery following either chemotherapy or concurrent chemoradiation. In reviewing patients that have undergone neoadjuvant therapy followed by resection, there was no difference between those who had completed neoadjuvant therapy with respect to morbidity and mortality [24]. The presence of neoadjuvant therapy alone is not an indication for elective ICU admission.

Timing of surgery after induction chemoradiotherapy is a common consideration given the deconditioning that occurs with the initial treatment. The majority of patients are taken to surgery between 3 and 6 weeks after chemoradiation. There is a significant drop in survival in patients that have a greater than 6 week break between chemoradiation and surgery [25].

Patients who have tumors that would require pneumonectomy for an R0 resection after induction therapy and restaging have been completed are considered a high-risk group. Based on the Intergroup 0139 trial, the operative mortality rate in this population was 27% for pneumonectomy [26]. Subsequent series have shown survival rates much higher for right-sided pneumonectomy than left (20% vs 9%) [27].

Failure to Rescue

Unplanned admission to the intensive care unit following pulmonary resection is an independent predictor of mortality [4, 5]. As previously stated, the leading admission diagnosis is respiratory failure, followed by cardiac, renal, and neurological events.

Failure to rescue patients from the before mentioned complications following lung resection ranges from 0.7% to 3.2% [28]. Farjah et al. noted in their study that variation between high- and low-mortality centers was present despite similar complication rates. Similar reviews have further illustrated this difference emphasizing the importance of the critical care management of this patient population [29].

This same difference in mortality holds true not only for lung cancer but also for cancers of the bladder, esophagus, colon, pancreas and stomach [30]. The commonality in these studies is that higher volume centers are better equipped to detect, manage, and rescue patients from their postoperative complications. Although a further discussion debating associated patient outcomes related to surgical volume is beyond the scope of this discussion, an emphasis on the common issues facing pulmonary resection patients is worth further review.

Common Issues

Respiratory

Single lung ventilation is required for the majority of pulmonary resections. This establishes an abnormal physiologic state that leads to decreases in oxygen partial pressure, activation of inflammatory processes, hypoxic pulmonary vasoconstriction, changes in cardiac output and barotrauma on the ventilated lung [31]. Measurements of cerebral oxygenation demonstrate significant decreases in cerebral saturation during single lung ventilation [32, 33].

Patients undergoing procedures requiring lung isolation have postoperative complication rates of 20% with evidence of acute lung injury (ALI) in anywhere from 4% to 15% depending on the extent of resection [34]. In fact, the leading cause of postoperative death in these patients is from ALI and ARDS [35, 36].

Atelectasis, surgical manipulation, and trauma occur on the operative lung, while the ventilated lung is exposed to baro- and volutrauma. Any preexisting underlying lung disease further exacerbates the effects of this insult. For example, patients with pulmonary fibrosis typically have noncompliant lungs, whereas patients with severe emphysema may have significant air trapping [37].

Intraoperative management of the ventilated lung is based on protective ventilation strategies. Tidal volumes (Vt) of 6 cc/kg are considered protective; however, reductions to 4–5 cc/kg may be required to minimize barotrauma [38]. Positive end-expiratory pressure (PEEP) is also routinely utilized for further protection of the lung [39].

Ventilator Management

Postoperative patients requiring continued mechanical ventilation as well as those intubated for respiratory failure require standard protective ventilation strategies [40]. Postoperative ARDS is an uncommon complication following pulmonary resection with an incidence of around 3% [41]. The incidence is higher among patients undergoing pneumonectomy (7.9%) when compared to lobectomy or a lesser resection (2.9%). As has been previously mentioned, the mortality rate is high and increases as the extent of the resection increases. Post-pneumonectomy ARDS has a mortality rate of 50–80% [38, 41].

Preventative strategies, such as noninvasive ventilation (NIV) for prevention of pulmonary complications, have had mixed results providing no overwhelming evidence for decreasing complication rates or mortality [42–44]. The early administration of NIV has been successful in some series with an overall success rate of 85.3% [45]. Underlying cardiac disease and lack of initial response to NIV were predictive of failure in this cohort.

ECMO utilization in ARDS following pulmonary resection is currently limited to case reports and small case series [46, 47]. Cardiopulmonary bypass is an intraoperative adjunct for complex resections of the trachea, tumors invading the heart, large mediastinal tumors, and lung transplant [15, 16, 18].

