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Review

A Breath of Fresh Air - Lung Transplantation Has Come of Age

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Abstract

A boundless spectrum of chronic lung diseases is said to effect over 500 million persons globally. Lung transplantation is a well-established therapeutic option for patients suffering from end-stage lung diseases, however waitlist mortality and primary graft failure remain major determinants as post-transplantation 5-year survival is just above 50 percent. Recent innovations in lung transplantation have been aimed at increasing organ availability, improving allograft quality, function, and longevity. Ex-vivo Lung Perfusion (EVLP) is an exciting modality responsible for multiple paths of lung allograft reconditioning as well as significantly extending preservation times. Mechanical circulatory support (MCS), specifically extracorporeal membrane oxygenation (ECMO) has consistently gained popularity not only for its use as a bridge to transplantation, but also its intraoperative role. In tandem, EVLP and ECMO have shown promising results in increasing the number of lung transplantations

performed, therefore decreasing waitlist mortality. Primary graft dysfunction (PGD) and chronic lung allograft rejection (CLAD) continue to be the most feared predictors of poor outcomes. In this review we will highlight the historical progression of lung transplantation, its encumbrance, and the most recent advancements in promising techniques for long-term allograft protection and patient survival.

Keywords
Lung transplantation; primary graft dysfunction (PGD); chronic lung allograft dysfunction (CLAD); ex-vivo lung perfusion (EVLP); mechanical circulatory support (MCS); extracorporeal membrane oxygenation; extracorporeal photopheresis; bronchial artery revascularization

1. Introduction

Chronic respiratory disease remains one of the most common non-infectious diseases, affecting over 500 million people worldwide [1]. The causes of chronic respiratory disease vary, presenting with multiple different phenotypic patterns including obstructive lung disease, pulmonary vascular disease, infectious lung disease, as well as those classified as restrictive lung diseases. Some of the common diagnoses requiring lung transplantation include chronic obstructive pulmonary disease (COPD), cystic fibrosis, alpha-1-anti-trypsin deficiency (AATD), idiopathic pulmonary arterial hypertension (IPAH), Idiopathic pulmonary fibrosis (IPD), pulmonary sarcoidosis, and pneumoconiosis. However mutable its past, lung transplantation remains a viable option and the current "gold standard" for carefully selected patients with end stage lung disease.

In June of 1963, Dr. James Hardy and his colleagues at Mississippi embarked on the first human lung transplant. However, the patient survived only 18 days [2]. Following nearly fifteen years of experience, there seemed to be little to offer to those suffering from respiratory failure, in dire need of a solution. Of the nearly 40 transplants attempted by the year 1980, there were no long-term survivors. Most lung transplant recipients had expired during the third post-operative week due to dehiscence of the bronchial anastomosis [2]. Following the advent of membrane oxygenation, Dr. Joel Cooper made an additional attempt at lung transplantation with hopes that respiratory support may increase chances of long-term survival [2]. The patient again succumbed to disruption of the bronchial anastomosis by the third postoperative week. This shortcoming led the Toronto group to become the epicenter for transplantation research in animals, postulating that the likely major limiting factors of success stemmed from allograft rejection, ischemia, and immunosuppressive drugs. It would later be discovered that bronchial complications could be consequent to the immunosuppressive and anti-inflammatory effect of azathioprine and prednisone, respectively [3, 4]. At the time, new immunosuppressive medications like cyclosporine, as well as advancements in surgical techniques, such as initiating angiogenesis via wrapping the omentum around the bronchial anastomosis, proved to be a step in the direction of long-term allograft survival [4]. In June of 1983, Dr. Joel Cooper and the Toronto Lung Transplant group would perform the first successful lung transplant [5]. Again, defying odds in 1986 the Toronto Lung Transplant group led by Dr. Cooper and Dr. Patterson performed the first successful double-lung transplant [5].

At the turn of the 21st century, increasing technology and refined surgical techniques proved to breathe life into the field of lung transplantation. According to the International Society for Heart and Lung Transplantation (ISHLT) the number of lung transplants performed from Jan 2001-Dec 2009 reached over 21,800, nearly double that of the previous decade [6]. Although the total number of lung transplants has steadily increased, so has the cohort of patients requiring treatment [7]. Per a recent UN report the global population was projected to reach its highest, at 8 billion persons as of November 2022. Population demographics have shown a shift to an aging population, living longer with more comorbidities. It is estimated that by 2050 the proportion of persons over 60 will nearly double, a cohort known to show age-associated changes in intrinsic lung mechanisms as well as a host of other comorbidities [8]. In 2017 the lung transplant waiting list sat at roughly 2,500 patients, with nearly 30% expected to die before lungs became available [7]. Advancements have continued to try and combat the main roadblocks that hinder lung transplant success (i.e donor shortage, proper candidate selection, primary graft dysfunction (PGD), and Chronic lung allograft dysfunction (CLAD)). In this review we aim to present the most recent advancements made in the field of lung transplantation as well as offer insight through our own professional experience in a high-volume transplant center. For clarity, these advancements have been categorized by respective stage within the lung transplant process known as pre-operative, intra-operative, and finally post-operative management. It is our hope to provide a thought-provoking discussion of potential therapeutics for those involved in the care of these most vulnerable patients.

2. Methods and Results

In order to analyze and understand advancements and future directions in lung transplantation, the authors completed a non-systematic narrative review of the current literature. The primary source used was PUBMED, using the following strings search:

(I) "Lung Transplantation" AND "Ex vivo Lung Perfusion" OR "EVLP"
(II) "Lung Transplantation" AND "Mechanical Circulatory support (MCS)" OR "Extracorporeal Membrane Oxygenation (ECMO)"
(III) "Lung Transplantation" And "Primary Graft Dysfunction (PGD)" AND/OR "Chronic Allograft Rejection"
(IV) "Lung Transplantation" AND "Preservation"
(V) Manual selection of manuscripts by authors.

We also evaluate the technical aspect of lung transplantation including management and surgical techniques, as we investigate our own professional experiences compared with that of other high-volume centers. Finally, we offer a technical and descriptive point of view regarding the advancements made in the field of lung transplantation and allograft protection, not only at our own institution but also in the global scenario.

2.1 Pre-operative Barriers – Expanding the Donor Pool

According to a recent Organ Procurement Transplantation Network (OPTN)/Scientific Registry of Transplant Recipients (SRTR) statement, over 3000 candidates were added to the lung transplant waiting list in 2021 [9]. Considering the continuance of evidence-based research, we have witnessed a steady decline in pre-transplant mortality from as high as 21.6 deaths per 100 waitlist years in 2010 to 17.6 deaths per 100 patient-years in 2021 [9]. However, donor availability remains a

significant factor in waitlist mortality, while its reported that procurement of transplantable lungs occurs in only 15-20% of all available donors [10]. Preoperative barriers halting the success of lung transplantation range from donor shortage, proper candidate selection, and organ viability. Increasing availability and access to high-quality organs remains a primary focus in improving both short and long-term patient outcomes. Several recent advancements have led to steadily increasing number of lung transplants performed annually, including expansion of donor criteria to include marginal donors, donation after circulatory death (DCD), living-donor lobar lung transplantation (LDLLT), and ex-vivo lung perfusion (EVLP).

2.1.1 Lung Allocation Score

In 2005, the lung allocation score (LAS) was first introduced in the United States, its purpose simply to decrease waitlist mortality by directing organs to individuals with the predicted greatest potential transplantation survival benefit [11]. Lungs were allocated based on donor and recipient compatibility, geography, as well as calculated expected survival benefit [11, 12]. Prior to introduction of the LAS, lung allocation was primarily based on time accrued on the waitlist, often leading to healthier patients with a slower disease progression being listed earlier and accruing more time allowing them to surpass the sickest patients who inevitably add to waitlist mortality. The main focus of the the LAS is on reducing waitlist mortality, since waitlist survival carries twice the weight of posttransplant survival [13]. In 2015, the Thoracic Organ Transplantation Committee proposed revisions to the LAS model in hopes of refining organ allocation and improving outcomes. Some of these included increased creatinine and bilirubin, elevated left atrial pressure or central venous pressure (CVP), 6-minute walk distance, and the need for oxygen therapy needed at rest [11].

In general, lung transplantation remains a last resort for patients with end stage lung disease that have exhausted all other therapeutic options, the ISHLT states acceptable candidates are those with chronic end stage lung condition who have a high 2- year mortality risk without a transplant (>50%), as well as high-likelihood (>80%) of short-term and long-term survival permitted by allograft survival [14]. In a recent update from the International Society for Heart and Lung Transplantation (ISHLT), Leard and colleagues presented a comprehensive consensus document on the selection of potential candidates for lung transplantation [14]. The authors went on to outline an abundance of caution that must be taken while selecting potential candidates. It imperative that lung allocation adheres to the fundamental ethical principles of utility, justice, and respect for persons [14]. The LAS promised stratification of these vulnerable patients based on clinical severity and appropriate organ allocation, with those in the mid-priority groups (LAS = 50-79), achieving the greatest survival benefit from transplantation without compromising overall transplant outcomes [12, 15]. However, the paradigm shift of medical urgency has led to sicker patients are presenting later in disease course. As recently as 2020, it was reported that 76% of lung transplant candidates were on the waiting list fewer than 90 days [16]. In fact, with increasing experience and technological advancements, many high-volume centers including our own are considering transplantation in older patients and those patients with increased comorbidities including coronary artery disease (CAD), previous sternotomy, previous coronary artery bypass graft (CABG), and previous lung volume reduction surgery. Indications for lung transplant and referral have been extensively studied and reported elsewhere [14, 17].

It is imperative that whilst clinical in nature, the approach to candidate selection be both patient-centered and disease specific. As of March 9th, 2023, the United States adopted a new continuous distribution framework for organ allocation termed the Composite Allocation Score (CAS). The Organ Procurement and Transplantation Network (OPTN)/United Network for Organ Sharing (UNOS) Lung Transplantation Committee sought and developed a new system hoping to improve transplantation access, avoiding futile transplants, efficiently placing organs, and reduce the role played by geography in organ allocation [13, 18]. The new CAS outlines organ equity through tabulating one composite score based on five main goals: medical urgency, posttransplant outcomes, biological disadvantages, patient access, and efficiency each with matched attributed [13, 18-20]. Under this new method, continuous, point-based priorities during each match run allow multiple factors to be considered, assigning each candidate a lung composite allocation score, with the highest score receiving offer first [19]. Hopes are high that with the removal of hard geographical boundaries and the combining of multiple scores during the match run will improve adaptability and consistency across organs, while decreasing waitlist mortality and increasing post-transplant survival [13, 19].

