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REVIEW

Primary graft dysfunction following lung transplantation: From pathogenesis to future frontiers

Sanjeet Singh Avtaar Singh, Sudeep Das De, Ahmed Al-Adhami, Ramesh Singh, Peter MA Hopkins, Philip Alan Curry

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Abstract

Lung transplantation is the treatment of choice for patients with end-stage lung disease. Currently, just under 5000 lung transplants are performed worldwide annually. However, a major scourge leading to 90-d and 1-year mortality remains primary graft dysfunction. It is a spectrum of lung injury ranging from mild to severe depending on the level of hypoxaemia and lung injury post-transplant. This review aims to provide an in-depth analysis of the epidemiology, patho-physiology, risk factors, outcomes, and future frontiers involved in mitigating primary graft dysfunction. The current diagnostic criteria are examined alongside changes from the previous definition. We also highlight the issues surrounding chronic lung allograft dysfunction and identify the novel therapies available for ex-vivo lung perfusion. Although primary graft dysfunction remains a significant

contributor to 90-d and 1-year mortality, ongoing research and development abreast with current technological advancements have shed some light on the issue in pursuit of future diagnostic and therapeutic tools.

Key Words: Primary graft dysfunction; Lung transplantation; Pathophysiology; Risk factors; Extracorporeal membranous oxygenation

Core Tip: Primary graft dysfunction is spectrum of lung injury ranging from mild to severe depending on the level of hypoxaemia and lung injury post-transplant. It has significant bearings on short and long term mortality and morbidity with chronic lung allograft dysfunction playing a major part. While the pathophysiology remains uncertain, it is felt to be a result of ischaemic reperfusion injury. The contributive factors, risks and treatment and management options are scrutinized in this manuscript to provide the readers with a clear insight into the enigma that is primary graft dysfunction.

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INTRODUCTION

Lung transplantation remains the only definitive treatment for patients with end-stage lung disease due to obstructive lung disease, fibrotic lung disease, vascular lung disease, and other causes (*e.g.*, infection). In highly selective conditions, it may also be used in pulmonary malignancy[1]. The first successful lung transplant procedure was performed in Toronto, 19 years after the first heart transplantation[2]. In the current era, just under 5000 adult lung transplants are performed annually worldwide[3]. Primary graft dysfunction (PGD) after lung transplantation represents a spectrum of lung injury ranging from mild to severe depending on the level of hypoxaemia and lung injury post-transplant[4]. It is characterised by radiographic findings of non-specific pulmonary infiltrates and hypoxaemia. It represents the leading cause of early mortality post-transplantation and phenotypically resembles acute respiratory distress syndrome (ARDS)[4]. Prior to 2005, there was no unified definition for PGD, making it difficult to ascertain a true incidence. Different terms were also used to define the syndrome, indicative of possible pathogeneses, such as ischaemic-reperfusion lung injury, primary non-function of the lung, early graft dysfunction, reperfusion oedema, re-implantation oedema, primary graft failure, post-transplant acute respiratory distress syndrome, acute lung injury and non-cardiogenic pulmonary oedema[5]. There were also significantly variable rates of associated risk factors and mortality indicating the need for a consensus definition[6-8].

It is a major cause of early morbidity and mortality at 90-d (up to 23%) and 1 year (up to 34%)[9]. Diagnosis initially relied on the degree of hypoxaemia but has since been updated to primarily be reliant on chest radiograph findings and the degree of support required[10].

INTERNATIONAL SOCIETY OF HEART AND LUNG TRANSPLANTATION 2005 AND 2016 STATEMENT

In 2005, the International Society of Heart and Lung Transplantation (ISHLT) published a standardised definition of PGD. In summary, the assessment was performed by evaluating the PaO_2/FiO_2 (P/F) ratio and the presence of bilateral infiltrates on a chest radiograph. These assessments are carried out at 6 h, 24 h, 48 h, and 72 h post-operatively and should be measured on FiO_2 of 1.0 with positive end-expiratory pressure (PEEP) of 5 cmH_2O.

Radiographic findings of PGD are relatively non-specific including perihilar ground glass opacities, reticular interstitial, and parenchymal opacities, alongside perivascular thickening.

In 2016, an updated ISHLT statement specified a 'start' time for the PGD clock beginning after the removal of the PA cross-clamp of the second lung. The commencement of reperfusion is noted to be T0 with assessments performed at T24, T48, and T72 h as per the 2005 edition. However, the absence of pulmonary oedema on radiographic imaging should be classified as grade 0 regardless of the PaO_2/FiO_2 ratio. This is highlighted in Table 1 below.

Table 1 The International Society for Heart and Lung Transplantation primary graft dysfunction definition and severity grading 2005 and 2016

PGD stage	PaO_2/FiO_2 ratio (mmHg)	Chest X-ray findings	2016 update
0	> 300	Normal	Any P/F ratio
1	> 300	Diffuse allograft infiltration/pulmonary oedema	No changes
2	200-300	Diffuse allograft infiltration/pulmonary oedema	No changes
3	< 200	Diffuse allograft infiltration/pulmonary oedema	No changes

PGD: Primary graft dysfunction.

Another pertinent detail is the inclusion of an adjunct for the PaO_2/FiO_2 ratio due to the high incidence of missing data from the lack of partial pressure of arterial oxygen (PaO_2) measurement using oxygen saturations instead (SaO_2/FiO_2), with different cutoffs of 235 and 315[10].

Despite this, the consensus statement remains a work in progress with several areas requiring further evaluation. For instance, subjects on mechanical ventilation with FiO_2 > 50% or requiring inhaled nitric oxide (iNO) beyond T48 are classified as grade 3 PGD alongside patients on mechanical circulatory support. In addition, the definition has not taken into account the debate of single versus double lung transplantation. In an era of increasing austerity in organ allocation, the need to compare outcomes is of utmost importance and has been highlighted. Oto *et al*[11] identified an increased rate of PGD grade 3 in recipients of single lung transplants compared to bilateral transplants although the authors noted several differences such as protective ventilation strategies in the single lung transplant cohort and earlier extubation times which would invariably affect the PaO_2/FiO_2 ratio. Their study shed some light on the applicability of the current definition, especially in the single lung transplant cohort. Other potential mechanisms for the higher incidence of PGD in single lung transplant recipients include the admixture of poorly oxygenated blood associated with shunting in the native lung, higher cardiac output *via* the relatively lower pulmonary vascular resistance of the graft vasculature, and increased relevance of changes in the unilateral transplanted lung. The use of MCS may also be misleading as the role of 'prophylactic' extracorporeal membranous oxygenation (ECMO) institutions in high-risk recipients may lead to an overestimation of the true incidence of PGD, which raises questions regarding an interventional-based severity grade[12].

EPIDEMIOLOGY

Early reports following the 2005 consensus definition indicated an incidence of around 30% early post-transplant and reduced to just under 20% at T72[8]. However, 10%-20% of these patients contract the severe form, PGD grade 3[8,9]. The higher incidence of PGD reported early on is probably due to the clinical and pathological similarities it shares with reversible pulmonary oedema, ARDS, and transfusion-related acute lung injury (TRALI). Analysis of the United Network for Organ Sharing (UNOS)/ISHLT database (1994-2000) noted a significantly higher all-cause mortality in all PGD *vs* non-PGD comparisons at 30 d (42.1% *vs* 6.1%, $P < 0.001$) and 1 year (64.9% *vs* 20.4% $P < 0.001$)[13]. A subsequent study by Diamond *et al* using the 2005 definition highlighted an overall PGD grade 3 rate of 30.8%, reducing to 16.8% after the exclusion of PGD Grade 3 classifications before T48[9]. Christie *et al*[4] noted increasing mortality with each grade of PGD. This ordinal pattern was present at all time points following the transplant (T24, T48, T72). PGD Grade 3 had the highest mortality which was also replicated in an analysis of biomarkers of insult severity. Many studies have used PGD grade 3 as a dichotomous outcome when discriminating between PGD and non-PGD due to the more distinct features *i.e.*, prolonged mechanical circulatory support, mechanical ventilation with FiO_2 > 50%, iNO or iEPO usage, and PaO_2/FiO_2 ratio < 200, leaving little room for ambiguity.