Postoperative Pneumonia

Postoperative pneumonia (POP) occurs in 2–30% of patients. Chronic obstructive pulmonary disease, male gender, and extent of resection are independent risk factors [48]. Among COPD patients, 19% have positive bacterial cultures compared with 10.5% for patients without COPD [49]. As a result, these patients have a fivefold increase in incidence of postoperative pneumonia (POP).

The bacteriology for postoperative pneumonias is most commonly community-acquired *Haemophilus* and *Streptococcus* species [48]. Appropriate preoperative antibiotics, early mobilization, good analgesia, and aggressive pulmonary toilet are keys to prevention as are smoking cessation. Liberal use of toilet bronchoscopy for management of retained secretions is standard practice for thoracic surgeons and should be employed as needed [50]. Minitracheostomy has been demonstrated to have a reduction in postoperative pneumonia but carries a complication rate of 5.6–57% [51].

Chest Tube Management

Few issues are as fraught with superstition, myth, and dogma as the management of chest tubes. The standard practice of connecting chest tubes to -20 cm H_2O suction should be reserved for cases in which drainage or apposition of the pleural space are critical such as pleurodesis or decortication [52]. Following pulmonary resection, resolution of an air leak is reduced on water seal when compared to continuous suction [53]. Patients who develop subcutaneous emphysema or large pneumothoraces on water seal will require a return to suction. Patients who have persistent air leaks on water seal can safely be discharged home with a chest tube in place to a Heimlich valve [54].

Early chest tube removal is an important part of postoperative recovery, removing a significant source of pain and allowing for better mobilization. In the absence of an air leak, chest tubes can be removed even with serous drainage of less than 500 cc/day [55]. Re-intervention rates for pleural space complications with this approach is less than 3%.

Mechanical ventilation is not a contraindication to the removal of a chest tube. In a study of mechanically ventilated trauma patients, 3% of patients required re-intervention for post-pull pneumothoraces [56]. The overall patient status, volume of drainage, and presence or absence of an air leak are the important factors when considering chest tube removal in the ventilated patient.

Fluid Management

Perioperative fluid administration in excess of 3 l over the first 24 h has been shown to increase the incidence of ALI [57, 58]. A significant decrease in the incidence of ALI has been seen with differences of intraoperative fluids administration of 1.2 l versus 1.6 l [7].

Strategies to minimize fluid administration without compromising end-organ perfusion are important. However, the rates of intraoperative fluid administration should not be in excess of 6 ml/kg/h [59].

Epidural analgesia, a common pain management tool for post-thoracotomy pain, can further complicate this due to hypotension. One must weigh the risks of fluid resuscitation for hypotension with the risks of impaired pulmonary toilet and mobilization by turning down the epidural infusion. Paravertebral catheters can ameliorate the need to treat hypotension with equivalent analgesia [60]. The use of peripheral infusion of phenylephrine often helps to bridge the gap between management of hypotension and the restriction of fluid resuscitation.

Acute kidney injury (AKI) is associated with an increase in pulmonary complications, hospital length of stay, and mortality [5, 61]. The risk appears to be decreased with VATS when compared to open thoracotomy. Fluid restriction, comorbidities, and overaggressive forced diuresis all contribute to the development of AKI.

Cardiac

The relationship between thoracic surgery and tachyarrhythmias has been well established [62]. Atrial fibrillation is the most common arrhythmia following noncardiac thoracic surgery with an incidence of 12.3–19% [63, 64]. Risks factors associated with the occurrence of atrial fibrillation include male sex, pneumonectomy, age >70 years, history of congestive heart failure (CHF), history of atrial fibrillation, and transfusion.

In isolation, atrial fibrillation is a relatively low-risk complication and a treatable arrhythmia. However, it is often a marker for the onset of further complications [64]. It is associated with an increased length of hospitalization and overall costs. As with all patients with atrial fibrillation, those with an elevated risk for stroke require anticoagulation unless contraindicated.

The etiology of postoperative atrial fibrillation (POAF) is multifactorial. It is typically seen on the second to fourth postoperative day and is usually self-limited with the majority of cases resolving by 6 weeks. Origination of the initiating aberrant foci is typically from the pulmonary veins [65]. While clearly surgical manipulation of the pulmonary veins during resection can be causative, local and systemic activation of the inflammatory cascade also plays a role [66]. In fact, stimulation of both the sympathetic and parasympathetic nervous system can initiate POAF [67].