2.1.2 Donation after Circulatory Death

Several strides have been made in recent decades to equate organ supply and its ever-increasing demand. One of the most significant methods used to close this gap has stemmed from non-heart beating donors. Donors are typically classified into either donation after brain death (DBD) or donation after circulatory death (DCD). Over the last 20 years, the Maastricht classification has evolved for the characterization of DCD scenarios in hopes of quantifying organ viability and long-term allograft survival [21]. In 2015, with the purpose of clarification, the European Society for Organ Transplantation (ESOT) working group, developed the modified Maastricht classification of DCD [21]. DCD donors are typically classified as either controlled (cDCD) (Maastricht category III and IV), or uncontrolled (uDCD) (Maastricht category I and II). Of note, countries such as the Netherlands, and Belgium where physician-assisted euthanasia is acceptable, a fifth category DCD-V has been proposed [22, 23].

Donation after circulatory death is made feasible when judicious efforts are made to preserve the organ *in situ*. Thomas Egan first reported on the unique properties of the lung, different from other solid organs in that it does not rely solely on vascular perfusion for cellular respiration but can be accomplished via simple diffusion [24]. In validation of this concept, prevention of alveolar collapse has been proved a critical factor in protection from warm ischemia damage, as well as inflation with room air being found equivalent to that of 100% FiO_2 [25]. With hopes of increasing the donor pool, several studies have reported the use of cDCD, with outcomes in PGD and mortality like those of traditional DBD organs [26]. However, largely due to ethical concerns, most of the experience with the use of uDCD has been limited to centers in Spain and Italy.

Operating under presumed consent, following a short “hands off” period, the Spanish DCD protocol allows for reinstitution of organ perfusion (VA-ECMO) and donor preservation methods (intrathoracic cooling) prior to judicial or familial consent [27]. Once consent is obtained, the donor can then be taken for procurement. Suberviola and colleagues reported a simpler lung-only protocol focusing solely on continuous chest compressions and mechanical ventilation prior to obtaining consent for donation [28]. Once consent is obtained the donor may be given heparin, as well as

insertion of bilateral chest tubes for the addition of Perfadex solution to achieve topical cooling [28]. A unique caveat to this protocol for cDCD is that it almost entirely occurs in the ICU. This significantly decreases donor warm ischemia times, associated with improved graft prognosis [28]. Interestingly, Valenza et al., reported *in situ* lung preservation with lung recruitment maneuvers, CPAP, and protective mechanical ventilation allowing up to 4 hours of total warm ischemia time [29]. In attempt to comply with ethical concerns in North America, Healey and the Toronto group recently reported good outcomes with simple in situ preservations methods allowed only after consent, including CPAP of 20 cm H_2O and prone positioning of the donor without reinstitution of circulation, subsequently followed by EVLP evaluation [30]. However, utilization rates remained low, likely due to irreversible warm ischemic damage during the initial hands-off period. In hopes of increasing utilization protocol modifications have allowed for lung inflation 15 minutes following death declaration [30].

Evidence continues to support the use of lungs from DCD donors as a valuable resource in expanding the donor pool. The DCD category has increased the number of available organs for transplantation, accounting for nearly 20% of all deceased organ donors [31]. Experience with the unique uDCD subgroup is slowly making its way to the US, calling for increased conversation on its ethical concerns, limitations, and cost to the healthcare system. It is possible that as advancements continue to be made these uDCD can alleviate a substantial burden, in turn decreasing waitlist mortality. Lung preservation methods including alveolar recruitment, extracorporeal circulation, preservation, and EVLP remain on the front line in overcoming the battle of supply and demand.

2.1.3 Living-Donor Lobar Lung Transplantation

The idea of lobar transplantation was developed as a hopeful alternative to whole-lung transplantation in children and small adult recipients due to lack of size matched cadaveric donors [32]. Starnes and his colleagues at the University of Southern California (USC) in 1993, first reported the use of living-donor lobar lung transplantation (LDLLT) in extremely ill patients with a high risk of short-term waitlist mortality [32]. In LDLLT, with the use of 3 transplant teams, right and left lower lobes are resected from 2 healthy donors and implanted in recipient in place of the whole right and left lung, respectively [33, 34]. Intermediate results proved promising in terms of functional outcome and survival [32]. In the first decade following its introduction, 123 patients underwent LDLLT at USC. Despite the critical condition of the majority of LDLLT recipients, survival rates of 70%, 54%, and 45% at 1-,3-, and 5-years respectively, was comparable to that reported of with double-lung cadaveric transplantation [35]. Likely due to ethical concerns involving associated risks to potential donors as well as changes in lung allocation, the use of LDLLT in the USA has steadily decreased. However, in Japan, experience with LDLLT provides a reasonable option in hopes of equating supply and demand, for DCD has yet to be approved and median waitlist times are greater than 24 months [36]. In fact, Kyoto University reported by the end of 2019 of the 760 lung transplantations performed, 234 were LDLLT (30.8%) [34]. The authors reported 5- and 10-year survival rates after LDLLT of 79% and 64.6% respectively, comparable to that of their cadaveric lung transplant 5- and 10-year survival rates of 65.7% and 60.3% respectively [34]. These results can likely be attributed to living-donor lobar grafts being healthier non-injured grafts with significantly shorter ischemic times compared to conventional cadaveric transplantation. As with DBD and DCD donation, CLAD remains a significant barrier to long term survival in LDLLT. Date and colleagues reported the

majority of their LDLLT recipients experienced unilateral CLAD however shown to develop later in postoperative period, proving the possible protective effect of using 2 donors for a single recipient [34, 36, 37]. In their most recent study, long-term survival after LDLLT was reported to be 73.3% at 15 years, with 5-year survival following diagnosis of CLAD still promising at 66.9% [36].

2.1.4 Bridging to Transplantation

Conventional therapies for those requiring respiratory support revolved around early initiation of mechanical ventilation (MV) with positive end-expiratory pressure with permissive hypercapnia, strict fluid regimens, and the use of pulmonary vasodilators. Historically, endotracheal intubation and mechanical ventilation were the sole strategy available to bridge critically ill patients experiencing respiratory compromise to transplantation. Although a significant number of these patients continue to have insufficient pulmonary gas exchange, requiring MV prior to transplant is now known to significantly lower 1-year survival rates [38]. Owing to its risk of severe complications (i.e, ventilation-induced lung injuries, infection, and need for sedation leading to profound deconditioning), bridging with mechanical ventilation has been associated with increased mortality both pre- and post-transplantation, necessitating the need for more invasive support strategies [39, 40]. Adoption of the LAS has effectively allocated organ transplantation to patients with the highest acuity, consequently driving the need for more invasive bridging to transplant (BTT) strategies in the form of mechanical circulatory support [41, 42].

In recent decades, the combination of significant technical advancements and extensive experience in high volume centers, extracorporeal membrane oxygenation (ECMO) has become a staple tool in lung transplantation. Once a considerable contraindication to lung transplant, ECMO-BTT is known to significantly improve survival outcomes without severe disability [43]. ECMO allows infusion of oxygenated blood directly into circulation while simultaneously clearing carbon dioxide. Several studies have shown ECMO-BTT is effective in reducing mortality, albeit dependent on carefully selected patient populations, institutional experience, and early ambulation [38, 41, 44]. Extracorporeal membrane oxygenation can effectively provide respiratory support, cardiac support, or both based on cannulation sites. In patients with isolated pulmonary failure in the absence of hemodynamic instability or RV dysfunction, veno-venous ecmo (VV-ecmo) is preferred to veno-arterial (VA-ecmo) [42, 45, 46]. However, it is not uncommon for worsening pulmonary vascular resistance and ensued right ventricular dysfunction to call for conversion to VA-ecmo, providing both cardiac and pulmonary support [42]. VV-ECMO cannot effectively address the high pulmonary vascular resistance or the right ventricular dysfunction commonly present in patients with fibrotic or vascular lung diseases [47]. These patients are best supported with venoarterial (VA) ECMO [42, 47]. The framework for mechanical circulatory support for BTT in the lung transplant candidate remains patient specific. If the patient does not have pulmonary hypertension with right ventricular dysfunction, we pursue a strategy of dual-lumen internal jugular cannulation VV ECMO to facilitate ambulation. In the presence of pulmonary hypertension and right ventricular dysfunction or hemodynamic instability, we initially pursue femoral VA cannulation with routing distal perfusion catheter placement. If North-South syndrome develops, flows are inadequate, or ambulation cannot be achieved with peripheral ECMO, the patient is converted to central ECMO.

The positive impact of early ambulation and aggressive physical therapy on outcomes in critically ill patients is a well-accepted theory. This is also true in ECMO-BTT patients and is associated with

both successful transplantation and post-transplantation survival [38, 44, 48-50]. Bain and colleagues reported a 22% reduction in total hospital cost, 73% reduction in post-transplant ICU cost, and 11% reduction in total cost when compared to non-ambulatory ecmo patients [38]. Aggressively pursuing early extubation and ambulation may prevent risks associated with patient deconditioning. Several cannulation strategies with this goal in mind have been reported, including femoral, internal jugular, and axillary access [48]. Particularly with use of the *Avalon Elite*™ or *Crescent*® dual-lumen veno-veno ECMO cannula single-site access via the right internal jugular or left subclavian vein can be achieved, allowing for easier participation in physical therapy, better ambulation, and improved patient comfort [45]. Although proven successful, ECMO comes with its own unique risks that can influence post-transplantation morbidity and mortality including renal dysfunction, infection, and bleeding [38, 51]. With the use of mechanical circulatory support (MCS), differences in institutional volume, proper candidate section, as well as the primary pathology can all influence patient outcomes throughout the entirety of the transplantation process. Institutional variations of success across on the international scale emphasizes the importance appropriate patient selection on patient outcomes [51]. In efforts to improve these outcomes Habertheuer et al., developed a 24-point risk stratification score based solely on recipient variables, termed the STABLE risk score [51]. Retrospective analysis of the UNOS database allowed selection of significant variables that could be used to quantify the risk of in hospital mortality associated with implementation of ECMO as a BTT. Those found to have significant prognostic value included age, days on waitlist, dialysis on waitlist, transplant center volume (+/- 50 Ltx/yr), and total bilirubin level [51]. Each 1-point increase offered a 22% increase in risk of in-hospital mortality [51]. Internal validation proved the STABLE risk score could reproducibly aide in pre-transplant selection, improving posttransplant outcomes [51].