Given the heterogeneity in the locoregional donor, recipient, and procedural characteristics, ascertaining the true epidemiology of the lesser grades of PGD is slightly more challenging and remains variable. Another important consideration for PGD is the link with chronic lung allograft dysfunction (CLAD). Table 2 shows the phenotypes of CLAD.

CLAD

Bronchiolitis Obliterans syndrome was the term initially coined to describe allograft dysfunction occurring after lung transplantation. Ischaemic reperfusion injury plays a major part in the pathophysiology as highlighted in Figure 1. This syndrome has since undergone several revisions and

Table 2 Basic phenotypes of chronic lung allograft dysfunction

Phenotypes	Spirometry changes	CT opacities
CLAD	Persistent ≥ 20% decline in FEV1 (based on 2 FEV1 values ≥3 wk apart) compared to baseline	
BOS	CLAD and obstruction (FEV1/FVC < 0.7)	No
RAS	CLAD and restriction (≥ 10% decline in TLC from baseline)	Yes
Mixed phenotype	CLAD with obstruction and restriction	Yes
Undefined phenotype	CLAD with obstruction and/or restriction	Yes/No

Adapted from the 2019 Consensus Definition. FVC: Forced vital capacity; BOS: Bronchiolitis obliterans syndrome; RAS: Restrictive allograft syndrome; CLAD: Chronic lung allograft dysfunction; CT: Computed tomography.

refinements with the most recent definition using the umbrella term CLAD highlighting a series of phenotypes post transplantation[14].

According to the 2019 consensus statement, CLAD is defined as a substantial and persistent decline [≥ 20% in measured forced expiratory volume in one second (FEV1)] in the baseline. This is broadly classified into obstructive ventilatory pattern, restrictive, or mixed[14].

The tipping point is the drop in FEV1 with/without a change in the forced vital capacity. Secondary causes should be ruled out such as surgical complications, infections, rejection, and mechanical obstructions (effusions, stenosis, tumours, *etc*)[14]. After investigating, managing, and ruling out the secondary causes, there should be at least 3 wk between the first and 2nd FEV1 readings that indicate the reduction (≥ 20%). The staging of CLAD is also shown in Table 3.

Pathophysiology

The exact pathophysiology behind PGD remains unclear but is thought to be a summation of multiple insults that occur during the procurement, storage, and implantation of the lung. Ischaemic-reperfusion injury (IRI) is thought to be a major contributor to the pathophysiology. Native lungs have a dual vascular supply *via* bronchial vessels and pulmonary circulation, alongside available oxygen from alveolar ventilation. The pathogenic mechanism of IRI in the lungs, therefore, differs from other end organs which are often rendered ischaemic on cessation of blood flow[15]. From an anatomical perspective, there is a change in the vasculature of the lungs post-transplantation. In the native lungs, the airways are supplied by a dual circulation derived from the bronchial arteries and the pulmonary artery[16]. The post-transplant lung has the pulmonary artery circulation surgically restored but the bronchial anastomosis and distal airways may be exquisitely susceptible to further ischemia and hypoxic injury due to the loss of these bronchial arteries.

On a molecular level, IRI is driven but the formation of reactive oxygen species (ROS) (Figure 2). Traditionally, the lung is hypothermically stored to reduce the metabolic oxygen demand - hence reducing the rate of biochemical reactions which results in attenuated degradation of cellular components[17]. Adenosine triphosphate (ATP) stores however continuously deplete, which inactivates the ATP-dependent membrane pumps[15]. This causes accumulation of cytosolic calcium alongside activation of inflammatory pathways causing eicosanoid formation and ROS generation - eventually leading to more inflammation and spiraling escalation of inflammation leading to cell death[18]. IRI also induces necroptosis and apoptosis in laboratory-based studies, which also contribute to ROS formulation *via* accumulation of cytosolic calcium leading to further necrosis of pulmonary epithelial cells[19,20].

ROS GENERATION

During aerobic metabolism, ATP is converted to urea and xanthine by xanthine dehydrogenase. Xanthine dehydrogenase either undergoes reversible sulfhydryl oxidation or irreversible proteolytic modification to form xanthine oxidase[21,22]. This irreversible modification occurs in IRI and breaks down hypoxanthine to ROS during rapid reoxygenation. In addition to the pathway illustrated in Figure 2, ROS is also generated by the NADPH (Nicotinamide Adenine Dinucleotide Phosphate) oxidase system. It is present on the membrane surfaces of phagocytic cells, where NADPH is oxidised to $NADP^+$, releasing an electron into the phagocytic vacuole, where oxygen is reduced to superoxide anions in large quantities[21]. It plays a major role in pathogen killing but may also be aggravated inflammatory diseases[21]. The superoxide anion, hydrogen peroxide, and hydroxyl radical form part of the family of ROS, which damage cellular membranes by lipid peroxidation[22] as shown in Figure 3.

Table 3 2019 chronic lung allograft dysfunction staging from the 2019 consensus definition

CLAD stage	Spirometric values
CLAD 0	Current FEV_1 > 80% baseline
CLAD 1	Current FEV_1 > 65%-80% baseline
CLAD 2	Current FEV_1 > 50%-65% baseline
CLAD 3	Current FEV_1> 35%-50% baseline
CLAD 4	Current FEV_1 ≤ 35% baseline

CLAD: Chronic lung allograft dysfunction; FEV_1: Forced expiratory volume in one second.

The inflammatory pathway is activated by ROS generation which causes a release of proinflammatory cytokines by macrophages. Neutrophils and lymphocytes are therefore recruited to the lung and extravasate into tissues due to increased vascular permeability as a sequalae of the acute inflammatory response[23]. The macrophages and recruited neutrophils generate more ROS alongside non-specific lysis proteins like proteolytic enzymes, lysozymes, and lactoferrin which contribute to cell damage[23]. Leukocytes can also mediate IRI through the elaboration of elastases and proteases, production of inflammatory cytokines, and neutrophil aggregation causing plugging of capillaries and no-reflow phenomena with endothelial damage[24].

ENDOTHELIAL DAMAGE

In addition to the activation of inflammatory pathways *via* neutrophil activation, the pulmonary endothelium also contributes to the pathophysiology of PGD. TNF-α and IL-1β are non-specific pro-inflammatory cytokines that promote molecule adhesion to the endothelial surface. Several processes have been implicated in the propagation of this chemotaxis including upregulation of receptors for advanced glycation end products[25], platelet aggregation[26], and increased levels of intercellular adhesion molecule-1 (ICAM-1)[27]. These promote the migration of macrophages and polymorphonuclear cells into the air spaces in the lungs.

During LIRI, the processes above occur resulting in the extravascular displacement of leukocytes through chemotaxis-induced migration. The reperfusion causes cell depolarization which disrupts the homeostatic mechanisms within the endothelium. Pulmonary artery pressure during reperfusion was shown to have a significant effect on the endothelial wall with an increased likelihood of developing Grade 3 PGD in patients with higher PA pressures in a cohort of patients with idiopathic pulmonary fibrosis (38.5 ± 16.3 mmHg *vs* 29.6 ± 11.5 mmHg for patients without PGD [mean difference, 8.9 mmHg (95%CI: 3.6 to 14.2); P = 0.001][28]. Recipient leukocyte depletion attenuated this effect, implicating the circulating host leukocytes in the pathophysiology as demonstrated by Schnickel *et al*[24]. In addition, some studies have identified the role of donor innate lymphoid cell subsets with some protective against PGD and some associated with PGD[29].