Management of POAF following pulmonary resection is similar for any patient with POAF with one notable exception. A study published in *Chest* in 1994 illustrated the risk of the development of ARDS following pneumonectomy with a cumulative dose of amiodarone over 2150 mg [68]. As with all patients with atrial fibrillation, management of hemodynamically unstable patients with DC cardioversion is appropriate.

Prevention of atrial fibrillation has been often studied but is also often underutilized [69]. Beta-blocker withdrawal is a well-recognized cause of POAF, and beta-blocker therapy should be continued up to the time of surgery and immediately afterward [67]. Magnesium replacement through intravenous infusion should be used judiciously to maintain normal serum levels [70]. Statin therapy in statin naïve patients has been demonstrated to reduce not only atrial fibrillation but also overall complications [69, 71].

Lung Transplant

Critical care management of lung transplant patients deserves specific attention. Since the first reported series of lung transplants done in the 1980s, there have been significant improvements in outcomes for these patients. These advances are largely due to an improved understanding of what is required before, during, and after their operation [72]. Pulmonary transplant represents a formidable challenge when considering the complexities surrounding the human lung. Surgical technique is unique as is the immunologic and infectious implications of utilizing a colonized organ for transplantation. This section aims to briefly familiarize the reader with perioperative issues specific to lung transplant with the hopes of providing guidance for effective execution of critical care during their stay in the ICU.

Preoperative Considerations

Recipient selection is typically accomplished regionally by multidisciplinary teams at high-volume centers. The International Society for Heart and Lung Transplantation (ISHLT) provides guidelines on patient selection. Patients who have severe pulmonary pathology, which is refractory to medical management, and are likely to perish in less than 2 years typically qualify for transplantation. Ideally, recipients have minimal or no other organ dysfunction, no comorbidities, and an acceptable psych profile with adequate social support [73]. Transplant is absolutely contraindicated in patients with uncontrollable infections or those who have been diagnosed with a malignancy within the preceding 2 years. Candidates with a BMI >35 or any substance dependency to include smoking, alcohol, or illicit drug use are also disqualified. Lung transplant is typically avoided in patients older than 65 who have low physiologic reserve and patients colonized with particularly virulent or resistant pathogens as outcomes tend to be poor [73].

The most common indications for lung transplant include idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), cystic fibrosis (CF), and bronchiectasis. Preoperative critical

care may be active in some patients. Although ventilation dependence does portend poor outcomes, it does not preclude patients from transplantation. Further, venous-venous extracorporeal membrane oxygenation (ECMO) can be used as a bridge to transplant in some patients. One distinct advantage of using ECMO is that it allows patients to be off the ventilator and an active participant in preoperative preparations [74, 75].

The critical care team should also be familiar with appropriate preparation of lungs in potential donors. The perfect lung donor is young (age <55) and with physiologically normal lung tissue. However, liberalization of strict criteria has been accepted to increase the donor pool. Final decisions on prospective donor candidates are usually determined by the operating surgeon [75]. Potential donors from patients with brain death should be managed in such a way that their left ventricular ejection fraction remains above 45% and mean arterial pressure should be maintained at 60 mmHg with a central venous pressure and pulmonary capillary wedge pressure no higher than 8 and 12 mmHg, respectively. There is no level-one evidence to support a specific type of fluid over another; however, intuitively colloids may help minimize pulmonary edema. Acidosis should be corrected if pH is less than 7.2, and this may be accomplished with hyperventilation or the addition of bicarbonate solutions to resuscitative fluids. Most transplant surgeons prefer lung protective strategies for ventilation as this has been shown to increase donor eligibility [76]. Finally, donor lung function may be improved with the administration of methyl prednisone by way of decreasing pulmonary edema [77].

Pertinent Operative Aspects

Lung transplant may be accomplished by using single, bilateral or lobar transplantation with or without the use of cardiopulmonary bypass (CPB or v-v ECMO). Variations in the intraoperative technique used as well as the anesthesia care provided during the operation often have implications in the postoperative care. Every transplanted lung is accomplished with the creation of three separate anastomoses which include the bronchus, the pulmonary artery, and the pulmonary vein. The indication for transplant often dictates the length of the operation as it relates to the dissection needed for transplantation, type of transplant completed, and need for bypass. Each of these factors ultimately affects the clinical picture postoperatively.