2.1.5 Organ Preservation

Hypothermia induced cellular damage is an often-underappreciated cause of PGD, leading to poor post-transplantation outcomes [31]. Conventional methods of transportation, which have been in practice for decades include static cold preservation with the lungs triple bagged and placed in a cooler of ice slurry. Per an ISHLT consensus statement, it is imperative to avoid direct contact between the allograft and ice as it can cause local tissue injury and damage to pulmonary endothelium, resulting in an increased risk of PGD [52]. As one can imagine with this method, it can be very difficult to maintain a uniform temperature across the allograft, leading to substantial temperature gradients across the organ interstitium [53]. Static cold preservation can often lead to unpredictable outcomes as allograft temperatures rapidly decrease, often below 2°C [54]. Intermittent freezing and thawing are undesirable as it can cause irreversible cellular damage not identified until the post-transplantation period [52]. For this reason, optimal storage temperatures are thought to range between 4-8°C, however limiting preservation times to 6-8 hours [31, 53]. Following report of excellent outcomes showing reduction in severe PGD, post-transplant MCS, as well as reduction in post-transplant ECMO/VAD in hearts preserved with the SherpaPak, efforts were made to bring this technology to the field of lung transplantation [55, 56]. The Paragonix LungGuard is an FDA cleared, CE marked donor lung preservation system reported to be able to maintain a homogeneous temperature for over 40 hours. The device consists of a rigid outer shell, triple bag system, temperature probe, as well as display and Bluetooth data transmission

throughout the entire transportation process. The Global Utilization And Registry Database for Improved preservAtion of doNor LUNGs (GUARDIAN-LUNG), is a multi-center retrospective-prospective registry comparing donor lungs preserved with conventional ice storage and those preserved with the Paragonix LungGuard [57]. Comparisons of peri-operative and short-term outcomes are currently underway.

With the goal of prolongation of preservation times, the Toronto Lung group recently published a pilot study on the effects of 10°C lung storage for a period of 36 hours [58]. In this proof-of-concept study, the lungs were found to poses higher levels of mitochondrial protective metabolites, less edema, and better physiological function compared to those stored at the standard 4°C [58]. The group went on to evaluate the use of intermittent normothermic ex-vivo lung perfusion and its ability to provide a cellular recharge allowing for up to 3 days of lung preservation [59]. Continued advancements in organ preservation and reconditioning open the door for the possibility of semi-elective lung transplantation and the associated better outcomes when performed during the day by a rested team [58, 59].

2.1.6 Unmanned Aircraft Systems (UAS)

The disparity between the number of recipients awaiting organs and number of available transplantable organs remains the limiting factor to successful patient outcomes. The current system for organ transportation hinges on commercial airlines and couriers, without any real ability for real-time monitoring of organ location or function [60]. Unmanned aircraft systems (UAS) or drones, have the unique ability to overcome the obstacle of geographic location with significant reduction in cold ischemic times [61]. In the current era, drone-delivery in the medical community has been used for delivery of biological samples, blood products, search and rescue, as well as automated external defibrillators (AED) [62, 63]. In 2021, Scalea et al., reported the first successful delivery of a human kidney that was ultimately transplanted into a recipient [64]. Although data regarding the use of UAS for organ delivery in the transplant community is scarce, this successful flight proves its possibility. The use of UAS has the potential to improve access to transplantable organs and decrease cold ischemia times, offering better post-transplant outcomes [61, 65]. Although interest is gaining in this innovative technology, several barriers including cost, healthcare policy, and acceptable risk still need to be addressed.

2.1.7 Ex-vivo Lung Perfusion (EVLP)

Over a decade of experience and clinical research has brought ex-vivo lung perfusion (EVLP) to the forefront of lung transplantation as an extraordinary asset. EVLP allows the lung allograft to remain perfused while permitting the opportunity for assessment, reconditioning, and treatment of marginal donor lungs. Lung donor availability has historically been low, often due to low number of neurologically determined death donors (NDD) and low rates of acceptable grafts thought to be as low as 18.6-30% [66]. The lungs are the only internal organ constantly exposed to the outside environment, putting them at increased risk for several complications that may ultimately lead to allograft failure. Common lung injuries often associated with the process of both brain and circulatory death include aspiration of gastric contents, pneumonia, ventilator associated barotrauma, as well as neurogenic and hydrostatic pulmonary edema [66]. These primary and secondary injuries lead to severe ischemia-reperfusion injury, recognized as a major cause of

primary graft dysfunction (PGD), the most common cause of early post-transplant mortality as well as chronic lung allograft dysfunction (CLAD) [67, 68]. Over recent years, the extension of donation criteria has led to the discovery of additional problems associated with DCD lungs, including aspiration, warm ischemia, hypoxia, and acute respiratory insufficiency syndrome (shock lung) [66, 69, 70]. The use of EVLP has been shown to successfully expand the lung donor pool with comparable short and long-term outcomes [15, 66, 69]. Jirsch et. al, first attempted to perform isolated EVLP in 1970, however they were unable to maintain the alveolar-capillary barrier, leading to significant edema and peripheral vascular resistance (PVR) related injuries [66]. It wasn't until 2001, when Steen and colleagues developed a buffered perfusate solution with a high dextran content and antioxidant properties (STEEN solution), to protect the vascular endothelium from ischemic changes that EVLP became a reality [70, 71]. Termed the Lund protocol, Steen and colleagues were able to use EVLP to evaluate the lungs of a non-heart beating donor, successfully transplanting the lungs [70]. As success ensued, EVLP began gaining traction globally as a way of physiologic assessment of marginal lungs. In 2011 Toronto group published their results in the New England Journal of Medicine (NEJM) reporting a series of 20 cases of lung transplantation using EVLP evaluated lungs with comparable outcomes to that of standard donors [66, 69, 70, 72]. By using an optimal lung protective strategy consisting of a low tidal volume ventilation and a low flow rate combined with a centrifuge pump permitted assessment and organ viability up to 12 hours, the Toronto group reported a near 70% increase in transplant volume without significant changes in the donor pool [72, 73].

There are currently 4 commercially available EVLP devices: the Organ Care System™ (OCS); XPS™ (XVIVO Perfusion AB); Lung Assist® (Organ Assist) and the Vivoline® LS1 [10, 66]. The basic set up of these systems typically consist of a centrifugal pump, heater/cooler, reservoir, membrane oxygenator, leukocyte filter, flow sensor, pressure transducers, ventilator, plastic organ chamber, bronchoscope set up, as well as specific cannulas and tubing. The OCS system is the only portable EVLP, in other words, this system is taken to the donor organ and is connected in the donor operating room. Rapid re-perfusion of the lung allograft mitigates the deleterious effects of cold ischemia maintaining it in a physiologic state [66]. Today the majority of high-volume transplant centers with an active EVLP program follow either the Toronto or Lund protocol. The main differences lie within the Toronto protocol and their use of an acellular perfusate, and a closed system via a silicone cuff anastomosed to the left atrium allowing for significantly increased preservation times [10, 70]. The Toronto protocol remains the most used protocol, as they are often credited for the significant role played in the advancement of EVLP technology as they continue to produce high quality EVLP based research. Their outcomes proved that the clinical use of EVLP provides equivalent outcomes when using DCD lungs and high-risk NDD lungs [66]. Several studies have reported validation of the use of EVLP. The INSPIRE trial showed non-inferiority of OCS lungs, while the EXPAND trial showed an 87% donor utilization rate with excellent post-transplant outcomes [66, 74]. At the inception of EVLP, lung function was finally able to be assessed in a physiological manner prior to transplantation. Continued measurements of pulmonary oxygenation, pulmonary vascular resistance, airway pressure, and pulmonary compliance for a minimum of 3 hours allows confident transplantation of once marginal lungs now with known good function [68]. Lengthened preservation times have opened the door to advancing diagnostics and targeted therapies. Recent advancements in molecular techniques including cell-based and gene therapy, as

well as pharmaceuticals have shown continued improvement in the rehabilitation of marginal donor lungs [68].

Several innovative trials have emerged using EVLP as a platform for treatment of infection, sepsis-induced injury, gastric-acid aspiration damage, and pulmonary embolism [75]. There continues to be promising results in the ability to mitigate infections like Hepatitis C (HCV), Cytomegalovirus (CMV), and Epstein-Barr Virus (EBV) [76-79]. Illicit drug use remains a significant problem across the US, with up to 20% of organ donors testing positive for Hepatitis C (HCV) [76]. Historically, seropositive HCV was an absolute contraindication for transplantation due to its high rate of transmission as well as significantly worse post-transplant outcomes prior to the advent of better anti-viral HCV therapy [76-78]. Several reports have shown success in initiating a course of DAAs such as sofosbuvir plus velpatasvir immediately post-transplant, to prevent vertical transmission from HCV positive donor lungs to seronegative recipients [76, 78]. The mechanical effect of EVLP to maintain lung function and decrease viral load prior to transplantation was first reported by the Toronto group in a 2016 case report [80]. The Toronto group reported after a 9-hour run of EVLP with a complete circuit change at the 3-hour mark reduced HCV RNA viral load by 86% and 84% in the perfusate and lung tissue itself, respectively [78, 80]. Although able to reduce viral load, EVLP alone was not found to be strong enough to prevent post-transplant viremia. After encouraging results, Toronto went on to evaluate the effect of light-based therapies (LbT) such as ultraviolet C (UVC) and photodynamic therapy (PDT) when added to the EVLP model. Although unable to provide complete viral elimination, positive results showed delayed and significantly lower HCV viral RNA concentration in HCV negative recipients [76, 78]. Latent human cytomegalovirus (CMV) is thought to be found among 83% of the world's population, and nearly 50% of donors [81]. CMV related complications are often due to post-transplant reactivation, ranging from tissue invasive viral disease, as well as PGD/CLAD [81]. Treatment modalities remain challenging due to the virus often being latent at time of transplantation, rendering antivirals ineffective. In a Toronto pre-clinical trial, the addition of an immunotoxin (F49A-FTP) to the standard EVLP protocol showed a significant reduction in post-transplant CMV reactivation [81]. Like CMV, Epstein-Barr virus can be found in up to 95% of the general population [79]. Immunosuppression is often required post-transplant, putting these patients at increased risk of uncontrolled proliferation of EBV-infected B-cells and ultimately posttransplant lymphoproliferative disorder (PTLD) [79]. It was recently reported that the addition of monoclonal antibody rituximab (RTX) to EVLP perfusate was successfully able to bind CD20+ cells and induce B-cell depletion within 24 hours post-transplantation, compared to two or more weeks when given to patient intravenously [79]. Cypel et. al also reported the addition of IL-10 therapy improved pulmonary function by inducing a shift from proinflammatory to anti-inflammatory state [82].

