Indian Journal of Thoracic and Cardiovascular Surgery (July 2022) 38 (Suppl 2):S260–S270
https://doi.org/10.1007/s12055-021-01178-1

REVIEW ARTICLE

Early postoperative complications in lung transplant recipients

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Received: 20 December 2020 / Revised: 8 March 2021 / Accepted: 10 March 2021 / Published online: 9 June 2021

Abstract
Lung transplantation has become an established therapy for end-stage lung diseases. Early postoperative complications can impact immediate, mid-term, and long-term outcomes. Appropriate management, prevention, and early detection of these early postoperative complications can improve the overall transplant course. In this review, we highlight the incidence, detection, and management of these early postoperative complications in lung transplant recipients.

Keywords Lung transplantation · Complications · Postoperative

Introduction

Lung transplantation has become an established therapy for progressive end-stage lung diseases refractory to maximal medical management. The immediate post-transplantation phase is crucial in determining short- and long-term survival and, ultimately, the quality of life of a lung transplant recipient. We continue to learn the risk factors and strategies to mitigate postoperative complications. Here, we present a concise review on the diagnosis and management of medical and surgical complications in the postoperative period, with major complications summarized in Table 1.

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Primary graft dysfunction

Primary graft dysfunction (PGD) can be seen immediately after reperfusion of the allograft lung and affects 10–25% of lung transplant recipients [1]. It is caused by prolonged ischemia time, reperfusion injury, and increased immunologic response from the innate immune pathway [2, 3]. Use of cardiopulmonary bypass (CPB) and single lung transplants have higher incidence of PGD [4]. Presence of fat embolism and thromboembolism increases the risk of PGD development by 25- and 5-fold respectively [5]. Risks are increased when donors are older, female, African American, have more than 20-year smoking history, and have high fraction of inspired oxygen (FiO2) requirements [2]. Recipients with obesity, preoperative sarcoidosis, pulmonary artery hypertension, and excessive blood transfusion perioperatively are at higher risk of developing PGD [2].

The International Society for Heart and Lung Transplantation (ISHLT) 2016 consensus group statement suggests a severity grading system of PGD based on the onset of changes in partial pressure of oxygen (PaO2)/FiO2 ratio and chest radiography at 24, 48, and 72 h after reperfusion (Table 2) [1, 2, 6]. A grade 3 PGD designation (PaO2/FiO2 ratio < 200 or SpO2/FiO2 ratio < 235, and diffuse allograft

Table 1 Summary of major complications after lung transplant

Complications	Incidence	Time of onset post-transplant	Management
Primary graft dysfunction	10–25%	Within 72 h	Lung-protective ventilation; restrictive fluid management; inhaled nitric oxide; ECMO initiation within 24 h of transplantation; empiric antimicrobials; immunosuppression; supportive [2]
Rejection	17–28%	Highest in the first year	
Acute cellular rejection	17.1–28%		Glucocorticoids; antithymocyte globulin; alemtuzumab; total lymphoid radiation; extracorporeal photopheresis [47]
Antibody-mediated rejection	12.5%		Intravenous immunoglobulin; plasmapheresis; rituximab; proteasome inhibitors [49]
Infection	Varies	Immediate and onwards	
Donor-derived pathogens (MRSA, *Pseudomonas*, *Enterobacter*, MDRO) Cytomegalovirus Fungal (*Candida*, *Aspergillus*, *Cryptococcus neoformans*, endemic mycosis, mucormycosis, *Scedosporium*, *Fusarium*) Invasive *Aspergillus* *Clostridium difficile*			Antimicrobials; perioperative antibiotic prophylaxis based on donor lung microbiology; CMV prophylaxis in the case of all but D−/R− cases; possible surgical intervention in severe cases of invasive species leading to dehiscence
Pleural complications	22–34%	Immediate and onwards	
Hemothorax	12–18%		Blood transfusions; surgical re-exploration if severe
Empyema	3–8%		Antimicrobial agents; chest tube
Airway complications	15–20%		
Bronchial stenosis		Within 9 months	Balloon bronchoplasty; stent placement [11–18]
Bronchial dehiscence		Within 5 weeks	Radiofrequency ablation [19]
Hematologic			
Thromboembolism	5–45%	Immediate	Systemic anticoagulation; thrombectomy
Bleeding		Immediate	Re-exploration for source of bleeding, supportive
Pulmonary vascular stenosis	1.8–5.2%	Within 9 days	Stent angioplasty, surgical intervention, re-transplantation [21, 24]
Diaphragm dysfunction	3.2–8.2%		Supportive measures including non-invasive ventilation [27]
Renal dysfunction			
Acute kidney injury	64.5–68.8%	Immediate	Supportive care; dialysis
Neurologic	9.2%	Within 2 weeks	
Stroke	41% of all neurological complications		Standard stroke care including transesophageal echocardiography and secondary stroke prevention [92–94]
Metabolic encephalopathy	37% of all neurological complications	Immediate	Identify and treat underlying causes, dialysis, reduction of immunosuppression, protein restriction, empiric fluoroquinolone, or macrolide if caused by hyperammonemia [90, 92]
Posterior reversible encephalopathy	Rare		Discontinuation of calcineurin inhibitor; strict blood pressure control [95]
Seizure			Antiepileptics; correction of underlying etiology [97]
Cardiovascular			