Cardiopulmonary Bypass

Mechanical circulation is required in just under half of all patients undergoing lung transplant. Although CPB has been

traditionally used, ECMO is now the modality of choice as it accomplishes the same bypass need for a lung operation as does CPB but has decreased postoperative morbidity and mortality [78]. Bypass is absolutely necessary in pediatric population as well as adults whom are undergoing transplant for pulmonary vascular disease. Patients with pulmonary fibrosis, pulmonary hypertension, and those bridged to transplant on ventilation or ECMO are more likely to require bypass. Patients who become hemodynamically unstable or hypoxic during the operation will often be converted mechanical circulation [79]. Patients returning to the ICU after bypass, particularly CPB, are at increased risk of bleeding and thus blood transfusions, primary graft dysfunction, delayed extubation, and renal failure [78, 80, 81]. It is imperative that any information related to CPB is communicated during the transition of care to the ICU team.

Type of Transplant

Bilateral transplant is the most commonly performed pulmonary transplant for all indications (75%) as it provides the best long-term outcomes. It is required for patients receiving transplant for pulmonary hypertension, infectious disease, and bronchiectasis [82]. It is typically performed using a transverse thoracosternotomy (clam shell). Single-lung ventilation is utilized first in the native lung then transitioned to the recently placed allograft, while each lung is removed and replaced sequentially.

Single-lung transplantation has the benefit of providing a greater number of individuals with lungs but is less commonly used as long-term outcomes are worse when compared to bilateral lung transplant. This operation is obviously less extensive and may be ideal in older or more debilitated patients. The choice to use single-lung transplant is center specific. This method may be more commonly utilized in patients with COPD. However, bilateral transplant still represents the vast majority of transplants completed for this population [82]. Single-lung transplant is accomplished through a posterior lateral thoracotomy, and the native lung is singly ventilated throughout the procedure. Hyperinflation of the native lung is a known postoperative issue, and in some cases overexpansion of the native lung may progress to compression of the newly transplanted lung, inhibiting respiration.

Lobar transplantation and live donor transplantation is rare in North America. It is typically only utilized as last resort in the small subset of patients who have located appropriate donor with regard to HLA serotyping and are also not likely to survive long enough for a cadaveric donor to become available.

Primary Graft Dysfunction

Primary graft dysfunction (PGD) due to reperfusion injury leading to diffuse alveolar damage is one of the most feared early complications of pulmonary transplantation. Despite prevention and treatment of this issue being an area of focus in the transplant community, it remains the leading cause of early death and is present in up to 25% of patients after lung transplant [82–84].

After the lung is transplanted, the effects of ischemia-reperfusion injury may be appreciated. Ischemia-reperfusion is a phenomenon that creates a physiologic environment that ultimately heralds tissue destruction. During times of no perfusion there is an upregulation of pro-inflammatory mediators causing thrombogenesis, cellular apoptosis/necrosis, complement activation, vasoconstriction, and immune-mediated destruction. In concern to leukocytes specifically, donor macrophages are first activated during ischemia, which is followed by attacks from recipient neutrophils and finally CD4+ T lymphocytes. The severity of this process is dependent on relative ischemic time and the state of the donor lung at the time of harvest [85–87].

Risk Factors

A number of factors are thought to contribute to the development of PGD. Generally, any change that induces or increases inflammation of the donor lung at any point throughout the entire transplantation process increases the risk of PGD. Many of the principles previously discussed for preparation of the donor lungs are aimed at preventing PGD. Protective lung strategies should be utilized when possible to prevent barotrauma from mechanical ventilation [76]. Further, hemodynamic regulation to maintain perfusion prior to procurement is critical. The administration of glucocorticoids prior to harvest may be beneficial in decreasing tissue insult due to inflammation [77]. During procurement, minimizing cold ischemia time is crucial in reducing the effects of oxidative stress, accumulation of intracellular sodium and calcium, and the release of cytokines such as tumor necrosis factor- α as well as various other pro-inflammatory molecules [88].