EVLP has proven itself to be an integral part of lung transplantation, successfully expanding the donor pool as well as providing opportunity for significant translational research. EVLP techniques allow the lung allografts to remain in a physiologically active and ventilated state, allowing a growing multitude of different treatment interventions that often require longer preservation times. However feasible, EVLP requires specific clinical expertise as well as substantial institutional costs. Specifically at low-volume transplant centers, delays in evaluation and donor management, and even operating room access has often led to poor organ recovery and poor outcomes. In order to overcome this obstacle, the creation of specialized donor care facilities across the United States, Spain, and Canada have been associated with better donor management and in turn improved

organ yield, decreased ischemic times, and decreased costs [83]. Centralized ex vivo lung assessment and repair centers have been gaining interest as a method of increasing utilization of marginal lungs, in return a higher transplant volume. In this centralized EVLP model, donor lungs are retrieved and transported to nearby dedicated EVLP center [83]. Following some time on EVLP, once the organ is considered suitable for transplant it can be offered to surrounding transplant centers and transported to accepting facility [83]. Continued success with EVLP has shown its potential to prolong organ preservation, treat marginal lungs, and improve transplantation outcomes. Centralization of EVLP allows for low-volume, small transplant centers to bring this revolutionary method to their patient population at a fraction of the cost [83].

2.2 Intra-operative

2.2.1 Mechanical Circulatory Support

In practice, the majority of lung transplants are successfully performed without the use of intraoperative support. In appropriately selected patients, off-pump lung transplantation can be associated with significantly shortened need for mechanical ventilation, decreased length of stay in ICU, as well as better post-op survival [84]. These results can likely be attributed to overall status of patients prior to transplant. However, as we've witnessed a shift in more high acuity patients presenting for lung transplant, intraoperative mechanical circulatory support is often required to maintain hemodynamic stability and optimize patient outcomes. The use of intraoperative MCS provides the ability to overcome severe pulmonary hypertension as well as right ventricle failure following clamping of the pulmonary artery. It is also useful in the event of global hypoxia or hypercapnia during single lung ventilation. For decades, cardiopulmonary bypass (CPB) has shown success in cardiac surgery, gradually becoming the method of choice for intraoperative support during lung transplantation [42, 84]. Of recent years, the utility of CPB in lung transplantation has come into question as it has been associated with activation of the inflammatory cascade, as well as data supporting its role in acute lung injury and acute respiratory distress syndrome when used for other procedures [85]. Recent literature has highlighted CPB as an independent risk factor for in-hospital mortality, increased rates intra- and post-op bleeding, increased requirements of blood products, renal failure requiring dialysis, as well as significantly higher rates of primary graft dysfunction [42, 84-88]. Based on the 2022 expert consensus document from the American Association for Thoracic Surgery (AATS), VA-ECMO is the preferred intraoperative extracorporeal support for lung transplantation [42]. Several reports have effectively compared the intraoperative use of VA-ECMO vs CPB, identifying superior short- and long-term outcomes in mortality and PGD [84-87]. An additionally important, well established perioperative factor is length of controlled reperfusion [89]. The ability of VA-ECMO to manage reperfusion to newly implanted lung following contralateral pneumonectomy, as well as postoperatively can significantly protect an already borderline organ [89-91].

2.2.2 Bronchial Artery Revascularization

Bronchial anastomotic dehiscence was the Achilles heel of Lung transplantation in its early years [92]. Lack of bronchial healing was thought to be due to a combination of transection of bronchial artery vascularization, rejection, and effect of immunosuppression [92]. In situ the lungs are

perfused via the pulmonary artery (PA) and bronchial artery (BA). As its name suggests, the bronchial artery serves an important role in the maintenance of bronchial homeostasis as it serves the bronchus with nutrient rich blood. Therefore, until neo-revascularization, thought to occur over 2-4 weeks postoperatively, the donor airways are dependent solely on retrograde flow from the poorly oxygenated pulmonary artery [93]. Airway ischemia, inflammation, and subsequent necrosis have been suggested in the inducement of chronic allograft dysfunction (CLAD), affecting up to 50% of patients at 5-year post transplantation [93-95]. Initial efforts to overcome airway complications and reduce the risk of tracheal anastomotic necrosis led to the incorporation of new surgical techniques to aide in early bronchial revascularization. One revascularization method was the use of an omental pedicle wrapped around the bronchial anastomosis [92]. For several years this was widely adopted across several high-volume centers and reported to restore bronchial circulation within days, significantly reducing complications due to bronchial dehiscence and stenosis [92]. An area of great debate across the lung transplantation community remains whether there is a substantial need for bronchial arterial revascularization (BAR) at time of transplantation. In a recent systematic review of the literature, Ahmad and colleagues assessed the outcomes of BAR after transplantation, in hopes of determining its ability to improve early tracheal healing and delay onset of CLAD [95]. Unfortunately, this was met with significant limitations as there is only a handful of surgeons and literature investigating the technique. Available documented experience in the clinical setting is sparse and is largely dated to the 1980-1990s [92, 96, 97]. Although a limited cohort, results did show BAR as a viable technique to improve bronchial healing when compared to the initial *en bloc* technique for bilateral lung transplant without BAR [98]. In the present day, BAR has been abandoned by most large-volume institutions owing to its associated bleeding risk, technically demanding and increased warm ischemia time dues to extended operative time. The procedure of choice today remains single sequential double lung transplant (SSLTx), with care during hilar dissection not to devascularize the recipient bronchial stump to avoid ischemic complications [99, 100].

2.3 Post Operative Management

Since Dr. Cooper's first successful lung transplant in 1983, nearly 70,000 adult lung transplant procedures have been reported to the International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation (ISHLT) [2, 94]. Despite ever changing patient characteristics, severity at timing of transplantation, and donor shortage the number of adult lung transplants has steadily increased, as have median survival rates from 4.2 years in the 1990s to the most recent era showing a median survival 6.7 years [94, 101]. However, lung transplant survival remains one of the lowest among other solid organs with 5-year patient survival of only 59% [102]. Despite the multitude of recent advancements made, a major barrier to long term graft and patient survival remains chronic lung allograft dysfunction (CLAD), occurring in nearly half of lung transplant recipients by the 5^{th} post-operative year [2, 94, 102]. CLAD is the term used to describe a persistent decline in FEV1 ≥20% from baseline FEV1 for at least 3 months, despite investigation and treatment of secondary causes [103]. CLAD is then subcategorized based on presenting phenotype as bronchiolitis obliterans syndrome (BOS) which is obstructive in nature, restrictive allograft syndrome (RAS) or mixed [103]. In the immediate postoperative period ≤72 hours, primary graft dysfunction (PGD) a form of acute respiratory distress syndrome (ARDS), is

characterized by pulmonary edema with diffuse alveolar damage [67]. Severe PGD still occurs in up to 30% of lung transplant recipients and is a known independent risk factor for development of CLAD [67].

2.3.1 Pain Control

Several entry incisions exist for lung transplantation. Whether it be an anterolateral or posterolateral thoracotomy, median sternotomy, or clamshell thoracosternotomy all are associated with significant postoperative pain that can impair both respiratory function and participation in physical rehabilitation [104, 105]. Painful incision sites following transplantation can significantly impair chest wall mechanics leading to ineffective chest wall expansion that may increase the risk of atelectasis, ventilation/perfusion mismatch, hypoxemia, and infection [104]. Additionally, poor management of acute post-operative pain is associated with post-thoracotomy pain syndrome (PTPS) [104-106]. PTPS is chronic pain that persists along a thoracotomy incision for at least 2 months post-op, it is described as typical neuropathic pain with features of burning and dysesthesia [106]. Therefore, adequate pain management remains a crucial piece of decreasing morbidity and mortality associated with lung transplantation. One of the simplest and easiest forms of pain control for decades has revolved around systemic opioid analgesia. Opioids however are associated with multiple adverse effects, including respiratory depression, sedation, post-operative nausea and vomiting, urinary retention, ileus, as well as eventual tolerance and dependence [105, 106]. Of recent years, thoracic epidural anesthesia (TEA) has become a technique of choice for post thoracotomy pain management as it adequately controls postoperative pain while allowing for continued dosing without the associated risk profile of systemic opioids [104, 105]. TEA has been found to be associated with decreased ICU length of stay as well as mechanical ventilation duration [105]. On the contrary, TEA is not always feasible due to its associated risks of epidural abscess, epidural hematoma, sympathetic blockade, and is often contraindicated in the setting of ECMO as bridge to recovery [104-106]. Recent alternatives to TEA include regional analgesia as intercostal nerve blockade with liposomal bupivacaine injections or intercostal cryoanalgesia. Intercostal nerve blockage interrupts pain signals to the spinal cord, allowing significant pain relief post-op, however this modality is short lived and may require additional techniques such as erector spinae plane block with a single injection or continuous intercostal catheter [104, 106]. A more recent modality to prevent both short and long-term post thoracotomy pain, cryoanalgesia has been gaining traction in the transplant community. Cryoanalgesia involves mechanical freezing and killing of intercostal axons while leaving the nerve sheath intact [107]. This allows for several months of significant pain control as the nerve fibers slowly regenerate within the undamaged nerve sheath [107]. Data around cryoanalgesia has been mainly limited to a few studies in posterolateral thoracotomy [108, 109]. In a recent single center retrospective study of 72 patients undergoing bilateral lung transplantation via clamshell incision, Isaza and colleagues found cryoanalgesia to be a safe alternative to TEA with equivalent postoperative analgesic effects [107]. At our institution we are currently using cryo nerve blocks from levels 3-7 in the posterior intercostal spaces for post operative pain control as well as TEA preop when feasible. Cryoanalgesia deserves continued investigation and large-scale studies demonstrating its true value to the transplant community.

2.3.2 Immunosuppressive Therapy

Prior to the introduction of cyclosporine in the 1980s, prolonged allograft survival was more of a wish than a reality [110, 111]. Primarily due to T-lymphocyte proliferation, recipients showed high incidence of acute cellular rejection (ACR), with frequency and severity shown to be associated with increased risk of CLAD [111]. Immunosuppression in lung transplantation requires a delicate balance aimed at preventing acute and chronic rejection while preventing infectious complications, drug toxicities, and malignancies [112]. Although advancements in understanding and clinical use have been evident, currently no FDA-approved immunosuppressants exist solely for lung transplantation [111]. Instead we rely on data compiled from other organ transplants and individual center experience, with the goal of developing an individualized approach to each patient [110-112]. Although heavily debated across institutions, induction immunosuppression is said to be used in >80% of lung transplant centers [94, 111]. Administered in the peri-operative or in the immediate post-operative period, induction immunosuppression is utilized to reduce the risk of t-cell mediated ACR through the inhibiting T-cell proliferation or overall depletion [110-112]. Commonly used agents for induction therapy include basiliximab, anti-thymocyte globulin (ATG), and alemtuzumab. The use of basiliximab, an interleukin-2 (IL-2) receptor antagonist, has increased in recent years due to its tolerability, benefits in reducing ACR, and improved long term survival [110-113]. Although there has not been a consensus in induction therapy, use of alemtuzumab and ATG continue to decline as can caused severe myelosuppression and cytokine storm [110-112].