Table 1 (continued)

Complications	Incidence	Time of onset post-transplant	Management
Arrhythmia	25–35%	2 days	Rate control and anti-arrhythmic agents with specialist consultation; emergent cardioversion if hemodynamically unstable [111]
Vasoplegia	32%	Immediate	Vasoactive agents; glucocorticoids; supportive care [112]

infiltration on chest radiography) at 72 h after transplant is an ominous sign for short- and long-term outcomes, and is associated with a 30-day mortality as high as 50% [1, 7]. Clinical signs of PGD include increased pulmonary vessel resistance, decreased compliance of the lungs, and formation of intrapulmonary shunts [2]. Limiting the length of cold ischemia, extending reperfusion time, and lung protective ventilation could help mitigate the development of PGD. Use of inhaled nitric oxide aids in the correction of oxygenation and ventilation-perfusion (V/Q) mismatch, while decreasing pulmonary artery pressure [2]. Extracorporeal membrane oxygenation (ECMO) can be lifesaving, improving survival by 50–80% [2], with expected survival to hospital discharge of 40–70% [8], 30-day survival of 82%, and a 1-year survival of 64% [9]. Maximal benefit is achieved when ECMO is implemented within 24 h post-transplant, with less benefits if instituted after 24 to 48 h post-transplant [10]. It is generally indicated when there is inadequate oxygenation through ventilator support requiring 60% FiO2 or higher, or when ventilator requirements reach a peak inspiratory pressure of 35 centimeters of water (cmH2O) with the goal of reducing oxidative stress and barotrauma to the allograft [9]. There are, however, no specific indications for use of ECMO post-transplant, and should be decided on a case-by-case basis. Supportive management remains the cornerstone for managing severe PGD.

Airway complications

There are 6 categories of airway complications post-lung transplantation: bronchial stenosis, bronchial dehiscence, exophytic excessive granulation tissue formation, tracheo-bronchomalacia, bronchial fistulas, and endobronchial infections [11]. Incidence of airway complications has been reported to be 15–20% of lung transplant recipients [12, 13], possibly due to ischemia of the donor bronchus [14]. Most complications occur after tissue remodeling and healing has taken place, but bronchial necrosis and dehiscence can present in the first 1 to 5 weeks, with an incidence of 1–10% [11]. Bronchial stenosis is the most common form of airway complication, presenting at around 2–9 months post-transplant, with a reported incidence of 1.6–32% [15]. It may be related to tracheo-bronchomalacia if there is 50% or greater narrowing of the airway lumen on expiration [15]. Balloon bronchoplasty is suggested for first-line therapy [11, 16]. Stent placement is used for severe bronchial stenosis with high complication rate from 48 to 75%, though with comparable survival rates to those without airway complications [17]. A study by Ma et al. reported that forced expiratory volume in 1 s (FEV1) may only improve in patients who could undergo stent placement, and ultimately can tolerate stent removal [18]. Various treatment strategies have been reported including radiofrequency ablation in airway dehiscence [19], single running suture technique to mitigate anastomotic complications [20], laser photoresection, and bronchial artery revascularization, with variable success [15].