Other studies have also shown that increased left-sided cardiac pressures have a detrimental effect and increase the risk of PGD development, further inculpating the role of endothelial integrity in the pathophysiology. Porteous *et al*[30] noted that preoperative diastolic dysfunction measured by echocardiography increased the risk of Grade 3 PGD. These patients had significantly higher mPAP and pulmonary vascular resistance. Li *et al*[31] noted a similar finding using LVEDP and mPCWP as a surrogate for increased left-sided pressures. The Toronto group highlighted a higher incidence of ECLS use post-transplant in patients with preoperative signs of diastolic dysfunction[32].

RISK FACTORS

Multiple risk factors have been identified through various studies since the PGD consensus definition. We have identified donor, recipient, and procedural variables as follows.

DONOR-SPECIFIC RISK FACTORS

Donor smoking history

Donor history of cigarette smoking is perhaps the best-reported risk factor of PGD. It has been

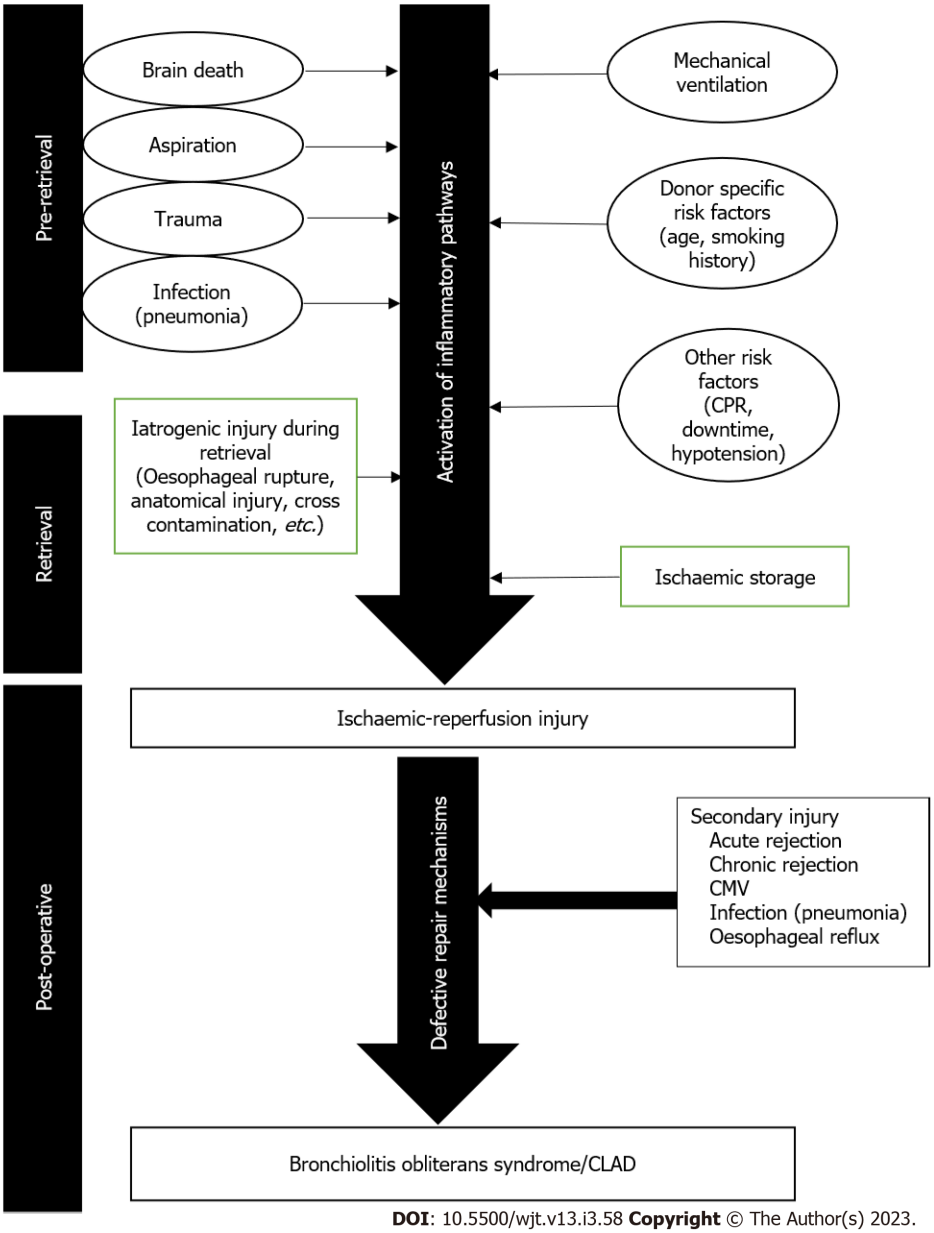

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Figure 1 Pathophysiological mechanisms that lead to ischaemic-reperfusion injury and subsequently chronic lung allograft dysfunction.
CLAD: Chronic lung allograft dysfunction.

associated with PGD in multiple studies[8,9,33]. In a large North American multicenter study, a positive donor smoking history was independently associated with PGD[9]. In addition to PGD, the United Kingdom national data revealed inferior post-transplantation survival showed inferior survival by donor history of smoking at 30 and 90 d after transplantation and sustained for up to 3 years post-transplant[34]. In addition, these patients also had a significantly higher perioperative morbidity with longer ICU and in-hospital length of stay[34]. Despite no mention of PGD in the study, one can infer that a high proportion of early morbidity and mortality would be directly related to PGD. The authors however did note that the survival benefit to recipients of smokers' lungs compared to those remaining on the waitlist and waiting for a non-smoking donor[34].

The exact role of smoking in the pathophysiology of PGD remains elusive. Ware *et al* noted that smokers' lungs had a higher incidence of pulmonary edema (408 *vs* 385 g, $P = 0.009$), lower median PaO_2/FiO_2 ratios (214 mmHg *vs* 266 mmHg, $P = 0.02$), higher levels of pro-inflammatory chemokine IL-8 levels, and lower Surfactant Protein D (SP-D) levels but similar rates of alveolar fluid clearance[35]. However, they noted a lower rate of alveolar fluid clearance in heavier smokers (≥ 20 pack-years)[35]. Higher IL-8 levels were also noted by Kuschner *et al*[36] in smokers' lungs *vs* non-smokers' lungs.

Oxidative injury with the generation of ROS may be potentiated by donor exposure to cigarette smoke[37]. Lipid peroxidation is a ROS-mediated chain of reactions that, once initiated, results in an oxidative deterioration of polyunsaturated lipids[38]. Biomarkers of lipid peroxidation such as thiobarbituric acid reacting substances are increased in bronchoalveolar lavage fluid of smokers (both acute