Following initial induction therapy, maintenance therapy can be regarded as one of the most important aspects of immunosuppression in transplant recipients. Taken indefinitely, the purpose of lifelong immunosuppression is to prevent acute and chronic rejection, however it must be approached with caution as these medications are often associated with significant toxicities [110]. The mainstays of maintenance therapy include a calcineurin inhibitor (tacrolimus or cyclosporine), an anti-metabolite (mycophenolate or azathioprine), and corticosteroids [110-112]. Calcineurin inhibitors (CNI) have been shown to reduce T-cell activation and proliferation through the inhibition of nuclear factor of activated T-cells (NFAT), preventing activation of acute phase reactants [111]. In recent years tacrolimus has surpassed the use of cyclosporine as the CNI of choice following the publishing of a large prospective, randomized, controlled, multicenter trial demonstrating its superiority resulting in a lower 3-year cumulative risk of CLAD compared to cyclosporine, however survival benefit was not significant [114, 115]. These results can likely be associated with its side effect profile including, neurotoxicity, hypertension, hyperlipidemia, and hyperkalemia in addition to its numerous drug interactions as it is primarily metabolized through the CYP 3A4 system [111, 112]. The prevalence of chronic kidney insufficiency is reported to be as high as 23.7%, 36.7%, 75.4% within 1-, 5-, and 10 years respectively [116]. The progressive decline in renal function seen in patients on CNIs offers a significant source of morbidity and mortality in the lung transplantation population. Thought to be renal-sparing, Belatacept inhibits T-cell co-stimulation, therefore preventing T-cell proliferation and cytokine production [111]. Following its 2011 approval to replace CNI immunosuppression in kidney transplant recipients, Timofte and colleagues evaluated its use as a renal-sparing agent. in their retrospective analysis of 8 patients Belatacept was associated with improvement in renal function and allowed reduction in CNI exposure without increased immune-mediated lung injury [116]. In a larger prospective cohort study of 85 lung recipients converted to belatacept from CNI within 1 year of transplant, Benninger et. al., reported no decline in graft

function with stabilization of renal function [117]. Mycophenolate is an anti-metabolite that preferentially inhibits *de novo purine synthesis* in T- and B-lymphocytes, preventing their proliferation [110, 112] In recent years mycophenolate has become the anti-metabolite of choice as it has demonstrated favorable effects in preventing ACR in other solid organ transplant, as well as beneficial effects in patients with existing CLAD [112]. Finally, corticosteroids provide widespread inhibitory effects on the immune system via multiple pathways, leading to a decrease in T-cell proliferation and macrophage activation, altered lymphocyte migration, as well as inhibition of cytokine production [111]. Although well documented side-effects associated are associated with long term corticosteroid therapy, data continues to support the indefinite use of low-dose regimens [112]. Appropriate immunosuppressive therapy in transplant recipients requires an extensive breadth of knowledge and should be tackled from a multidisciplinary approach to ensure best possible patient outcomes.

2.3.3 Detection of Rejection

Despite several advancements and shifts toward more potent immunosuppressive therapy, acute and chronic allograft rejection continue to be a significant source of morbidity and mortality in lung transplant recipients. Acute rejection is estimated to occur in nearly 30-50% of lung transplant recipients and is a major risk factor for chronic rejection, the most common cause of death after the first year [118]. Early recognition of rejection and aggressive treatment throughout the immediate short-term and long-term post operative period is imperative to patient survival. ABO-identical matching of transplanted organs with recipients prevents erythrocyte destruction by donor lymphocytes, which is a major cause of hyperacute rejection and earlier onset of CLAD [119]. Hyperacute rejection can occur within minutes of transplantation up to 24 hours postoperatively and is an antibody mediated reaction that can range in severity leading to significant alveolar injury and subsequent death [120]. Due to these concerns, historically ABO-identical matches in solid organ transplants have been preferred. Unfortunately, sensitized candidates often have worse outcomes as well as longer waitlist times due to difficulty finding a suitable donor. Perioperative desensitization techniques aimed to reduced donor-specific antibodies such as plasma exchange, intravenous immune globulin, and antithymocyte globulin have been reported, showing promising results with equivalent graft survival compared to unsensitized recipients [121]. In a recently published follow up study, the Toronto group reported long-term graft survival as well as CLAD-free survival of patients desensitized with their protocol did not differ from those non-sensitized recipients [122].

The most common complication in the early postoperative period is primary graft dysfunction (PGD), responsible for nearly 50% of early (30-day) deaths [123, 124]. PGD is characterized by noncardiogenic pulmonary edema caused by ischemic pulmonary vascular injury and increased pulmonary vascular permeability resulting in diffuse alveolar damage and hyaline membrane formation [120]. It often occurs within the first 72 hours following transplant becoming most severe by post-op day 4 or 5, presenting as progressive dyspnea and decline in lung function [120]. PGD can be classified based on presence of radiographic pulmonary infiltrates and a decline PaO_2/FiO_2 (P/F ratio) ranging from grade 0-3, of which grade 3 being the most severe with a P/F ratio <200 and presence of infiltrates consistent with pulmonary edema [125]. Several risk factors for PGD have been reported as described by the ISHLT working group on PGD, as recipient comorbidities, prior

thoracic surgery, underlying disease, and surgical complications [123]. The main treatment modality for PGD remains supportive therapy and ECMO-BTT techniques [67, 120, 124].

Rejection continues to be a significant barrier to long term survival in lung transplantation. Nearly 30% of lung transplant recipients are reported to experience at least one episode of acute rejection during the first postoperative year, with severity and frequency reported as a major cause of CLAD [120, 126, 127]. As mentioned previously, an immunosuppressive maintenance immunosuppressive regimen is crucial to is prevention, however at the cost of increased risk of an infection which is also an important risk factor of acute rejection [126]. Recipients experiencing acute rejection can present sub-clinically or clinically with dyspnea, cough, sputum production, and pyrexia. Acute rejection is often diagnosed based on the presence of perivascular and interstitial mononuclear cell infiltrates in lung tissue, requiring repeated surveillance transbronchial biopsies along with its inherent risks [120, 126, 127]. Histopathologic grading of acute rejection ranges from A0 (none) to A4 (severe), which is described as diffuse perivascular, interstitial, and air-space infiltrates of mononuclear cells; alveolar pneumocyte damage and endothelialitis [128]. In the most recent era, significant advancements in the sensitivity of genomic sequencing have fought to overcome the limitations of histopathology and presented as an elusive counterpart to repeated transbronchial biopsies. Donor-derived cell-free DNA (ddcfDNA) are short cell-free DNA fragments released into circulation by dying cells and has recently been reported to accurately detect acute rejection in lung transplant patients [129-131]. In a recent multicenter cohort study, Jang and colleagues reported on ddcfDNA and its correlation with spirometry and histopathology, reliability in detecting rejection with a high negative predictive value, as well as rising ddcfDNA levels preceding acute rejection capturing those patients possibly missed by histopathology [130].

Chronic Lung allograft Dysfunction (CLAD) remains the most fearful diagnosis in lung transplant recipients. It is the leading cause of death after the first year, reported to develop in as many as 50% of recipients in 5 years [126, 127, 132]. CLAD is defined by the ISHLT as a persistent decline in forced expiratory volume (FEV1), ≥20% from baseline for at least 3 months [132-134]. CLAD can then be sub-classified based on obstructive or restrictive pathology. Restrictive allograft syndrome (RAS) is defined as a persistent decline lung function accompanied by a decrease ≥10% total lung capacity [120]. RAS is associated with a significantly worse prognosis, with a median survival of 6-18 months [120]. Bronchiolitis obliterans syndrome (BOS) represents the most common form of CLAD occurring in over 67% of cases of chronic rejection [120, 132]. BOS thought to be caused to a variety of immune-mediated and non-immune processes leading to chronic inflammation and occlusive fibrosis of the terminal bronchioles [120]. Due to its peripheral predilection, detection modalities are often limited to non-invasive spirometry and imaging. High-resolution computed tomography (HR-CT) has been an important tool to aide in the diagnosis, with characteristic findings including mosaicism and expiratory air trapping [135]. Treatment of BOS is often difficult and is often characterize by stabilization or slowing of functional decline instead of complete resolution [118]. Owing to its anti-inflammatory and anti-microbial properties, azithromycin is an established treatment option. Azithromycin, a macrolide antibiotic, has been shown to improve FEV1 in patients suffering from BOS is often recommended as initial treatment unless contraindicated [132, 136]. Extracorporeal photopheresis (ECP) has been reported as salvage therapy in the setting of BOS, however, may deserve early introduction. ECP is an immunomodulatory treatment that uses leukapheresis and light-based therapy. Of significance, unlike many immunosuppressant drugs, ECP is not associated with an increased risk of infection [118]. Several reports have highlighted the

favorable effect of ECP on transplant recipients with BOS. In reviewing their single center experience with ECP, Benden and colleagues reported a significant reduction in the rate of lung function decline as well as the ability to reach clinical stabilization in those with acute rejection [137]. More recently, in a retrospective descriptive audit of their experience with ECP as a rescue therapy, Vaziani and colleagues described ECP and its ability to arrest lung function decline in 67% of patients with CLAD who failed previous immunosuppressive augmentation [138].

3. Discussion

In the modern era, lung transplantation is a well-established treatment modality for those experiencing life-threatening respiratory compromise. Since the first successful lung transplantation in 1983, the last 40 years have produced several innovative methods that have been responsible for the propulsion of the field. The constant push for better results has revolutionized lung organ allocation, expansion of donor criteria with comparable outcomes across DBD and DCD donors and living lobar transplants. Largely owed to the advent of membrane oxygenation, advancements in mechanical circulatory support strategies have had major leaps as ECMO now shows usefulness in bridging to transplant, intraoperative mechanical circulatory support, as well as postoperative recovery. The ability to revive lungs ex-vivo is no small accomplishment. EVLP has and continues to become an integral part in the field of lung transplantation while different clinical applications are constantly explored. Significant strides have been made in the understanding of the pathophysiology of graft failure and rejection. Immunosuppressive therapy, cell-free DNA, and extracorporeal photopheresis are just a few of the innovative ways aimed at decreasing allograft failure and increasing long-term patient survival.