Independent risk factors have been identified that are related to both donor and recipient characteristics. Donor lungs that come from older females of African-American ethnicity seem to be at higher risk for PGD as do those that have a smoking history [89]. Increased risk for developing PGD has been identified in recipients who have pulmonary hypertension or patients receiving their lungs who have higher pulmonary artery pressures due to fibrosis, although it



Fig. 20.1 International Society for Heart and Lung Transplant proposed primary graft dysfunction (PGD) severity grading scale. CXR chest X-ray, PaO₂ arterial oxygen, FiO₂ inspired oxygen

may be that these populations are more likely to need for CPB during their cases and thus are more likely to develop PGD as a sequelae of mechanical circulation. Innately, recipients with preformed autoantibodies are also at higher risk of developing PGD [89].

Diagnosis, Prevention, and Treatment

Primary graft dysfunction is ultimately a diagnosis of exclusion. It should be suspected in any patient with unexplained hypoxia and pulmonary infiltrates within the first 3 days following their transplant operation. Differential diagnoses to be ruled out include pulmonary edema, pneumonia, pulmonary embolism or thrombus, aspiration, and hyperacute rejection. Once the diagnosis has been made, a grading system shown in Fig. 20.1 has been proposed by the ISHLT and may help identify patients who will benefit from early aggressive management [90].

Prevention of PGD is geared to limiting the effects surrounding the pathophysiology. Minimizing the cold ischemia time is perhaps the most controllable variable and thus every effort should be made to prevent prolongation of the ischemic time. There is some data in animal models suggesting that slow reperfusion (over a 10-min period intraoperatively) decreases the effects of reperfusion injury. The addition of prostaglandins to preservative fluids may also be beneficial according to some animal models [91–93]. Although it has been suggested, the use of inhaled nitrous oxide (iNO) does not seem to have any preventative effects on the development of PGD.

Unfortunately, the treatment of PGD is mainly supportive. Strategies to improve oxygenation are similar to those used for acute respiratory distress syndrome (ARDS) using low tidal volumes and positive end-expiratory pressure (PEEP). Severe dysfunction (PGD Grade 3) may require treatment by decreasing the ventilation-perfusion mismatch with iNO. In addition to improved oxygenation, iNO decreases pulmonary artery pressures and has been shown to decrease the number of days mechanical ventilation is required. Methemoglobinemia is a common side effect of iNO. Prompt identification and treatment with methylene

blue is necessary to reverse this complication. Recent and growing data suggests that ECMO should be initiated early (within 24 h) in patients with severe PGD and may be a life-saving intervention in this subset of patients [92].

Airway Complications

The bronchial anastomosis is the operative element most susceptible to postoperative complications. As such, the surgical technique used for the creation of the bronchial anastomosis is an area that has been thoroughly evaluated for lung transplant. Currently, the preferred method involves an end-to-end anastomosis that no longer incorporates coverage with an omental flap or a bronchial artery anastomosis [94, 95]. This technique has led to the lowest reported airway complication rates in pulmonary transplant history, but airway complications still represent the most common postoperative complication with rates as high as 18%. Bronchial necrosis, due to a relative decrease in blood supply, is seen to some degree in nearly all post-op lung transplant patients. The effects of necrosis can range from sloughing of the mucosa to total anastomotic dehiscence [96].

Patients with necrosis limited to the mucosa are typically asymptomatic, while development of anastomotic dehiscence may present as a persistent air leak, dyspnea, or difficulty weaning from the vent. Necrosis and breakdown are often discovered after investigation with flexible bronchoscopy [96]. Asymptomatic necrosis confined to bronchial mucosa can be effectively managed conservatively with antibiotics and close observation. Patients who experience a small partial dehiscence may be managed with the temporary placement of an uncovered metallic stent with the hope the stent will induce granulation tissue [97]. Unfortunately stents have not been found to be consistently successful in the management of dehiscence and those who fail to improve with stent placement may benefit from primary repair with biologic glue products [98].

Bronchial necrosis may lead to local infection and abscess formation that can ultimately progress to fistulae development between the bronchus and surrounding spaces or vessels. Fistulae formation is uncommon but associated

with high morbidity [96]. Clinically, patients will appear to be worsening, potentially with new or increasing pneumothorax, hypotension, and fever. A CT scan of chest usually confirms the diagnosis. Fistulae communication with a vessel may present with hemoptysis and signs of sepsis. Fistulae development represents a difficult problem with no one right answer. Drainage of any fluid collections and the initiation of appropriate antibiotics are imperative. Small fistulas may be managed with bronchoscopic application of fibrin glues or stent placement. Large fistulas frequently require surgical correction with either a surgical flap or reconstruction [96].