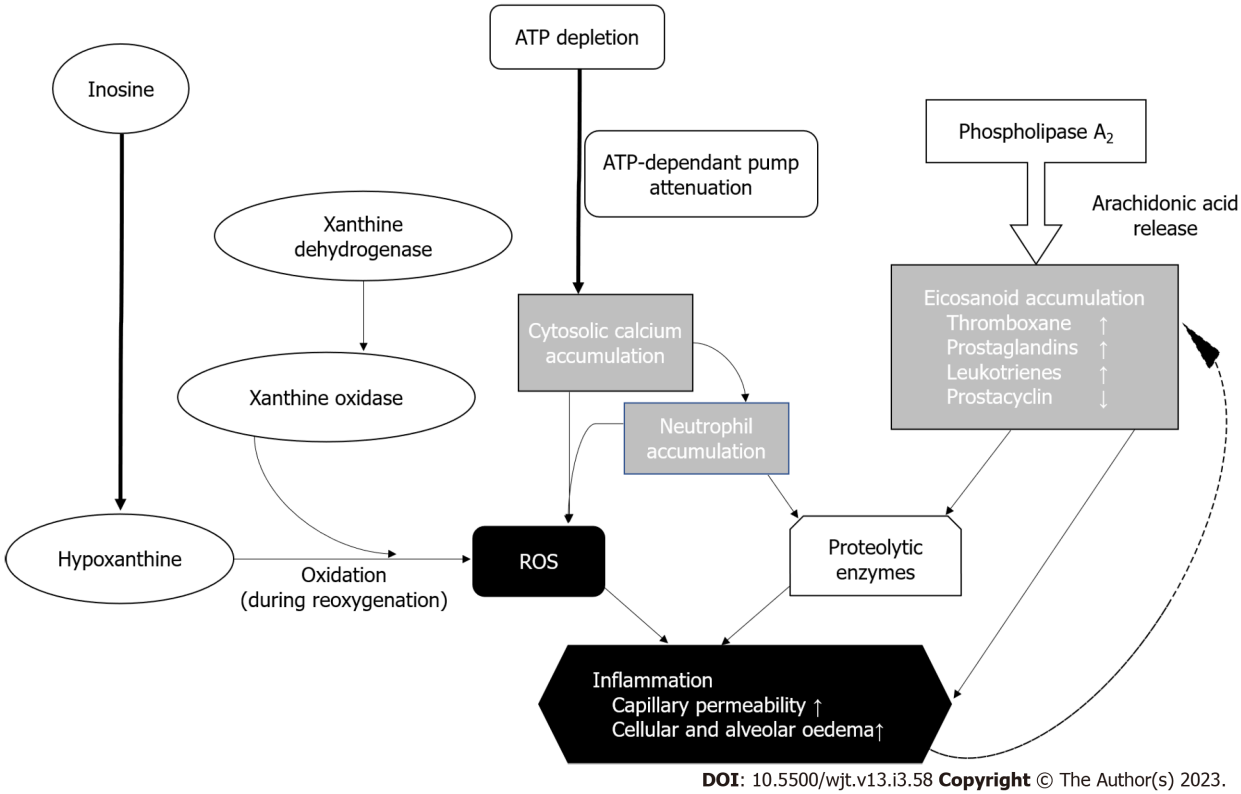

Figure 2 Pathophysiology of lung ischemia-reperfusion injury. ROS: Reactive oxygen species.

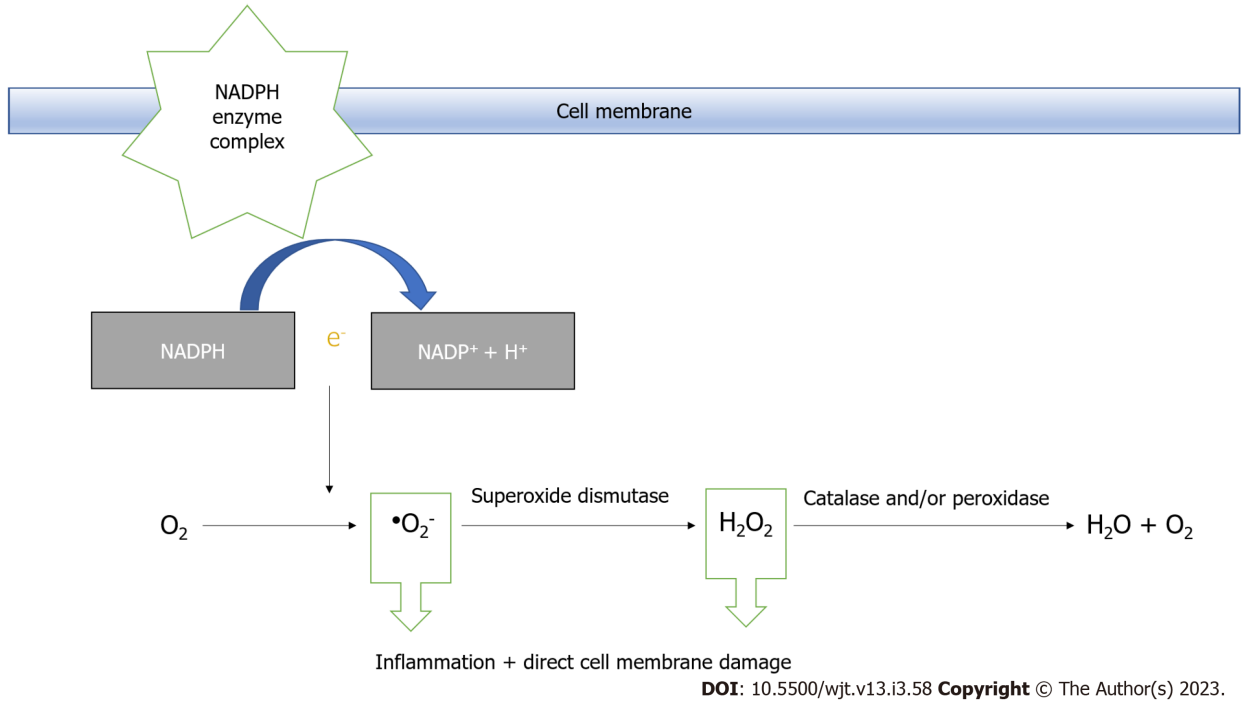

Figure 3 Nicotinamide adenine dinucleotide phosphate oxidase system and the generation of superoxide anion. NADPH: Nicotinamide adenine dinucleotide phosphate.

and chronic) compared to non-smoking controls[39]. It is therefore conceivable that the lungs of smokers are more susceptible to IRI due to the increased accumulation of the byproducts of lipid peroxidation[37].

DONOR ALCOHOL CONSUMPTION

Chronic alcohol consumption has been linked with an increased risk of developing ARDS based on a metanalysis of 17 case-controlled and cohort studies with a total of 177674 patients[40]. Extending this to lungs for transplantation was reproducible in one study which showed 8.7 times greater odds of developing severe PGD following lung transplant compared to recipients whose donors did not consume alcohol after controlling for other variables (P = 0.0190)[41]. However, there was no difference in risk of developing PGD in recipients of donors with moderate alcohol consumption as compared to donors with no alcohol use[41]. The same study also showed worse acute lung injury post-transplant with poorer gas exchange and a trend of poorer survival following transplantation when lungs from heavy alcohol consumers were implanted[41]. Heavy alcohol use in donors was also related to a higher rate of PGD in another retrospective single-center study[42]. Heavy intake of alcohol is also linked with other high-risk behaviors including road traffic accidents, violence[43,44], and self-injuries including suicide attempts[45], thus, at risk of trauma and subsequent brain death, representing a significant proportion of donors. The exact pathophysiology of this is speculative but is probably a combination of poor mucociliary clearance, a degree of epithelial dysfunction, and impaired immune responses in the alveolar spaces which increases the susceptibility to oxidative stressors[41]. There is also evidence that chronic alcohol abuse impairs surfactant production in pneumocytes, impairing the epithelial barrier function[46]. There is also some evidence of glutathione depletion which increases susceptibility to oxidative stressors such as reperfusion injury post-cold ischaemic storage[47]. Animal models have been utilized to demonstrate the effects of modulating ischaemia-reperfusion. In a rat tracheal transplant model, alcohol intake increased inflammatory signaling with transforming growth factor-beta (TGF-β) and interleukin 13 (IL-13), which may induce fibrosis[48].

DONOR AGE

Donor age is a significant risk factor for PGD in other organs such as the heart[49], kidney, liver, and pancreas[50]. Analyzing the American Organ Procurement and Transplantation Network database, Baldwin *et al*[51] noted that there was a higher risk of graft failure at 1 year when using lungs from donors < 18 years old and > 65 years, and echoed by De Perrot[52]. This was not reproduced in other studies by the Pittsburgh group[53] and the Hannover group[54]. The 2016 ISHLT Working Group on Primary Lung Graft Dysfunction Report noted that recent data suggest the age-related risk of PGD is lower than previously believed and restricted to the extremes of ages[8].