Vascular complications

Incidence of vascular anastomotic complications ranges from 1.8 to 5.2% [21, 22] with higher incidence of pulmonary artery stenosis compared to pulmonary venous stenosis due to surgical technique and orientation of donor and recipient vasculature. It can present with non-specific symptoms including cough, dyspnea, pulmonary edema, hypoxia, and a need for mechanical ventilation. Mean time to diagnosis has been reported to be 9 days. Different imaging modalities including contrast-enhanced computed tomography (CT), echocardiography, magnetic resonance imaging (MRI), V/Q scans, and intraoperative ultrasound have been used for diagnosis of vascular complications [21]. There are 5 types of vascular complications: kinking due to excessive length of donor and recipient vasculature and misalignment, transposition of donor vessel, stricture of anastomosis from overtightening or misalignment of suture line, obstruction from thrombosis or dissection, and extra luminal mass

Table 2 2016 International Society for Heart and Lung Transplantation primary graft dysfunction definition

Grade	Pulmonary edema on chest radiograph	PaO2/FiO2 ratio
0	No	>300
1	Yes	>300
2	Yes	200 to 300
3	Yes	<200

PaO2 serum partial pressure of oxygen, *FiO2* fraction of inspired oxygen

effect. Pulmonary artery stenosis is defined as anastomotic diameter of less than 75% compared to surrounding vessels [23]. Pulmonary vascular stenosis is rare and usually occurs in the first 48 h after lung transplantation [21]. In severe cases, endovascular intervention including thrombectomy, stent angioplasty [24], repeat surgery, re-transplantation, or lobectomy may be required.

Diaphragm injury

Diaphragm dysfunction can occur during lung transplant secondary to phrenic nerve injury. Several retrospective studies report a 3.2–8.2% incidence of diaphragmatic paralysis [25–27]. Diaphragmatic dysfunction could be further characterized by decreased force and electrical activity caused by slowed phrenic nerve conduction from myelin dysfunction, and weakness [28]. Diaphragm electromyography has been used in assessing the degree of diaphragm dysfunction [29]. Spontaneous diaphragm rupture has also been reported [30]. Prolonged CPB use, prior cardiothoracic surgery, and prior ECMO increase the risk of severe diaphragm dysfunction [27]. Consequences of diaphragmatic injury include longer duration of mechanical ventilation time and prolonged intensive care unit (ICU) stay. A large single-center study demonstrated that diaphragmatic injury is related to increase in PGD, decrease in survival, and increase in mortality [27]. Diaphragmatic paresis can ultimately recover with time and supportive measures with non-invasive ventilation if needed are the mainstay therapy for those with carbon dioxide retention.

Pleural complications

The incidence of pleural complications following lung transplant is 22–34% [31, 32]. They include hemothorax, chylothorax, pneumothorax, empyema, and air leaks. Uncomplicated effusions occur in all cases and are ipsilateral to the transplanted lung [31]. Uncomplicated effusions usually resolve within 2 weeks [33, 34]. Complicated effusions are associated with poor patient outcomes [31, 32, 35] and occur more commonly in double lung transplant recipients [32]. The incidence of hemothorax is between 12 and 18% with a trend towards increase in sarcoidosis and re-transplantations [31, 36, 37]. Morbidity and mortality are related to hemodynamic instability, need for vasopressor use, and surgical re-exploration in up to 46–65% of cases [31, 37]. Patients have longer ICU and hospital length of stay, decreased ventilator-free days, decreased 30- and 90-day survival, but similar 1-, 3-, and 5-year survival [37, 38].

Chylothorax occurs due to interruption of the thoracic duct and leakage of chyle into the pleural space. In a case series, 7 of 504 (1.38%) patients developed chylothorax, 5 of which had underlying pulmonary fibrosis [35]. Dietary modifications with low-fat, medium-chain-triglyceride diet or total parenteral nutrition along with chest tube drainage and octreotide were insufficient for treatment and most required surgical intervention [35].