Bronchial necrosis and infection predispose lung transplant patients to airway stenosis. Though this is not typically an acute issue, it is the most common long-term airway complication seen, and regular surveillance, endoscopic dilation, and occasionally stent placement are required to prevent vanishing bronchus or complete occlusion of the airway [99, 100].

Standard Critical Care Management

Typical day-to-day intensive care of the postoperative lung transplant patient does not vary greatly from the care provided for patients undergoing major pulmonary resection as previously discussed in this chapter. However, there are a few salient points worth mentioning with regard to ventilator support and the management of fluids that should be more specifically addressed.

Mechanical Ventilation

The vast majority of patients will remain intubated after their transplant and be observed for a period in the intensive care unit prior to extubation. The typical post-op lung transplant patient will be able to wean quickly from mechanical ventilation, and early extubation is preferred whenever possible. When prolonged ventilator support is required, lung protective strategies using lower tidal volumes and positive end-expiratory pressure (PEEP) should be employed [101]. However, there are some caveats in lung transplant populations. Those receiving transplant for pulmonary hypertension should remain intubated for the first 24 h at minimum to best address any hypoxia or hemodynamic instability [101]. Minimal amounts limited to only physiologic levels of PEEP should be utilized in patients undergoing single-lung transplant. This is particularly true when transplant is performed for predominantly obstructive disease pattern as the use of PEEP can cause overinflation of the remaining native lung [101]. Hypoxia despite appropriate ventilator support should be swiftly evaluated keeping in mind that PGD is the most common cause of hypoxia post-lung transplant.

Fluid Management

It is common for patients returning to the ICU after lung transplant to be hemodynamically labile. Most recipients will arrive with appropriate invasive monitoring devices including pulmonary arterial catheters and arterial lines. All patients will arrive with some degree of pulmonary edema concomitantly due to loss of lymphatic drainage and inflammation driven vessel permeability. Resuscitation should strike a fine balance directed at maintaining tissue perfusion and cardiac output while avoiding fluid overload. There is not conclusive evidence advocating for one type of resuscitative fluid over another, but most centers prefer albumin colloid as it provides the theoretical advantage of promoting fluid shifts out of the interstitium.

Unexplained hypotension should be considered to be postoperative bleeding until proven otherwise which should be promptly investigated then treated with the appropriate intervention and product resuscitation. Systemic inflammation causing transient but severe vasoplegia leading to profound hypotension is not uncommon after transplantation particularly if CPB has been utilized. Vasoplegia may be resistant to standard vasopressors, and the use of methylene blue should be considered for refractory hypotension [102, 103].

Patients with high pulmonary artery pressures may present a formidable challenge postoperatively, and vigilant and decisive management of any lability should be employed. Management of these patients typically begins in the operating room by the anesthesia team with the monitoring of right heart function using transesophageal echocardiography. Right ventricular afterload can be effectively reduced by the use of pulmonary dilators such as milrinone or inhaled agents such as NO and prostacyclin [72, 104, 105]. These agents will usually be continued upon arrival to the ICU but should be weaned within the first 24–48 h as tolerated.

Immunosuppression

Postoperative management of immunotherapy is best approached with the aid of experienced pulmonologist and immunotherapy specialist. A full review of the methods and agents used are beyond the scope of this discussion. Issues pertinent to the critical care setting include induction immunosuppression, recognition, and management of hyperacute and acute rejections as well as a brief review of the opportunistic infections transplant patients are susceptible to.