PULMONARY EMBOLISM

In the 1990s, 2 case reports were published describing the impact of donor-related pulmonary emboli diagnosed by lung biopsy after transplantation from fat emboli following multiple fractures in a donor for an RTA[55] and cerebral emboli[56] respectively. Oto *et al* showed a significant association between donor pulmonary embolism and PGD in lungs[57]. On multivariate analysis, PGD rates following lung transplantation were 20.6-fold (P = 0.0002) higher with fat emboli and 4.8-fold (P = 0.02) with pulmonary embolism compared with those who received lungs without pulmonary embolism[57]. In a subsequent study by the same authors, emboli were diagnosed using retrograde flushing of the pulmonary arteries at the time of retrieval. They noted that donor death due to trauma with fractures and a smoking history of more than 20 pack-years were significant risk factors for pulmonary embolism [58]. The pathophysiology suggested by the authors is the failure to correct the ventilation-perfusion mismatch by the denervated lung in addition to a localized inflammatory response which may aggravate the IRI. They noted increased interstitial infiltration and opacities on chest radiographs in up to 93% of lungs post-transplantation. However, studies examining donor causes of death have shown no differences between donors with traumatic causes of death *vs* non-traumatic[59].

SIZE MISMATCH

A likely issue that may account for PGD includes lung size mismatch, or specifically undersizing[60]. This is thought to be due to the changes in the pulmonary vasculature and potentially detrimental tidal volumes during mechanical ventilation. The undersized pulmonary vasculature provides increased resistance and thus a higher pulmonary artery pressure at reperfusion which is thought to be a contributing factor. The Lung Transplant Outcome Group noted that donor undersizing (Donor Lung < Recipient Lung) rather than donor sex or race conferred an increased risk as male lungs were generally larger than females[8,60]. A quotient called the predicted donor-recipient total lung capacity ratio (donor pTLC/recipient pTLC) of < 1 was noted as a risk factor for PGD post-bilateral lung trans-

plantation[60]. In addition, a recent study by the Toronto group noted that patients with donor pTLC/recipient pTLC ratio of ≥ 0.8 or < 1.2 for double lung transplantation significantly improved overall survival and CLAD-free survival[61]. This benefit however was not noted in the single lung transplant group.

RECIPIENT SPECIFIC RISK FACTORS

Aetiology of disease

The causative pathology of lung disease has also been implicated as a risk factor for PGD. Diamond *et al*[9] noted that patients with pre-operative sarcoidosis (OR: 2.5; 95%CI: 1.1 to 5.6; $P = 0.03$) or pulmonary arterial hypertension (OR: 3.5; 95%CI: 1.6 to 7.7; $P = 0.002$) were at an increased risk of developing PGD. Pulmonary hypertension is linked to right ventricular dysfunction and the sudden peripheral vascular resistance reduction in the transplanted lungs may result in endothelial shear stressors, further worsening the reperfusion injury. However, similar findings were not noted in patients with cystic fibrosis regardless of pulmonary hypertension based on ISHLT database findings, indicating a disease process rather than the presence of elevated pulmonary pressures may be causative[62]. Fang *et al*[28] noted that secondary pulmonary hypertension in patients with idiopathic pulmonary fibrosis (IPF) was independently associated with PGD development. This could be explained by the progressive nature of the disease and implicate the role of vasoactive mediators (*e.g.*, Endothelin-1, fibroblast growth factor) which have been linked with the pathogenesis of IPF[63]. The restrictive pattern of lung disease may also result in smaller-than-predicted total lung capacity. This causes progressive changes to the chest wall which may result in poorer graft function due to the irreversible mechanics of remodeling within the recipient's chest wall to accommodate the 'shrinking' lung[64,65].

Body mass index

A raised body mass index (BMI) was previously shown to be a risk factor for prolonged ICU length of stay and mortality in lung transplant recipients[66,67]. Diamond *et al*[9] also conducted a large cohort study and showed a direct relationship between a raised BMI and PGD. Specifically, the odds ratio for developing PGD increased to 1.8 for BMI 25-30 and 2.3 for BMI > 30.

This may be directly related to the technical surgical challenges in obese recipients alongside the inflammatory milieu produced during IR. Leptin is a protein encoded by the obese gene located on human chromosome 7[68]. It is classically noted to be a hormone due to its effects in regulating food intake and energy exposure. In addition, it is also a member of the type 1 cytokine family. Other conditions such as type II diabetes are associated with hyperleptinemia and acquired resistance to signaling through the leptin receptors[69]. Serum levels of leptin are directly correlated to BMI and are increased in sepsis and ARDS, suggesting a pathogenic contribution[70]. A study by Jain *et al*[71] showed that lung leptin levels were increased in mice with acute lung injury. The Lung Transplant Outcomes Group then published data on over 500 patients who underwent transplantation for either COPD or ILD indicating a higher risk for PGD in patients with higher plasma leptin levels. In their study, the graphical depiction showed a stark increase in the risk of PGD with an inflection point noted just above 10 ng/mL. The associations between leptin and PGD were stronger when the cardiopulmonary bypass was not used[72]. The role of other modulators such as resistin and adiponectin have been postulated in the past from work done in animal models but have yet to be translated into clinical practice[73].

Previous pleurodesis or pleural diseases

In humans, two pleurae (visceral and parietal) line the thoracic cavity and lungs. The pleurae are serous membranes that fold back onto themselves to form a two-layered membranous structure with a small amount of pleural fluid which plays a role in transmitting movements of the chest wall to the lungs during respiration[74]. Pleural symphysis or pleurodesis is a commonly performed procedure for the treatment of pneumothoraces and effusions. The team at the University of Pittsburgh noted that patients with prior pleurodesis had the highest incidence of severe PGD, alongside other early post-operative complications such as re-exploration for bleeding, phrenic nerve injury, chylothorax, and respiratory complications[75]. Although the post-operative rate of other complications was also increased in patients with prior thoracic surgery, the increased rate of PGD was specific to pleurodesis alone. On multivariate analysis, they noted an increased risk of death post-transplant in patients with prolonged cardiopulmonary bypass (CPB) time, chemical pleurodesis, and high transfusion requirements (> 20 units). The technical challenges intraoperatively due to the multiple adhesions post pleurodesis, combined with heparinization during CPB contribute to the high transfusion requirements, making elucidation of the exact pathophysiological mechanism difficult. The Harefield group noted that recipients with pleural disease defined as pleural thickening, plaque, or fibrosis either confirmed on a computed tomographic scan during assessment for transplantation or detected intraoperatively at the time of the transplantation, had worse 3-mo mortality and a trend toward poorer 30-d mortality despite similar CPB usage, albeit with significantly higher transfusion rates[76].

Extracorporeal life support as a bridge to transplant

The use of extracorporeal life support (ECLS) preoperatively increases the risk of PGD postoperatively [77,78]. While the use of ECMO for treatment for severe PGD is well established, its use preoperatively as a bridging strategy to transplantation has been condemned in the past due to poor outcomes[79]. Analysis of the UNOS database in 2012 identified that only 1.3% of patients transplanted were bridged with ECMO[80]. Unadjusted survival of these patients was significantly worse compared to non-bridged recipients[81]. The increased acuity and deconditioning of these recipients due to the inability to mobilize and multiple pre-transplant interventions potentially creates a hostile environment for the donor graft[82]. It should be noted that the current devices used for ECLS last longer and are less prone to malfunctioning (improved oxygenators and circuits)[83]. Center-specific outcomes also denote improved survival with ECLS pre-transplant in larger, more experienced centers with similar survival outcomes to non-bridged patients reported, supporting its use in the current era[84,85].

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ECLS during implantation

Lung transplantation can be performed with or without ECLS. CPB was the traditional method for intraoperative cardiopulmonary support to permit low-pressure reperfusion in cases of severe pulmonary arterial hypertension, failing oxygenation, poor hemodynamic tolerance, or acute bleeding from major vessels[86]. Caveats of the use of CPB include its proinflammatory effects and the associated complications of full systemic heparinization[86]. Other techniques that are now more commonly used to avoid the use of CPB include transplantations with the use of ECMO support or transplantations with single lung ventilation without ECLS[86].