Incidence of empyema ranges from 3 to 8% [31, 32, 39, 40]. There is no difference between single and double lung transplant recipients, and no increased risk due to differences in demographics [39, 40]. Recognition is difficult due to blunted clinical manifestations in immunosuppressed patients [33, 40]. Causative organisms range from gram-negative bacteria (25%) to fungi (61%), most commonly *Candida albicans*. Infections are monomicrobial in 71.4% of cases and polymicrobial in 14.3%. In 14.3% of cases, no causative organism is identified [33, 39, 40]. Empyema causes increased morbidity and mortality in lung transplant recipients. In one study, 2 out of 3 patients with empyema died [31]. Herridge et al. reported that 7 of 30 patients with para-pneumonic effusion developed empyema, and 3 of those 7 died from septic shock [32]. Another study reported a mortality rate of 28.6% [39]. Wahidi et al. reported an overall 1-year survival rate post-lung transplant of 87%, with a statistically significant lower survival rate of 67% if empyema occurred [40]. Cystic fibrosis has not been shown to have an increased rate of development of postoperative empyema [39].

Air leaks and pneumothorax

Air leaks and pneumothorax can occur due to donor-recipient size mismatch, bronchopleural fistulas, dehiscence of bronchial anastomoses, infection, rejection, or ischemia [31–34]. Herridge et al. reported 14 pneumothoraces out of 138 patients [32]; Ferrer et al. reported 8 out of 100 patients [31]. Two of the patients died, one due to anastomotic rupture, one due to *Aspergillus* infection from a concomitant air leak [41]. Air leaks can be transient or persistent if they last longer than 7 days. The prevalence of prolonged air leak ranges from 1 to 10% [31, 32]. In a series by Ferrer et al., 10 out of 100 patients had persistent air leak, of which 7 had undergone bilateral lung transplant. Five of 7 died in the postoperative period. Among the 5 who survived, 3 air leaks resolved spontaneously and 2 required operative intervention [31].

Rejection

Incidence of acute rejection in the first year has decreased from 55% to 17–28% [42–44]. Though rarely the cause of death, acute rejection is the greatest risk factor for development of chronic rejection, limiting median post-transplant survival to about 6 years [44]. Mangi et al. showed that acute rejection was most common and severe (54% ≥ A1) in the first 2 months. Young age, blunt trauma, non-black race, class II

panel-reactive antibody (PRA) exceeding 10%, human leukocyte antigen (HLA) mismatch at the DR locus, and use of non-O blood-group donors were associated with increased rate of rejection [45]. Increased incidence is also seen after infections with human influenza A, respiratory syncytial virus, rhinovirus, coronavirus, parainfluenza, and human metapneumovirus [46]. Grade A2 acute cellular rejection or higher is treated with pulse steroids. Persistent or refractory rejection can be treated with additional intravenous glucocorticoids, antithymocyte globulin, alemtuzumab, total lymphoid radiation, and extracorporeal photopheresis [47].

Diagnostic criteria for antibody-mediated rejection (AMR) were newly established in 2016. It is diagnosed when there is presence of antibodies against donor HLA seen on lung biopsy of the lung allograft, with or without the presence of complement 4d within the graft [48]. Importantly, AMR may be clinical (dysfunction of the allograft without symptoms) or sub-clinical (normal allograft function) [48]. True incidence and prevalence of AMR are unknown as its diagnostic criteria have only recently been standardized. Witt et al. found 21 cases of AMR among 501 lung transplant recipients. Median time to development was 258 days after transplantation; 7 recipients developed AMR within 45 days. Fifteen patients improved and survived to hospital discharge; 5 died of refractory AMR. One survivor had bronchiolitis obliterans syndrome (BOS) at the time of AMR diagnosis, and the other 14 developed it during follow-up. Median survival after AMR diagnosis was 593 days [49].

Treatment for AMR includes administration of intravenous immunoglobulin (IVIG), plasmapheresis, and rituximab alone or in combination. Proteasome inhibitors like carfilzomib or bortezomib have been used, as well as eculizumab, an antibody targeting the C5 complement protein. Data is lacking regarding the best combination strategies in management of AMR [49, 50].

Infection

Infections account for significant morbidity and mortality in lung transplant recipients leading to accelerated graft failure. Risk factors for infectious complications include prolonged illness, organ dysfunction, immunosuppression, antimicrobial use, and poor nutritional state [51].