4. Conclusions

For the majority, the act of breathing is an unconscious and effortless process necessary for everyday life. Our lungs are responsible for capturing precious oxygen for delivery to the entire body while simultaneously expelling carbon dioxide. However, when patients are affected by pulmonary conditions breathing becomes a burden that consumes their day-to-day activity, often limiting their function and most importantly, quality of life. Lung transplantation has become a valuable tool that is able to reduce patients' suffering while adding quality years to their life. As to be imagined, this is no mean task. Each lung transplant is made possible by a multidisciplinary team composed of physicians, nurses, technologists, therapists, researchers and countless other healthcare providers all with the goal of successfully giving the gift of breath to a patient in need. It is often said, "it takes a village". Over the last 4 decades we have made significant strides in the art and science of lung transplantation, and it is now the fold standard for patients with end stage lung failure. There is however much more work to be done. As patients continue to present at different stages, each with their own unique set of co-morbidities and disease progression we rely on the continued experience and innovations aimed at increasing access and improving long-term results while alleviating suffering and improving quality of life. All of this would not be possible without the generosity of the organ donor. Truly a selfless gift of life, and second wind affording a breath of fresh air!

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References

1. Labaki WW, Han MK. Chronic respiratory diseases: A global view. Lancet Respir Med. 2020; 8: 531-533.
2. Venuta F, Van Raemdonck D. History of lung transplantation. J Thorac Dis. 2017; 9: 5458-5471.
3. Lima O, Cooper JD, Peters WJ, Ayabe H, Townsend E, Luk SC, et al. Effects of methylprednisolone and azathioprine on bronchial healing following lung autotransplantation. J Thorac Cardiovasc Surg. 1981; 82: 211-215.
4. Saunders NR, Egan TM, Chamberlain D, Cooper JD. Cyclosporin and bronchial healing in canine lung transplantation. J Thorac Cardiovasc Surg. 1984; 88: 993-999.
5. Okereke IC, Cassivi SD, Moon MR. Historical perspectives of The American Association for Thoracic Surgery: Joel D. Cooper. J Thorac Cardiovasc Surg. 2016; 151: 1440-1443.
6. Perch M, Hayes D, Cherikh WS, Zuckermann A, Harhay MO, Hsich E, et al. The International Thoracic Organ Transplant registry of the International Society for Heart and Lung Transplantation: Thirty-ninth adult lung transplantation report—2022; focus on lung transplant recipients with chronic obstructive pulmonary disease. J Heart Lung Transplant. 2022; 41: 1335-1347.
7. McCurry KR, Budev MM. Lung transplant: Candidates for referral and the waiting list. Cleve Clin J Med. 2017; 84: 54-58.
8. Cho SJ, Stout-Delgado HW. Aging and lung disease. Annu Rev Physiol. 2020; 82: 433-459.
9. Valapour M, Lehr CJ, Schladt DP, Smith JM, Goff R, Mupfudze TG, et al. OPTN/SRTR 2021 annual data report: Lung. Am J Transplant. 2023; 23: S379-S442.
10. Keshavamurthy S, Rodgers-Fischl P. Donation after circulatory death (DCD)-lung procurement. Indian J Thorac Cardiovasc Surg. 2021; 37: 425-432.
11. Gottlieb J. Lung allocation. J Thorac Dis. 2017; 9: 2670-2674.

12. Russo MJ, Worku B, Iribarne A, Hong KN, Yang JA, Vigneswaran W, et al. Does lung allocation score maximize survival benefit from lung transplantation? J Thorac Cardiovasc Surg. 2011; 141: 1270-1277.
13. Valapour M, Lehr CJ, Wey A, Skeans MA, Miller J, Lease ED. Expected effect of the lung composite allocation score system on US lung transplantation. Am J Transplant. 2022; 22: 2971-2980.
14. Leard LE, Holm AM, Valapour M, Glanville AR, Attawar S, Aversa M, et al. Consensus document for the selection of lung transplant candidates: An update from the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2021; 40: 1349-1379.
15. Young KA, Dilling DF. The future of lung transplantation. Chest. 2019; 155: 465-473.
16. Valapour M, Lehr CJ, Skeans MA, Smith JM, Miller E, Goff R, et al. OPTN/SRTR 2020 annual data report: Lung. Am J Transplant. 2022; 22: 438-518.
17. Shweish O, Dronavalli G. Indications for lung transplant referral and listing. J Thorac Dis. 2019; 11: S1708-S1720.
18. US Department of Health and Human Services. Continous distribution of lungs concept paper [Internet]. Washington, DC: US Department of Health and Human Services; 2019. Available from: https://optn.transplant.hrsa.gov/media/3111/thoracic_publiccomment_201908.pdf.
19. US Department of Health and Human Services. Public comment proposal: Establish continuous distribution of lungs [Internet]. Washington, DC: US Department of Health and Human Services; 2021. Available from: https://optn.transplant.hrsa.gov/media/4772/continuous_distribution_of_lungs-public_comment.pdf.
20. Lehr CJ, Wey A, Skeans MA, Lease ED, Valapour M. Impact of incorporating long-term survival for calculating transplant benefit in the US lung transplant allocation system. J Heart Lung Transplant. 2022; 41: 866-873.
21. Thuong M, Ruiz A, Evrard P, Kuiper M, Boffa C, Akhtar MZ, et al. New classification of donation after circulatory death donors definitions and terminology. Transpl Int. 2016; 29: 749-759.
22. Ceulemans LJ, Vanluyten C, Monbaliu D, Schotsmans P, Fieuws S, Vandervelde CM, et al. Lung transplant outcome following donation after euthanasia. J Heart Lung Transplant. 2022; 41: 745-754.
23. Evrard P. Belgian modified classification of Maastricht for donors after circulatory death. Transplant Proc. 2014; 46: 3138-3142.
24. Egan TM, Lambert Jr CJ, Reddick R, Ulicny Jr KS, Keagy BA, Wilcox BR. A strategy to increase the donor pool: Use of cadaver lungs for transplantation. Ann Thorac Surg. 1991; 52: 1113-1121.
25. Van Raemdonck DE, Jannis NC, Rega FR, De Leyn PR, Flameng WJ, Lerut TE. Extended preservation of ischemic pulmonary graft by postmortem alveolar expansion. Ann Thorac Surg. 1997; 64: 801-808.
26. Krutsinger D, Reed RM, Blevins A, Puri V, De Oliveira NC, Zych B, et al. Lung transplantation from donation after cardiocirculatory death: A systematic review and meta-analysis. J Heart Lung Transplant. 2015; 34: 675-684.
27. Campo-Cañaveral de la Cruz JL, Crowley Carrasco S, Tanaka S, Romero Román A, Hoyos Mejía L, Gil Barturen M, et al. Lung transplantation from uncontrolled and controlled donation after circulatory death: Similar outcomes to brain death donors. Transpl Int. 2021; 34: 2609-2619.

28. Suberviola B, Mons R, Ballesteros MA, Mora V, Delgado M, Naranjo S, et al. Excellent long-term outcome with lungs obtained from uncontrolled donation after circulatory death. Am J Transplant. 2019; 19: 1195-1201.
29. Valenza F, Citerio G, Palleschi A, Vargiolu A, Fakhr BS, Confalonieri A, et al. Successful transplantation of lungs from an uncontrolled donor after circulatory death preserved in situ by alveolar recruitment maneuvers and assessed by ex vivo lung perfusion. Am J Transplant. 2016; 16: 1312-1318.
30. Healey A, Watanabe Y, Mills C, Stoncius M, Lavery S, Johnson K, et al. Initial lung transplantation experience with uncontrolled donation after cardiac death in North America. Am J Transplant. 2020; 20: 1574-1581.
31. Munshi L, Keshavjee S, Cypel M. Donor management and lung preservation for lung transplantation. Lancet Respir Med. 2013; 1: 318-328.
32. Starnes VA, Barr ML, Cohen RG, Hagen JA, Wells WJ, Horn MV, et al. Living-donor lobar lung transplantation experience: Intermediate results. J Thorac Cardiovasc Surg. 1996; 112: 1284-1291.
33. Date H. Living-related lung transplantation. J Thorac Dis. 2017; 9: 3362-3371.
34. Nakajima D, Date H. Living-donor lobar lung transplantation. J Thorac Dis. 2021; 13: 6594-6601.
35. Starnes VA, Bowdish ME, Woo MS, Barbers RG, Schenkel FA, Horn MV, et al. A decade of living lobar lung transplantation: Recipient outcomes. J Thorac Cardiovasc Surg. 2004; 127: 114-122.
36. Sugimoto S, Date H, Miyoshi K, Otani S, Ishihara M, Yamane M, et al. Long-term outcomes of living-donor lobar lung transplantation. J Thorac Cardiovasc Surg. 2022; 164: 440-448.
37. Date H, Aoyama A, Hijiya K, Motoyama H, Handa T, Kinoshita H, et al. Outcomes of various transplant procedures (single, sparing, inverted) in living-donor lobar lung transplantation. J Thorac Cardiovasc Surg. 2017; 153: 479-486.
38. Bain JC, Turner DA, Rehder KJ, Eisenstein EL, Davis RD, Cheifetz IM, et al. Economic outcomes of extracorporeal membrane oxygenation with and without ambulation as a bridge to lung transplantation. Respir Care. 2016; 61: 1-7.
39. Singer JP, Blanc PD, Hoopes C, Golden JA, Koff JL, Leard LE, et al. The impact of pretransplant mechanical ventilation on short-and long-term survival after lung transplantation. Am J Transplant. 2011; 11: 2197-2204.
40. Yusen RD, Edwards LB, Kucheryavaya AY, Benden C, Dipchand AI, Goldfarb SB, et al. The registry of the International Society for Heart and Lung Transplantation: Thirty-second official adult lung and heart-lung transplantation report—2015; focus theme: Early graft failure. J Heart Lung Transplant. 2015; 34: 1264-1277.
41. Hayanga JA, Hayanga HK, Holmes SD, Ren Y, Shigemura N, Badhwar V, et al. Mechanical ventilation and extracorporeal membrane oxygenation as a bridge to lung transplantation: Closing the gap. J Heart Lung Transplant. 2019; 38: 1104-1111.
42. Panel EC, Hartwig M, van Berkel V, Bharat A, Cypel M, Date H, et al. The American Association for Thoracic Surgery (AATS) 2022 expert consensus document: The use of mechanical circulatory support in lung transplantation. J Thorac Cardiovasc Surg. 2023; 165: 301-326.
43. Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): A multicentre randomised controlled trial. Lancet. 2009; 374: 1351-1363.