In most institutions worldwide, ECLS is reserved for patients who cannot tolerate single-lung ventilation, complex patients, or those who become haemodynamically unstable during the procedure. ECMO has, by and large, replaced CPB in this setting. CPB has been linked with the activation of cytokines, leukocytes, and the complement cascade alongside a higher transfusion requirement and postoperative coagulopathy probably secondary to the higher levels of anticoagulation required[62,86]. Several reasons have been cited such as the increased blood-activating surfaces present in the CPB tubing, venous reservoir, oxygenator, and cardiotomy compared to ECMO circuits which are closed circuits, without venous reservoirs or additional cardiotomy suction thereby eliminating the air-liquid interface and avoiding blood being washed and returned[87]. Newer ECMO systems have increased biocompatibility by using heparin-coated tubing with polymer-coated centrifugal pumps and oxygenators, permitting prolonged usage pre and post-transplant with limited metabolic derangement [87]. When CPB was used, patients had longer intubation times, higher rates of PGD, and reduced survival[62]. However, it should be noted that the use of CPB is also often linked with adverse donor-recipient characteristics, which may not directly infer causality. A metanalysis comparing the use of ECMO and CPB highlighted that CPB was more likely used in patients with severe pulmonary hypertension, increased risk of intraoperative bleeding, and combined cardiac defects[86].

Moreover, in a recent Austrian study, Hoetzenecker *et al*[88] compared bilateral lung transplantations performed without ECLS with those performed with the routine use of intraoperative ECMO support. The authors favoured central venoarterial ECMO intraoperatively and converted it to peripheral femoral venoarterial cannulation postoperatively if this was deemed necessary. They reported improved 1-, 3-, and 5-year survival compared to non-ECMO patients (91% *vs* 82%, 85% *vs* 76%, and 80% *vs* 74%; log-rank $P = 0.041$) along with a trend towards a reduced incidence of grade 2 and 3 PGD in the intraoperative ECMO group. The authors attribute these findings to the ability to ventilate patients with low tidal volumes and low ventilation pressures (protective ventilation conditions) during the implantation of the second lung, hemodynamic stability even with extensive heart manipulation, and shorter operation times by reducing unnecessary hands-off periods.

Ischaemic time and donation after circulatory death

Ischaemic time has been shown to be a risk factor for PGD in multiple studies for other solid organs[89-91]. The link between ischaemic time and PGD in the lungs, however, is slightly less prominent. Multiple studies have published conflicting findings in this respect[92-95]. One reason for this could be due to the variability in reporting ischaemic times across the different centers[96]. Thabut *et al*[92] noted that prolonged ischaemic time led to increased tissue oedema and poorer 30-d survival. Snell *et al*[97] noted that in their series in the early 90s, ischaemic times exceeding 5 h led to poorer survival ($P = 0.02$, hazard ratio: 3.44, 95%CI: 1.12 to 9.8). Gammie showed no differences in early survival and late (3-year) survival with increased ischaemic time[98]. A recent Swedish study noted that there were early differences in outcomes with increasing ischaemic times alongside increased mortality of up to 24% within 5 years for every 2 h of ischaemic time increment[99].

The lungs also have shown to be less affected by ischaemia compared to the other organs as noted by the good outcomes of lungs procured in donation after circulatory death (DCD)[100]. There is also a probable threshold ischaemic time for the development of ischaemic reperfusion injury which is

dependent on both warm and cold ischaemic times. Conflicting results may therefore be attributed to the variable definitions of ischaemic time which is even more variable in the DCD cohort[101]. Although DCD donors (Maastricht Category III) are not affected by the catecholamine surge and inflammatory milieu after brainstem death, they are exposed to several different ischaemic insults. After the withdrawal of life-sustaining therapy (WLST) during the process of procurement, the donor becomes hypoxemic and hypercarbic. The functional warm ischemia time ensues after WLST when the systolic blood pressure is less than 50 mmHg, with some centers also utilizing the oxygen saturations < 70% as a cut-off. There is then a universal stand-off period of 5 min before organ retrieval commencement[102]. This warm ischemia is associated with intracellular acidosis, activation of the Na^+/H^+ exchanger causing accumulation of intracellular Ca^{2+} worsening IRI. Reducing warm ischemia remains challenging during DCD lung procurement.

A bronchoscopic examination is usually performed and any aspiration is suctioned while the retrieval is happening. As the perfusion fluid is delivered, cyclic ventilation is performed to evenly distribute the preservation fluid followed by inflation to about 50%-75% of the lung capacity and a retrograde flush. Rat model studies have shown that inflation of the lungs with oxygenated air ensures the integrity of pulmonary surfactant alongside improved epithelial fluid transport[103,104]. Healey *et al*[105] recently published a case series of uncontrolled DCD donors and noted no PGD in their cohort, probably signifying a degree of tolerance towards ischaemia. Another study showed an increased incidence of PGD early on, but similar rates at 6 h onwards between DCD and DBD lungs[106]. The Harefield group had a similar finding with an increased PGD incidence in their propensity-matched analysis in the DCD group[107]. One reason to explain this could be the lack of assessments and optimization in DCD donors compared to DBD donors[108]. A metanalysis from 2015 showed similar outcomes from DCD and DBD lung donations[109]. It should be noted that DCD lungs remain an underused resource and are still growing with preservation techniques for other organs such as the thoracoabdominal normothermic regional perfusion and ex-vivo lung perfusion (EVLP) postulated to increase its use[110].

Polytransfusion

A metanalysis highlighted polytransfusion of blood products to be a risk factor for PGD[62]. Although the exact relationship remains unclear, it is probably a combination of increased technical difficulty which invariably results in increased transfusion requirement[111], a degree of TRALI[112], a result of a significant IRI resulting in an ARDS type presentation or systemic inflammatory response (SIRS)[25]. Each of these has been implicated and may play a role in accentuating the severity of IRI. In addition, the need for transfusion shares some co-linearity with other risk factors such as primary pulmonary hypertension and the use of CPB[62]. Therefore, it is difficult to elucidate whether this occurs due to causality or as a response to the abovementioned insults. The transfusion of red blood cells (RBC) alone is associated with increased mortality in a study in Zurich[113]. RBC transfusion is also associated with an increased amount of soluble receptors for advanced glycation end products (sRAGE), which is a marker of alveolar epithelial injury[25]. On the other hand, intraoperative use of fresh frozen plasma has been shown to increase mortality[113], albeit these were more often used in sicker patients[114].

Timing of surgery

In 2018, a multicenter group published a unique study that highlighted an increased risk of PGD in lungs reperfused between 0400-0759[115]. Following the pilot study of 25 patients, a larger retrospective cohort study of 563 patients revealed a significantly increased risk of PGD (OR: 1.12, 95%CI: 1.03 to 1.21; P = 0.01) on univariate binary logistic regression and OR: 1.299, 95%CI: 1.004 to 1.681; P = 0.046 on multivariable binomial logistic regression. There were no differences in ischaemic times or operation lengths although they could not directly account for operator fatigue. The authors attributed the results to 'internal desynchrony between donor and recipient as a result of organ preservation' The circadian clock oscillations were thought to play a part in this and using a mouse model, the authors showed delayed oscillation for lungs that were kept in cold storage compared to lungs maintained at 37 °C. The authors highlighted the role of the clock protein, REV-ERBα which has previously been studied for its role in regulating neuroinflammation[116], and poorer outcomes following cardiac surgery[117]. We currently know that the nuclear receptor REV-ERBα is involved in the cell-autonomous mammalian circadian transcriptional/translational feedback loops as transcriptional repressors and hence indirectly mediates regulation of metabolic, neuronal, and inflammatory functions including bile acid metabolism, lipid metabolism, and production of inflammatory cytokines[118]. In an animal model, Cunningham *et al*[115] noted that in a panel of PGD biomarker gene expression was repressed by a synthetic REV-ERBα ligand. Conversely, 6 out of 7 biomarkers in this panel however demonstrated increased expression of macrophages in REV-ERBα knockout mice[115]. Though it is of interest, its current role remains limited to experimental research, although the introduction of normothermic ex-vivo perfusion devices may change the timing of the surgical aspect of transplantation.