In the immediate postoperative period, donor-derived pathogens account for most infections and include community- and hospital-acquired pathogens like methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas*, *Enterobacter*, and multidrug-resistant bacteria. Bacterial infections can present as pneumonia, para-pneumonic effusions, mediastinitis, empyema, cholangitis, anastomotic leaks, catheter-associated infections, and surgical wound dehiscence. Rapid diagnosis is warranted to identify source and pathogens to minimize drug toxicity and prolonged antimicrobial use. Meticulous attention is required to identify the source as features of sepsis may be absent and timely surgical interventions are critical.

Cytomegalovirus (CMV) infections most commonly occur in the first 6 months after transplant without prophylactic therapy. The greatest risk for primary infection is seronegative recipients of seropositive organs with up to 91.9% incidence of viremia and 50–65% of symptomatic infections by 90 days [52]. Lung recipients (D+ or R+) are at high risk for viral reactivation and for adverse effects of CMV infection [53]. Though many viremic infections remain asymptomatic, organ manifestations include pneumonitis, hepatitis, pancolitis with ulceration, and less commonly retinitis and encephalitis.

Common fungal pathogens seen in transplant recipients include *Candida*, *Aspergillus*, *Cryptococcus neoformans*, and endemic mycoses. Highly aggressive species like mucormycosis, *Scedosporium*, and *Fusarium* are becoming more common and demonstrate high levels of resistance to antifungals. Common risk factors include prior colonization, neutropenia, lymphopenia, immunosuppression, viral co-infections such as CMV and human herpes virus 6 (HHV6), diabetes, and use of antimicrobial agents [54]. In the early post-transplant period, *Candida* infections typically present as candidemia, superinfection of esophageal lesions due to herpes simplex virus (HSV), CMV, as well as infections of tracheal anastomoses. One dreaded manifestation is mycotic aneurysm formed by vascular anastomotic infections that can rupture. *Aspergillus* is a common colonizer with >25% rate of colonization in lung transplant recipients. Invasive aspergillosis accounts for 6% of infections and includes tracheobronchitis, bronchial anastomotic infections, and invasive pulmonary (32%) and disseminated (22%) infections. The rates are higher in patients with cystic fibrosis and single lung recipients [55].

Clostridium difficile (*C. difficile*) affects up to 30% of solid organ transplant (SOT) recipients with the highest incidence in lung recipients (7–31%) [56]. Risk factors unique to SOT recipients are use of antithymocyte globulin, hypogammaglobulinemia, re-transplantation, and the type of organ transplanted [56]. Diagnosis and treatment of *C. difficile* infection in transplant recipients present unique challenges and require a multidisciplinary approach.

Bleeding and thromboembolic events

There is increased incidence of bleeding and thromboembolic events in the immediate post-transplant period. In patients requiring ECMO or CPB, increased incidence of bleeding is observed due to the need for full systemic anticoagulation [8, 57, 58]. One study described a 12.9% incidence of hemothorax occurring on average 9-days post-transplant, with delayed hemothorax occurring in patients on anticoagulation. In some

cases, re-thoracotomy is needed due to severe bleeding [59]. At the Ochsner Multi-Organ Transplant Institute, 5 out of 208 patients who required CPB required re-explorations for bleeding occurring in the perioperative period [60].

Venous thromboembolism (VTE) is a well-known complication of lung transplantation [61–65] and is associated with lower survival rates among lung transplant recipients [66]. The reported incidence of VTE in the immediate postoperative period, however, is variable, with some reporting an incidence of 5–15% for pulmonary embolism (PE) and 20–45% for deep vein thrombosis (DVT) [66–68]. A single-center review of lung transplant recipients described a median interval to diagnosis of upper extremity DVT of 8 days, that of lower extremity DVT of 5.4 months, and that of PE of 7.5 months [66]. Intraoperative CPB or ECMO was associated with lower incidence of PE. All PEs observed were in the allograft. Patients who had developed VTE within the first 5 days postoperatively had higher risk of later developing VTE; chemical prophylaxis for VTE was noted to be a modifiable risk factor [68]. All patients with PE had evidence of DVT at some point during their postoperative course. Patients with lower extremity DVT are twice as likely to die than those without lower extremity DVT [66].

Treatment varies from full systemic anticoagulation with enoxaparin, warfarin, or heparin, to inferior vena cava filter placement, embolectomy, and surgical revision of venous anastomosis.