44. Hakim AH, Ahmad U, McCurry KR, Johnston DR, Pettersson GB, Budev M, et al. Contemporary outcomes of extracorporeal membrane oxygenation used as bridge to lung transplantation. Ann Thorac Surg. 2018; 106: 192-198.
45. Biscotti M, Gannon WD, Agerstrand C, Abrams D, Sonett J, Brodie D, et al. Awake extracorporeal membrane oxygenation as bridge to lung transplantation: A 9-year experience. Ann Thorac Surg. 2017; 104: 412-419.
46. Loor G, Chatterjee S, Shafii A. Extracorporeal membrane oxygenation support before lung transplant: A bridge over troubled water. JTCVS Open. 2021; 8: 147-154.
47. Xia Y, Ragalie W, Yang EH, Lluri G, Biniwale R, Benharash P, et al. Venoarterial versus venovenous extracorporeal membrane oxygenation as bridge to lung transplantation. Ann Thorac Surg. 2022; 114: 2080-2086.
48. Keshavamurthy S, Bazan V, Tribble TA, Baz MA, Zwischenberger JB. Ambulatory extracorporeal membrane oxygenation (ECMO) as a bridge to lung transplantation. Indian J Thorac Cardiovasc Surg. 2021; 37: 366-379.
49. Kukreja J, Tsou S, Chen J, Trinh BN, Feng C, Golden JA, et al. Risk factors and outcomes of extracorporeal membrane oxygenation as a bridge to lung transplantation. Semin Thorac Cardiovasc Surg. 2020; 32: 772-785.
50. Pasrija C, Mackowick KM, Raithel M, Tran D, Boulos FM, Deatrick KB, et al. Ambulation with femoral arterial cannulation can be safely performed on venoarterial extracorporeal membrane oxygenation. Ann Thorac Surg. 2019; 107: 1389-1394.
51. Habertheuer A, Richards T, Sertic F, Molina M, Vallabhajosyula P, Suzuki Y, et al. Stratification risk analysis in bridging patients to lung transplant on ECMO: The STABLE risk score. Ann Thorac Surg. 2020; 110: 1175-1184.
52. Copeland H, Hayanga JA, Neyrinck A, MacDonald P, Dellgren G, Bertolotti A, et al. Donor heart and lung procurement: A consensus statement. J Heart Lung Transplant. 2020; 39: 501-517.
53. Hendry PJ, Walley VM, Koshal A, Masters RG, Keon WJ. Are temperatures attained by donor hearts during transport too cold? J Thorac Cardiovasc Surg. 1989; 98: 517-522.
54. Horch DF, Mehlitz T, Laurich O, Abel A, Reuter S, Pratschke H, et al. Organ transport temperature box: Multicenter study on transport temperature of organs. Transplant Proc. 2002; 34: 2320.
55. Voigt JD, Leacche M, Copeland H, Wolfe SB, Pham SM, Shudo Y, et al. Multicenter registry using propensity score analysis to compare a novel transport/preservation system to traditional means on postoperative hospital outcomes and costs for heart transplant patients. Asaio J. 2022; 69: 345-349.
56. Bitargil M, Haddad O, Pham SM, Garg N, Jacob S, El-Sayed Ahmed MM, et al. Packing the donor heart: Is SherpaPak cold preservation technique safer compared to ice cold storage. Clin Transplant. 2022; 36: e14707.
57. Hartwig M, Bush E, Langer N, Haney J. Report of the GUARDIAN-LUNG registry: An analysis of advanced hypothermic preservation on lung transplantation. J Heart Lung Transplant. 2022; 41: S37.
58. Ali A, Wang A, Ribeiro RV, Beroncal EL, Baciu C, Galasso M, et al. Static lung storage at 10°C maintains mitochondrial health and preserves donor organ function. Sci Transl Med. 2021; 13: eabf7601.

59. Ali A, Nykanen AI, Beroncal E, Brambate E, Mariscal A, Michaelsen V, et al. Successful 3-day lung preservation using a cyclic normothermic ex vivo lung perfusion strategy. EBioMedicine. 2022; 83: 104210.
60. Scalea JR, Restaino S, Scassero M, Blankenship G, Bartlett ST, Wereley N. An initial investigation of unmanned aircraft systems (UAS) and real-time organ status measurement for transporting human organs. IEEE J Transl Eng Health Med. 2018; 6: 4000107.
61. Scalea JR, Restaino S, Scassero M, Bartlett ST, Wereley N. The final frontier? Exploring organ transportation by drone. Am J Transplant. 2019; 19: 962-964.
62. Kozioł A. Usage of unmanned aerial vehicles in medical services: A review. In: Terotechnology XII. Millersville, PA: Materials Research Forum LLC.; 2022. pp. 288-293.
63. Thiels C, Aho J, Zietlow S, Jenkins D. Use of unmanned aerial vehicles for medical product transport. Air Med J. 2015; 34: 104-108.
64. Scalea JR, Pucciarella T, Talaie T, Restaino S, Drachenberg CB, Alexander C, et al. Successful implementation of unmanned aircraft use for delivery of a human organ for transplantation. Ann Surg. 2021; 274: e282-e288.
65. Sage AT, Cypel M, Cardinal M, Qiu J, Humar A, Keshavjee S. Testing the delivery of human organ transportation with drones in the real world. Sci Robot. 2022; 7: eadf5798.
66. Watanabe T, Cypel M, Keshavjee S. Ex vivo lung perfusion. J Thorac Dis. 2021; 13: 6602-6617.
67. Suzuki Y, Cantu E, Christie JD. Primary graft dysfunction. Semin Respir Crit Care Med. 2013; 34: 305-319.
68. Nakajima D, Date H. Ex vivo lung perfusion in lung transplantation. Gen Thorac Cardiovasc Surg. 2021; 69: 625-630.
69. Pan X, Yang J, Fu S, Zhao H. Application of ex vivo lung perfusion (EVLP) in lung transplantation. J Thorac Dis. 2018; 10: 4637-4642.
70. Rosso L, Zanella A, Righi I, Barilani M, Lazzari L, Scotti E, et al. Lung transplantation, ex-vivo reconditioning and regeneration: State of the art and perspectives. J Thorac Dis. 2018; 10: S2423-S2430.
71. Carnevale R, Biondi-Zoccai G, Peruzzi M, De Falco E, Chimenti I, Venuta F, et al. New insights into the steen solution properties: Breakthrough in antioxidant effects via NOX2 downregulation. Oxid Med Cell Longev. 2014; 2014: 242180.
72. Cypel M, Yeung JC, Liu M, Anraku M, Chen F, Karolak W, et al. Normothermic ex vivo lung perfusion in clinical lung transplantation. N Engl J Med. 2011; 364: 1431-1440.
73. Prasad NK, Pasrija C, Talaie T, Krupnick AS, Zhao Y, Lau CL. Ex vivo lung perfusion: Current achievements and future directions. Transplantation. 2021; 105: 979-985.
74. Divithotawela C, Cypel M, Martinu T, Singer LG, Binnie M, Chow CW, et al. Long-term outcomes of lung transplant with ex vivo lung perfusion. JAMA Surg. 2019; 154: 1143-1150.
75. Lautner LJ, Freed DH, Nagendran J, Acker JP. Current techniques and the future of lung preservation. Cryobiology. 2020; 94: 1-8.
76. Galasso M, Feld JJ, Watanabe Y, Pipkin M, Summers C, Ali A, et al. Inactivating hepatitis C virus in donor lungs using light therapies during normothermic ex vivo lung perfusion. Nat Commun. 2019; 10: 481.
77. Englum BR, Ganapathi AM, Speicher PJ, Gulack BC, Snyder LD, Davis RD, et al. Impact of donor and recipient hepatitis C status in lung transplantation. J Heart Lung Transplant. 2016; 35: 228-235.

78. Ribeiro RV, Ali A, Cypel M. Ex vivo perfusion in lung transplantation and removal of HCV: The next level. Transpl Int. 2020; 33: 1589-1596.
79. Ku TJ, Ribeiro RV, Ferreira VH, Galasso M, Keshavjee S, Kumar D, et al. Ex-vivo delivery of monoclonal antibody (Rituximab) to treat human donor lungs prior to transplantation. EBioMedicine. 2020; 60: 102994.
80. Khan B, Singer LG, Lilly LB, Chaparro C, Martinu T, Juvet S, et al. Successful lung transplantation from hepatitis C positive donor to seronegative recipient. Am J Transplant. 2017; 17: 1129-1131.
81. Ribeiro RV, Ku T, Wang A, Pires L, Ferreira VH, Michaelsen V, et al. Ex vivo treatment of cytomegalovirus in human donor lungs using a novel chemokine-based immunotoxin. J Heart Lung Transplant. 2022; 41: 287-297.
82. Cypel M, Liu M, Rubacha M, Yeung JC, Hirayama S, Anraku M, et al. Functional repair of human donor lungs by IL-10 gene therapy. Sci Transl Med. 2009; 1: 4ra9.
83. Bery A, Ali A, Cypel M, Kreisel D. Centralized organ recovery and reconditioning centers. Thorac Surg Clin. 2022; 32: 167-174.
84. Ohsumi A, Date H. Perioperative circulatory support for lung transplantation. Gen Thorac Cardiovasc Surg. 2021; 69: 631-637.
85. Biscotti M, Yang J, Sonett J, Bacchetta M. Comparison of extracorporeal membrane oxygenation versus cardiopulmonary bypass for lung transplantation. J Thorac Cardiovasc Surg. 2014; 148: 2410-2415.
86. Ius F, Kuehn C, Tudorache I, Sommer W, Avsar M, Boethig D, et al. Lung transplantation on cardiopulmonary support: Venoarterial extracorporeal membrane oxygenation outperformed cardiopulmonary bypass. J Thorac Cardiovasc Surg. 2012; 144: 1510-1516.
87. Hoechter DJ, Shen YM, Kammerer T, Günther S, Weig T, Schramm R, et al. Extracorporeal circulation during lung transplantation procedures: A meta-analysis. Asaio J. 2017; 63: 551-561.
88. Magouliotis DE, Tasiopoulou VS, Svokos AA, Svokos KA, Zacharoulis D. Extracorporeal membrane oxygenation versus cardiopulmonary bypass during lung transplantation: A meta-analysis. Gen Thorac Cardiovasc Surg. 2018; 66: 38-47.
89. Bhabra MS, Hopkinson DN, Shaw TE, Onwu N, Hooper TL. Controlled reperfusion protects lung grafts during a transient early increase in permeability. Ann Thorac Surg. 1998; 65: 187-192.
90. Buckberg GD. Controlled reperfusion after ischemia may be the unifying recovery denominator. J Thorac Cardiovasc Surg. 2010; 140: 12-18.e2.
91. Halldorsson A, Kronon M, Allen BS, Bolling KS, Wang T, Rahman S, et al. Controlled reperfusion after lung ischemia: Implications for improved function after lung transplantation. J Thorac Cardiovasc Surg. 1998; 115: 415-425.
92. Cooper JD. The evolution of techniques and indications for lung transplantation. Ann Surg. 1990; 212: 249-256.
93. Crespo MM, McCarthy DP, Hopkins PM, Clark SC, Budev M, Bermudez CA, et al. ISHLT Consensus Statement on adult and pediatric airway complications after lung transplantation: Definitions, grading system, and therapeutics. J Heart Lung Transplant. 2018; 37: 548-563.
94. Chambers DC, Perch M, Zuckermann A, Cherikh WS, Harhay MO, Hayes Jr D, et al. The International Thoracic Organ Transplant registry of the International Society for Heart and Lung Transplantation: Thirty-eighth adult lung transplantation report-2021; Focus on recipient characteristics. J Heart Lung Transplant. 2021; 40: 1060-1072.