Retransplantation

The association between PGD and re-transplantation is not well established with some centers highlighting no differences in the rates of PGD compared to primary transplants[119,120], but others

generally highlighting poorer survival outcomes especially if used in patients with severe PGD at the primary transplant[119,121,122]. Outcomes were also similar in single or bilateral lung transplantation during the re-transplant irrespective of the primary transplant[123]. The true incidence of PGD in the re-transplant setting is perhaps under-represented due to the higher incidence of secondary causes which include chest wall bleeding due to significant adhesions, coagulopathy, and infections, all of which preclude a diagnosis of PGD[119].

TREATMENT AND PREVENTION

Treatment of PGD is primarily supportive with the exception of severe PGD which requires circulatory support (ECMO). The challenge with PGD is usually establishing a diagnosis as mild and moderate PGD (Grade II and III) may often be mistaken for other conditions such as pulmonary oedema, TRALI, or superimposed infection. Treatment management is therefore directed at managing the ARDS-type picture.

Lung protective strategies and low tidal volume ventilation

The target tidal volume for low tidal volume ventilation (LTVV) is usually 4-8 mL/kg calculated based on predicted body weight (PBW)[124]. This is calculated using the following formula for

PBW males = 50 + 0.91 (centimeters of height - 152.4)

PBW females = 45.5 + 0.91 (centimeters of height - 152.4)

It is performed using a volume-limited assist control mode and the plateau pressure is usually kept below 30 cmH_2O with PEEP which usually starts at 5 cmH_2O and is titrated upwards. The ventilation should be set at ≤ 35 breaths/min to mimic the baseline minute. It is important to reassess the patient and increase or decrease tidal volume based on the plateau pressure. A summary of the Acute Respiratory Distress Syndrome Network trial on LTVV settings is included in Table 4.

The reasoning behind LTVV is lower tidal volumes may attenuate some of the alveolar overdistension and the release of inflammatory mediators induced by mechanical ventilation[124,125]. The ARDS network trial noted that patients randomized to the LTVV group had a lower mortality rate *vs* the control group (TV ≥ 12 mL/kg PBW) (31% *vs* 39.8%, $P = 0.007$) and more ventilator-free days within the initial 28 d (12 ± 11 d *vs* 10 ± 11 d, $P = 0.007$)[124]. A Cochrane review noted a reduction in 28-d mortality (27.4% *vs* 37%, RR: 0.74, 95%CI: 0.61 to 0.88) and in-hospital mortality using LTVV for ARDS compared to normal ventilation (34.5% *vs* 43.2%, RR: 0.80, 95%CI: 0.69 to 0.92)[126]. Evidence regarding volume-controlled *vs* pressure-controlled ventilation remains controversial in the management of patients with ARDS[127]. Protective lung ventilation strategies are advocated for PGD given its similarities with ARDS[125]. Its role may also be extended to donors with the group in Missouri identifying donor lung-protective ventilation with a tidal volume protocol of 6 to 8 mL/kg of donor ideal body weight and plateau pressure < 30 cmH_2O with lower incidence of PGD[128].

Reperfusion strategies

During reperfusion, the ischaemic lung is suddenly exposed to the recipient's circulation whereby there is rapid recruitment of neutrophils and ongoing propagation of ROS which as described above, results in a cascade of events heralding a viscous cycle of oxidative stress with increased vascular permeability and pulmonary hypertension[18]. Rapid reperfusion is also associated with mechanical stress failure of the alveolar/capillary barrier[129].

Hence altering the reperfusion process is a strategy to enervate PGD. The UCLA group utilized a modified reperfusion strategy by using buffered leukocyte-depleted blood and reperfused at the pressure of < 20 mmHg before cross-clamp release and noted a reduction in IRI in their cohort[130]. Leukocyte depletion has since been utilized with EVLP in several animal models with similar outcomes [131,132].

Diamond *et al*[9] noted that the odds ratio for PGD increased by 10% for every 10% increase in FiO_2 at the time of reperfusion. However, it should be noted that this may have been a response to poor oxygenation during reperfusion, hence implying an association rather than causality. However, to date, no studies have been conducted examining FiO_2 at reperfusion as a risk factor for PGD.

Inhaled NO usage

NO has been investigated as a therapeutic option for the prevention or treatment of PGD due to its pulmonary vasodilatory effects[133]. Given the effect of pulmonary hypertension, NO is believed to attenuate the effects of reperfusion. There is however a lack of randomized studies showing the survival benefit of the ubiquitous use of NO in treating PGD. Benefits noted from studies with ARDS did not result in improved mortality[134]. Moreno *et al*[135] published the only clinical study which elucidated a reduction in PGD by inhaled NO administration. The authors noted a significantly lower incidence of PGD in the iNO group *vs* the control group (17.2% *vs* 45%) ($P < 0.035$) alongside significant reductions in IL-6 (in blood at 12 h), IL-8 (in blood and BAL at 12 and 24 h), and IL-10 (in blood at 12 and 24 h and BAL at 24 h)[135]. In Moreno's study, iNO was commenced at the beginning of surgery and continued

Table 4 Oxyhemoglobin saturation and positive end-expiratory pressure combinations for low tidal volume ventilation in managing acute respiratory distress syndrome by the Acute Respiratory Distress Syndrome Network[124]

Arterial oxygenation and PEEP	
Target Oxygenation PaO_2 = 55-80 mmHg (7.35-10.7 kPa)or O_2 saturations (SpO_2) = 88%-95%	
FiO_2/PEEP combinations	
FiO_2 (%)	PEEP (H_2O)
30	5
40	5-8
50	8-10
60	10
70	10-14
80	14
90	14-18
100	18-24

PaO_2: Arterial oxygen tension; SpO_2: Oxyhemoglobin saturation; PEEP: Positive end-expiratory pressure; FiO_2: Fraction of inspired oxygen.

for 48 h postoperatively. Similar findings were noted by Yerebakan in their cohort with a similar length of iNO administration[136]. Other studies have not shown similar outcomes with the caveat that iNO was used either before reperfusion or at the beginning of the case and not as prolonged as Moreno's group[137]. The beneficial effects of NO may be transient and therefore not result in reductions in mortality[138]. Current evidence does not support the widespread routine use of NO for PGD prevention, although these studies were underpowered to detect minuscule differences in outcomes[12].

Prostaglandin E1

Prostaglandin E1 (PGE1) causes similar vasodilatory effects on pulmonary circulation and may therefore improve oxygenation. In addition, it may also play a role in attenuating IRI by reducing the expression of certain mediators such as IL-12 and TNF-α and increasing the expression of IL-10, an anti-inflammatory mediator[139]. The use of PGE1 has been proven in ARDS with improvements in oxygenation and reduction in PA pressures[12]. Hypotension was also a key feature in the metanalysis. Several studies have noted the benefits of using injected PGE1 during organ retrieval in transplantation. The Pittsburgh group noted an improvement in long-term survival following a change in their protocol in 1994 to include PGE1 addition to the graft preservation fluid[140]. Similarly, a group from Taipei noted that the addition of PGE1 to preservation fluid during pulmonary artery flushing resulted in the increased attenuation of IRI[141].