Renal dysfunction

Renal dysfunction in lung transplant patients is associated with worse outcomes and increased risk for death [69, 70]. Preoperative risk factors include increase in systolic blood pressure, decline in renal function, and a history of pulmonary hypertension [71]. Postoperative risk factors include irregularity in hemodynamics and use of nephrotoxic immunosuppressants like cyclosporine, a calcineurin inhibitor [72]. Cyclosporine-induced acute nephrotoxicity is caused by the constriction of afferent arterioles, which is presumed to be due to renin-angiotensin activation, sympathetic nervous system stimulation, increased endothelin-1 and thromboxane production, and nitric oxide suppression [73]. While acute nephrotoxicity of cyclosporine is dose-dependent and reversible upon discontinuation, chronic nephrotoxicity—caused by a change in renal architecture including atrophy of renal tubules, glomerulosclerosis, and tubulointerstitial fibrosis—can lead to permanent damage [73].

The use of tacrolimus instead of cyclosporine and basiliximab induction therapy can be protective against acute kidney injury (AKI) [74]. However, hemolytic uremic syndrome (HUS) can occur with use of cyclosporine or tacrolimus [75, 76]. Laboratory results would show elevated lactate dehydrogenase, thrombocytopenia, and signs of azotemia and schistocytes on peripheral blood smear [77].

AKI can occur in the early post-lung transplant period [70, 78]. It is associated with increased short- and long-term mortality [78]. In one retrospective study, 64.5% of the patients developed AKI in the first 2 weeks post-transplant [70]. Patients with AKI had significantly diminished survival rates than those without [74]. Patients with AKI were also kept on invasive mechanical ventilator longer, received more tracheostomies, had higher need for ECMO, and required vasoactive administration for longer periods of time compared those without [74]. In another retrospective cohort study, 68.8% of lung transplant patients developed AKI within the first week after transplant, 51.3% of which had early recovery [79]. Those with transient AKI experienced fewer complications such as tracheostomy, lower incidents of chronic kidney disease (CKD) at 1- and 3-years post-transplant, and shorter need for invasive mechanical ventilation [79]. Higher body mass index (BMI), use of immunosuppressant drugs such as cyclosporine, longer duration of mechanical ventilator, and CKD stages II and III are some of the factors associated with persistent AKI [79].

AKI increases the chance of developing CKD after lung transplant [70]. The incidence of CKD at 1-year post-lung transplant was reported as 5.8% in those recipients who did not develop AKI in the immediate post-transplant period. This incidence increased to 12.8–24.5% in those who developed some degree of AKI [70]. CKD development among non-renal transplant recipients is associated with a 4-fold increase in the risk of death [69].

Gastrointestinal complications

Gastrointestinal (GI) complications after lung transplantation are common and carry significant morbidity and mortality [80]. GI complications range from nausea, vomiting, gastritis, and diarrhea, to emergencies like bowel perforation or bleeding from the GI tract [81]. The rate of GI complications in lung transplant recipients can be as high as 50% or more [80, 81]. The majority of complications are associated with immunosuppressive medications and manifest as biliary tract disease—at times requiring cholecystectomy—opportunistic infections, mucosal injury, viscus perforations, pancreatitis, or malignancies [81–83].

There is high incidence of motility disorders after lung transplant [84]. Anatomical proximity and hemodynamic changes can cause injury to the vagus nerve during surgery, resulting in delayed gastroparesis and bowel obstruction [84, 85]. *C. difficile* colitis and CMV gastroenteritis are also common [86].

There is a high preoperative prevalence of gastroesophageal reflux disease (GERD) in end-stage lung disease patients

[80, 87, 88], and lung transplantation may increase the risk of GERD and peptic ulcer disease [88]. Several studies showed a link between GERD and aspiration that may result in the development of BOS [88, 89].

Serious GI complications can occur that require surgical management. A study reported that over a period of 19 months, about 10% of recipients with acute abdomen needed surgical intervention [83]. Rare complications like superior mesenteric artery syndrome and pneumatosis intestinalis were are also reported [86].