95. Ahmad D, O'Malley TJ, Jordan AM, Maynes EJ, Saxena A, Prochno KW, et al. Bronchial artery revascularization in lung transplantation: A systematic review and meta-analysis. J Thorac Dis. 2022; 14: 3285-3294.
96. Baudet EM, Dromer C, Dubrez J, Jougon JB, Roques X, Velly JF, et al. Intermediate-term results after en bloc double-lung transplantation with bronchial arterial revascularization. J Thorac Cardiovasc Surg. 1996; 112: 1292-1300.
97. Date H, Trulock EP, Arcidi JM, Sundaresan S, Cooper JD, Patterson GA. Improved airway healing after lung transplantation. An analysis of 348 bronchial anastomoses. J Thorac Cardiovasc Surg. 1995; 110: 1424-1433.
98. Andreasson AS, Dark JH. Revascularisation of the bronchial arteries in pulmonary transplant; does it ever have a role? J Thorac Dis. 2022; 14: 4578-4581.
99. Santacruz JF, Mehta AC. Airway complications and management after lung transplantation: Ischemia, dehiscence, and stenosis. Proc Am Thorac Soc. 2009; 6: 79-93.
100. Karami M, Mandigers L, Miranda DD, Rietdijk WJ, Binnekade JM, Knijn DC, et al. Survival of patients with acute pulmonary embolism treated with venoarterial extracorporeal membrane oxygenation: A systematic review and meta-analysis. J Crit Care. 2021; 64: 245-254.
101. Miller CL, O JM, Allan JS, Madsen JC. Novel approaches for long-term lung transplant survival. Front Immunol. 2022; 13: 931251.
102. Bos S, Vos R, Van Raemdonck DE, Verleden GM. Survival in adult lung transplantation: Where are we in 2020? Curr Opin Organ Transplant. 2020; 25: 268-273.
103. Bedair B, Hachem RR. Management of chronic rejection after lung transplantation. J Thorac Dis. 2021; 13: 6645-6653.
104. Soto RG, Fu ES. Acute pain management for patients undergoing thoracotomy. Ann Thorac Surg. 2003; 75: 1349-1357.
105. Lewis TC, Sureau K, Katz A, Fargnoli A, Lesko M, Rudym D, et al. Multimodal opioid-sparing pain management after lung transplantation and the impact of liposomal bupivacaine intercostal nerve block. Clin Transplant. 2022; 36: e14512.
106. Gupta R, Van de Ven T, Pyati S. Post-thoracotomy pain: Current strategies for prevention and treatment. Drugs. 2020; 80: 1677-1684.
107. Isaza E, Santos J, Haro GJ, Chen J, Weber DJ, Deuse T, et al. Intercostal nerve cryoanalgesia versus thoracic epidural analgesia in lung transplantation: A retrospective single-center study. Pain Ther. 2023; 12: 201-211.
108. Moorjani N, Zhao F, Tian Y, Liang C, Kaluba J, Maiwand MO. Effects of cryoanalgesia on post-thoracotomy pain and on the structure of intercostal nerves: A human prospective randomized trial and a histological study. Eur J Cardiothorac Surg. 2001; 20: 502-507.
109. Müller LC, Salzer GM, Ransmayr G, Neiss A. Intraoperative cryoanalgesia for postthoracotomy pain relief. Ann Thorac Surg. 1989; 48: 15-18.
110. Benvenuto LJ, Anderson MR, Arcasoy SM. New frontiers in immunosuppression. J Thorac Dis. 2018; 10: 3141-3155.
111. Nelson J, Kincaide E, Schulte J, Hall R, Levine DJ. Immunosuppression in lung transplantation. Pharmacol Immunosuppr. 2022; 272: 139-164.
112. Chung PA, Dilling DF. Immunosuppressive strategies in lung transplantation. Ann Transl Med. 2020; 8: 409.

113. Mangi AA, Mason DP, Nowicki ER, Batizy LH, Murthy SC, Pidwell DJ, et al. Predictors of acute rejection after lung transplantation. Ann Thorac Surg. 2011; 91: 1754-1762.
114. Treede H, Glanville AR, Klepetko W, Aboyoun C, Vettorazzi E, Lama R, et al. Tacrolimus and cyclosporine have differential effects on the risk of development of bronchiolitis obliterans syndrome: Results of a prospective, randomized international trial in lung transplantation. J Heart Lung Transplant. 2012; 31: 797-804.
115. Penninga L, Penninga EI, Møller CH, Iversen M, Steinbrüchel DA, Gluud C. Tacrolimus versus cyclosporin as primary immunosuppression for lung transplant recipients. Cochrane Database Syst Rev. 2013. doi: 10.1002/14651858.CD008817.pub2.
116. Timofte I, Terrin M, Barr E, Sanchez P, Kim J, Reed R, et al. Belatacept for renal rescue in lung transplant patients. Transpl Int. 2016; 29: 453-463.
117. Benn L, Chizinga M, Scheuble V, Nandavaram S, Shahmohammadi A, Pipkin M, et al. Does belatacept provide a safe renal sparing immunosuppression in lung transplant recipients? A single-center experience. J Heart Lung Transplant. 2021; 40: S77-S78.
118. Knobler R, Berlin G, Calzavara-Pinton P, Greinix H, Jaksch P, Laroche L, et al. Guidelines on the use of extracorporeal photopheresis. J Eur Acad Dermatol Venereol. 2014; 28: 1-37.
119. Hunt BJ, Yacoub M, Amin S, Devenish A, Contreras M. Induction of red blood cell destruction by graft-derived antibodies after minor ABO-mismatched heart and lung transplantation. Transplantation. 1988; 46: 246-249.
120. Sun H, Deng M, Chen W, Liu M, Dai H, Wang C. Graft dysfunction and rejection of lung transplant, a review on diagnosis and management. Clin Respir J. 2022; 16: 5-12.
121. Tinckam KJ, Keshavjee S, Chaparro C, Barth D, Azad S, Binnie M, et al. Survival in sensitized lung transplant recipients with perioperative desensitization. Am J Transplant. 2015; 15: 417-426.
122. Aversa M, Martinu T, Patriquin C, Cypel M, Barth D, Ghany R, et al. Long-term outcomes of sensitized lung transplant recipients after peri-operative desensitization. Am J Transplant. 2021; 21: 3444-3448.
123. Barr ML, Kawut SM, Whelan TP, Girgis R, Böttcher H, Sonett J, et al. Report of the ISHLT Working Group on primary lung graft dysfunction part IV: Recipient-related risk factors and markers. J Heart Lung Transplant. 2005; 24: 1468-1482.
124. Jin Z, Suen KC, Wang Z, Ma D. Review 2: Primary graft dysfunction after lung transplant-pathophysiology, clinical considerations and therapeutic targets. J Anesth. 2020; 34: 729-740.
125. Christie JD, Carby M, Bag R, Corris P, Hertz M, Weill D. Report of the ISHLT Working Group on primary lung graft dysfunction part II: Definition. A consensus statement of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2005; 24: 1454-1459.
126. Subramani MV, Pandit S, Gadre SK. Acute rejection and post lung transplant surveillance. Indian J Thorac Cardiovasc Surg. 2022; 38: 271-279.
127. Parulekar AD, Kao CC. Detection, classification, and management of rejection after lung transplantation. J Thorac Dis. 2019; 11: S1732-S1739.
128. Stewart S, Fishbein MC, Snell GI, Berry GJ, Boehler A, Burke MM, et al. Revision of the 1996 working formulation for the standardization of nomenclature in the diagnosis of lung rejection. J Heart Lung Transplant. 2007; 26: 1229-1242.
129. Agbor-Enoh S, Wang Y, Tunc I, Jang MK, Davis A, De Vlaminck I, et al. Donor-derived cell-free DNA predicts allograft failure and mortality after lung transplantation. EBioMedicine. 2019; 40: 541-553.

130. Jang MK, Tunc I, Berry GJ, Marboe C, Kong H, Keller MB, et al. Donor-derived cell-free DNA accurately detects acute rejection in lung transplant patients, a multicenter cohort study. J Heart Lung Transplant. 2021; 40: 822-830.
131. Lian QY, Chen A, Zhang JH, Guan WJ, Xu X, Wei B, et al. High-throughput next-generation sequencing for identifying pathogens during early-stage post-lung transplantation. BMC Pulm Med. 2021; 21: 348.
132. Arjuna A, Olson MT, Walia R, Bremner RM, Smith MA, Mohanakumar T. An update on current treatment strategies for managing bronchiolitis obliterans syndrome after lung transplantation. Expert Rev Respir Med. 2021; 15: 339-350.
133. Verleden GM, Raghu G, Meyer KC, Glanville AR, Corris P. A new classification system for chronic lung allograft dysfunction. J Heart Lung Transplant. 2014; 33: 127-133.
134. Venado A, Kukreja J, Greenland JR. Chronic lung allograft dysfunction. Thorac Surg Clin. 2022; 32: 231-242.
135. Brun AL, Chabi ML, Picard C, Mellot F, Grenier PA. Lung transplantation: CT Assessment of chronic lung allograft dysfunction (CLAD). Diagnostics. 2021; 11: 817.
136. Hachem R, Corris P. Extracorporeal photopheresis for bronchiolitis obliterans syndrome after lung transplantation. Transplantation. 2018; 102: 1059-1065.
137. Benden C, Speich R, Hofbauer GF, Irani S, Eich-Wanger C, Russi EW, et al. Extracorporeal photopheresis after lung transplantation: A 10-year single-center experience. Transplantation. 2008; 86: 1625-1627.
138. Vazirani J, Routledge D, Snell GI, Watson D, Paraskeva M, Westall GP, et al. Outcomes following extracorporeal photopheresis for chronic lung allograft dysfunction following lung transplantation: A single-center experience. Transplant Proc. 2021; 53: 296-302.