Induction Immunotherapy

The use of induction immunotherapy has increased since 2001 and, according to the 2013 ISHLT registry, is currently

Table 20.2 Commonly used induction immunotherapy used in major pulmonary transplant centers

Drug	Dosing ^a	Mechanism	Adverse effects	Notes
Basiliximab	20 mg on DOS	T-cell inhibition through CD25 inhibition and IL-2 inhibition	Well tolerated with few side effects	Used most commonly in transplant centers
	20 mg on POD4			
Anti-thymocyte globulin	1.5 mg/kg (rabbit ab) or 7.5–15 mg/kg (horse ab) over 6 h on DOS and then every 24 h × 3 days	Nonspecific T-cell inhibition via polyclonal antibodies	Thrombocytopenia, leukocytopenia. Effects of polyclonal ab: Serum sickness, nephritis. Cytokine release syndrome	Requires premedication with steroids, acetaminophen and diphenhydramine 1 h prior to infusion
Alemtuzumab	30 mg over 2 h intraoperatively	T and B cell inhibition via CD52	Prolonged lymphopenia	Not well studied
Daclizumab	1 mg/kg on DOS then every 2 weeks × 5 doses	T-cell inhibition through CD25 inhibition and IL-2 inhibition	Well tolerated with few side effects	Not available in the USA
Muromonab-CD3 (OKT3)	2.5–5 mg/day × 7–14 days	T-cell depletion via CD3	Cytokine release storm	Not available in the USA

Note: References [106] and [107]

^aThere is no consensus on dosing. The dosing shown here are recommendations based on commonly used doses at transplant centers. DOS day of surgery, POD post-op day, USA United States

being used in over half of lung transplant patients [82]. Induction immunosuppression is the early use of potent agents to curb the effects of early T-cell mediated destruction. Arguably, this begins intraoperatively with the stress dosing of steroids administered just prior to perfusion of the new lung. Induction therapies are generally tailored on a patient-by-patient basis. The mechanism of action for these agents is by either inhibition of the effects of IL-2 or directly inhibition of T lymphocytes. A list of potential agents and associated side effects are listed in Table 20.2. There is no consensus on whether induction therapy should be routinely used and no conclusive studies supporting one agent over another. Some evidence does suggest a slight increase in survival in the first 2 weeks following transplant based on reports from the ISHLT looking at all transplants done in 2014 [82]. The same registry provides evidence that rejection within the first year may be lower in patients who received induction therapy when compared to no induction therapy (26% vs 34%, respectively) [82]. However, these positive outcomes do not account for confounders such as increased risk of infection or the resulting airway stenosis from early infection. Larger prospective randomized trials will need to be done before any solid recommendations can be made.

Rejection

Hyperacute or humoral rejection from preformed antibodies is exceedingly rare in the age of highly sensitive preoperative HLA antibody testing. Although case reportable, when it does occur, it presents within minutes to hours after transplant and can be devastating. Clinical indicators include pro-

found hypoxia accompanied by pink frothy sputum, hypotension, and diffuse coagulopathy. If identified, early plasmapheresis and aggressive immunotherapy with allograft removal should be completed. Even with prompt and accurate treatment, prognosis is extremely poor [72].

Acute rejection typically occurs in the first 6 months following transplant, but there have been reports of presentation as early as a few weeks. When present during the acute postoperative period, it can prolong ICU stay, and aggressive immunotherapy may predispose patients to opportunistic infections and renal insufficiency. Immunotherapy may need to be curtailed to treat worsening infections or renal failure. It is evident that this back and forth can create the potential for a vicious cycle which may ultimately result in significant morbidity [72].

Infection

Lung transplant represents a unique cohort of transplant patients in that the transplanted organ is naturally colonized. This simple fact predisposes the transplanted environment to constant inoculation by bronchial organisms. Utilization of a multidisciplinary approach, involving transplant infectious disease specialist, is recommended. Prophylactic antibiotics that cover for common gram-positive and gram-negative nosocomial infections are given prior to incision and typically continued for at least 72 h postoperatively. Cultures should be obtained preoperatively from both the donor and recipient, and both prophylactic and treatment antibiotics should be tailored based on drug resistance data and local antibiograms. Prophylaxis with trimethoprim-sulfamethoxazole

has the added benefit of covering multiple opportunistic pathogens such as *Pneumocystis jirovecii* in addition to strep species. A higher instance of multidrug-resistant flora may be seen in patients with cystic fibrosis and bronchiectasis specifically pseudomonas and rapidly growing nontuberculous mycobacteria, and treatment should be based on preoperative cultures in these populations [72]. Clinically significant viral infections are rare in the acute postoperative period, but recipients should be provided prophylaxis to the common influenza virus as well as cytomegalovirus (CMV).

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