Neurological complications

A study of 700 lung transplant recipients found a 9.2% incidence of neurologic complications in the first 2-weeks post-transplantation including stroke and metabolic encephalopathy [90–92]. Patients with neurologic complications have an increased 90-day mortality compared to lung transplant recipients without [92]. Approximately 5–10% of lung transplant recipients suffer from stroke [93, 94]. In a large retrospective study ($n = 759$), 90-day mortality rate in patients with neurological complications was 15%, versus 4% among recipients who did not develop neurological complications [92]. Recipients with neurological complications had a prolonged length of stay and increased duration of mechanical ventilation [92, 93]. Lung transplant recipients with suspected stroke should undergo timely imaging with CT or MRI of the brain with angiography to identify large vessel occlusion. A transthoracic or transesophageal echocardiography should also be done if cardioembolic stroke is suspected. As with standard of care, secondary stroke prevention includes consideration for antiplatelet therapy or anticoagulation.

Severe hyperammonemia has been described with a 1% incident rate 2-weeks post-transplant [90]. Treatment of hyperammonemia includes dialysis, reduction of immunosuppression, protein restriction, and use of empiric fluoroquinolone or macrolide to eradicate urea-splitting organisms [90].

Posterior reversible encephalopathy (PRES) is rare after lung transplantation associated with calcineurin inhibitor use, with an incidence of about 1.9% [95]. Patients usually present with headache, altered mental status, visual disturbances, focal neurological deficits, and seizures. Recipients with PRES may require temporary discontinuation of calcineurin inhibitor use and tight blood pressure control [96]. Lung transplant recipients can also have seizures due to stroke, medication toxicity, PRES, and hyperammonemia [97]. It is crucial to initiate antiepileptic medications while managing underlying etiology of seizures.

Musculoskeletal and neuropathic complications

Several studies show a significant reduction in skeletal muscle strength and function including respiratory and limb muscles in lung transplant recipients [98, 99]. Critical illness myopathy or neuropathy is a persistently observed complication in lung transplant recipients, unrelated to the pre-transplant diagnosis and the type of surgery [98, 100]. Reduced muscle mass and strength are consistently seen in patients with end-stage lung disease. In a systemic review, quadriceps muscle weakness was found to be further decreased in the early postoperative phase [98, 99]. Possible etiology includes reduced postoperative activity and deconditioning, corticosteroid-induced muscle damage, critical illness-related neuropathy or myopathy, therapy with calcineurin inhibitor, and impaired skeletal muscle oxidative capacity [34, 99]. Duration of mechanical ventilation, use of sedatives and steroids, longer duration of immobilization, and inactivity are significantly related to ICU-acquired weakness [101].

Aggressive pre-transplant and early post-transplant rehabilitation is crucial to maintain functional status [98, 99]. A randomized controlled trial noted a significant improvement in quadriceps muscle force and functional capacity in uncomplicated lung transplant recipients with a 3-month rehabilitation program [102]. Identifying risk factors, early mobilization in ICU, and frequent bedside neuromuscular examination can help alleviate the impact of critical illness-related weakness.

Local wound complications after lung transplant

Wound dehiscence can occur even after careful suturing and closure, and is a potential complication in lung transplantation, especially in patients with a clamshell incision [103–105]. Wound dehiscence is commonly seen in the first week after surgery, but may present later due to poor wound healing. Mechanical factors including continuous motion and tension in the thoracic region, and individual factors including older age, hemodynamic stability, wound infection, and underlying comorbidities are associated with increased wound dehiscence [106]. Various pathogens that are associated with nosocomial infections such as *Pseudomonas aeruginosa*, *S. aureus*, *Mycoplasma hominis*, and *Candida* are associated with the wound infections [107–109]. However, infection of the skin and soft tissues around the surgical site is not very common.

Cardiovascular complications

Atrial arrhythmias including atrial flutter, atrial fibrillation, and supraventricular tachycardia (SVT) are frequently encountered in the early postoperative period after lung transplantation [34]. Incidence is high, occurring in 25–35% of recipients. Age, pre-transplant diagnosis of idiopathic pulmonary fibrosis, left atrial enlargement, diastolic dysfunction, and coronary artery disease (CAD) are major risk factors for

developing atrial fibrillation, while age, right ventricular enlargement, elevated right atrial pressure, and right ventricular dysfunction were predictors of atrial flutter or SVT [110]. Rate control is the first-line therapy; however, many required a combination of rate control and anti-arrhythmic medications, with a study showing dofetilide/ibutilide to be a helpful addition [111]. Cardioversion may be indicated if hemodynamic instability presents.

Shock is common after lung transplantation generally due to postop vasoplegia. Vasoplegia is characterized by the pathological loss of vasomotor tone refractory to fluid resuscitation or vasopressors, normal to high cardiac index, and hypotension. It occurs at high rates in the early post-transplant period and contributes to significant morbidity. Manikavasagar et al. found 32% incidence of vasoplegia and suggest the potential involvement of oxidative stress in the development of this syndrome [112]. Use of CPB has been implicated in vasoplegia due to immunogenic effect. Anecdotally, use of methylene blue in CPB-induced vasoplegia has been effective in increasing mean arterial pressure intraoperatively [113].

Myocardial infarction incidence in lung transplant recipients is not fully described in current literature. It often occurs late after transplantation and can be caused by air embolism from bronchial-coronary fistula [114] or arterial thrombosis related to inflammation and immunosuppressive therapy [115].

Other rare causes of post-lung transplant cardiac complications include cardiac tamponade secondary to pneumopericardium [116, 117], and pericardial constriction causing cardiac diastolic dysfunction—of which only 2 cases have been reported post-transplantation [118].

Heart-lung transplantation

Combined heart-lung transplantation developed in parallel with heart transplantation and lung transplantation, with the first operation performed in 1981 [119] and growth in the 1980s driven by improvements in surgical techniques and immunosuppressive therapy. However, heart-lung transplants have become much less common in the recent era, with ISHLT reporting a peak of 263 cases in 1989 and 62 cases in 2017 [120]. This decrease has been driven by growth in isolated lung and heart transplantation, better perioperative management of isolated lung and heart transplant recipients, and optimizing use of scarce donor organs.

Heart-lung transplantation is performed by anastomosis of the donor and recipient trachea, ascending aorta, and superior and inferior vena cavae. These bronchial and vascular structures are susceptible to the same technical complications as in isolated lung transplantation, but at a lower frequency due to their larger size.

Lung transplants are more susceptible to dysfunction than heart transplants, and this experience carries into the population with combined heart-lung transplants. Additionally, there is some evidence to support that combined heart-lung transplantation is protective of dysfunction of both allografts [121].

Conclusion

The medical and surgical community is tasked with the great challenge of caring for lung transplant recipients. There have been immeasurable improvements since the first human lung transplant was performed in 1963. With ever-changing innovations in treatment strategies, however, decisions should be informed by the development of guidelines and consensus statements. A multidisciplinary approach which leverages specialists from surgical, medical, and rehabilitation services is key to improving post-lung transplant survival.

Abbreviations AKI, Acute kidney injury; AMR, Antibody-mediated rejection; BOS, Bronchiolitis obliterans syndrome; BMI, Body mass index; *C. difficile*, *Clostridium difficile*; CAD, Coronary artery disease; CAV, Cardiac allograft vasculopathy; CKD, Chronic kidney injury; CMV, Cytomegalovirus; CPB, Cardiopulmonary bypass; CT, Computed tomography; D+, CMV-seropositive donor; DVT, Deep vein thrombosis; ECMO, Extracorporeal membrane oxygenation; FEV1, Forced expiratory volume in 1 s; GERD, Gastroesophageal reflux disease; GI, Gastrointestinal; HHV6, Human herpes virus 6; HLA, Human leukocyte antigen; HSV, Herpes simplex virus; HUS, Hemolytic uremic syndrome; ICU, Intensive care unit; ISHLT, International Society for Heart and Lung Transplantation; IVIG, Intravenous immunoglobulin; MRI, Magnetic resonance imaging; MRSA, Methicillin-resistant *Staphylococcus aureus*; PE, Pulmonary embolism; PGD, Primary graft dysfunction; PRA, Panel-reactive antibody; PRES, Posterior reversible encephalopathy; R+, CMV-seropositive recipient; SOT, Solid organ transplant; SVT, Supraventricular tachycardia; V/Q, Ventilation-perfusion; VTE, Venous thromboembolism

Funding None.

Declarations

Research involving human participants and/or animals Not applicable as the scientific information presented in the paper does not fall into category of clinical trial or usage of experimental modalities.

Informed consent Not applicable as this is a literature review and no subjects were involved.

Conflict of interest The authors declare no competing interests.

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