Inhaled prostacyclin analogue (PGI_2)

As with PGE1, iloprost is a prostacyclin analogue that primarily functions as a pulmonary vasodilator. In addition to the benefits of PGE1, PGI_2 also plays a role in inhibiting neutrophil adherence to improve endothelial integrity[142] and in reducing platelet aggregation[143]. Animal model studies have also shown some benefit in ameliorating IRI[144,145]. However, its use in the treatment and prevention of PGD is limited to a single retrospective study by Lee *et al*[143]. In a propensity-matched analysis, patients who were administered inhaled iloprost immediately after reperfusion of the grafted lung had significantly lower severity of pulmonary infiltration on postoperative days (PODs) 1 to 3 compared to the non-intervention arm. The PaO_2/FiO_2 ratio was also significantly higher in the treatment group compared to the control group (318.2 ± 74.2 mmHg *vs* 275.9 ± 65.3 mmHg, P = 0.022 on POD 1; 351.4 ± 58.2 mmHg *vs* 295.8 ± 53.7 mmHg, P = 0.017 on POD 2; and 378.8 ± 51.9 mmHg *vs* 320.2 ± 66.2 mmHg, P = 0.013 on POD 3, respectively). Finally, PGD3 prevalence was significantly lower on POD1 [2 (6.7%) *vs* 9 (30%), P = 0.042], POD2 [1 (3.3%) *vs* 8 (26.7%), P = 0.026] and POD3 [0 (0) *vs* 6 (20%), P = 0.024]. It should be noted however there was a higher rate of PGD1 (mild) in the iloprost arm of the study on all 3 d[143]. Larger prospective studies are needed to validate the above findings.

Surfactant

The surfactant depletion theory is another potential pathogenetic mechanism of PGD. In a prospective open-label randomized study, a study based in Israel investigated the role of surfactant therapy post bronchial anastomosis[146]. The authors noted that patients who received surfactant had improved mean PaO_2/FiO_2 (418.8 ± 123.8 mmHg *vs* 277.9 ± 165 mmHg, P = 0.004) post-operatively, lower PGD

grades (0.66 *vs* 1.86, $P = 0.005$), fewer cases of severe PGD (1 *vs* 12, $P < 0.05$)[146]. The same group then published a case series of 5 patients with severe PGD treated with surfactant instead of ECMO[147]. They noted a significant improvement in PaO_2/FiO_2 ratios within h of treatment (pretreatment mean PaO_2/FiO_2 *vs* post-treatment PaO_2/FiO_2 (98.8 ± 21.7 mmHg *vs* 236.8 ± 52.3 mmHg, $P = 0.0006$) who were still alive 6 mo post-treatment.

ECMO

ECMO is usually reserved for PGD grade 3 refractory to medical treatment. Outcomes post-ECMO are better with early initiation (< 24 h)[12,148]. The use of Veno-Venous ECMO (VV-ECMO) is currently preferred over Veno-Arterial ECMO (VA-ECMO) if the patient is haemodynamically stable due to the complications attributed to VA-ECMO[12]. The Pittsburgh group noted survival after both VV-ECMO and VA-ECMO were similar at 30 d, 1 year, and 5 years (58% *vs* 55%, $P = 0.7$; 42% *vs* 39%, $P = 0.8$; 29% *vs* 22%, $P = 0.6$)[149]. The Duke group noted that their VV-ECMO patients had better survival and medium-term outcomes, with all VV ECMO patients were successfully weaned from ECMO support, but only 50% (7 of 14) of the VA ECMO survived weaning ($P = 0.02$). The 30-d graft and patient survival for the VV ECMO group was 87.5% *vs* 0 in the VA-ECMO group[150]. In a subsequent study, the same group noted their VV-ECMO survival to be 82% at 30 d, 64% at 1 year, and 49% at 5 years which is arguably better compared to the previous report[151]. The poor outcomes for VA-ECMO are probably multifactorial, ranging from the severity of the SIRS response which necessitated VA-ECMO in the first place to the genuine complications attributed to VA-ECMO. Peripheral VA-ECMO has significant limb ischaemia complications reported to be around 16.9% (95%CI: 12.5% to 22.6%) with a 10.3% risk of fasciotomy or compartment syndrome (95%CI: 7.3% to 14.5%) and lower limb amputation rate of 4.7% (95%CI: 2.3% to 9.3%)[152].

The incidence of neurologic complications for VA-ECMO was 13.3% (95%CI: 9.9% to 17.7%), acute kidney injury, 55.6% (95%CI: 35.5% to 74.0%) with almost half requiring renal replacement therapy [95%CI: 46.0% (36.7% to 55.5%)][152]. The risk of bleeding complications in VA-ECMO is 46.0% (95%CI: 36.7% to 55.5%) with re-exploration for bleeding or tamponade reported around 41.9% (95%CI: 24.3% to 61.8%) alongside a significant infection rate of 30.4% (95%CI: 19.5% to 44.0%) in the post-cardiotomy cohort alone[152]. The risks of the above in the post-transplant setting have not been noted *via* a metanalysis but one can only assume the risks of renal impairment and infections to be higher with the administration of immunosuppressive medications.

Delayed chest closure

Delayed chest closure (DCC) was initially thought to be a marker for PGD with one study identifying patients with increased CXR changes as being at risk for DCC[153]. It is perhaps a surrogate marker for prolonged CPB usage, challenging intraoperative conditions, and polytransfusion. The Pittsburgh group showed no increased mortality in this group despite the increased PGD incidence, potentially indicating that DCC may be of benefit in these sub-select groups of patients as long as the skin closure method was applied[154]. They noted that acute lung oedema, oversized grafts, and coagulopathy were the most common reasons for DCC followed by haemodynamic instability. The authors noted that improved the haemodynamics and physiology of lung allografts especially when LPVV with high PEEP was utilized [154]. There is a delicate balance between the physiological and haemodynamic benefits *vs* the loss of the barrier function against infections, particularly in an immunosuppressed patient[154].

Aprotinin

Aprotinin is a nonspecific serine protease inhibitor that has shown evidence of attenuating ischemia-reperfusion lung injury by inhibiting the inflammatory response and suppressing NADPH oxidase [155]. Using a rat model, the team from Tokyo noted that by using aprotinin in the flush preservation solution during organ retrieval, and 18-h lung preservation at 4 ℃ followed by normothemic reperfusion with blood, the malondialdehyde (MDA) and IL-8 levels in the lung tissue after reperfusion were reduced in the aprotinin group. The aprotinin-treated lungs also showed significantly better oxygenation throughout the reperfusion period[155]. This preservative effect of aprotinin was also confirmed by the prevention of an increase in peak airway pressure in aprotinin group. They highlighted 2 key issues which were: cold ischemic preservation followed by reperfusion results in interstitial edema and neutrophil extravasation into alveoli, secondly, aprotinin prevented these pathological changes[155]. Similar outcomes were reproduced from 2 other animal model studies[156-158]. Bittner *et al* and the Leipzig group then translated this into a clinical study whereby 59 patients were managed perioperatively with aprotinin infusion using a historical cohort for comparison[159]. Despite advancing donor age in the aprotinin group and longer ischaemic times, the incidence of post-transplant reperfusion injury was markedly lower than in the historical cohort[159]. There were however several limitations to their study including the use of a historical cohort, alongside the multiple interventions used by the team during the aprotinin study, namely iNO usage, and controlled reperfusion.

Prone ventilation

Prove ventilation involves the delivery of mechanical ventilation with the patient in a prone position [160]. The oxygenation is improved due to improved lung perfusion and reduced lung compression [161]. It is a technique that is used as part of the lung-protective strategy to improve survival in severe cases of ARDS with some studies showing improvements, especially in the COVID-19 pandemic[162, 163]. Its role in lung transplantation however is slightly more limited due to the incision sites which tend to be *via* sternotomy or clamshell for bilateral lung transplants although posterolateral thoracotomies can also be performed. A team in Padua, Italy, utilized high-frequency percussive ventilation (HFPV) along with proning to good effect in 3 patients with infiltrates on CXR[164]. They noted a gradual improvement in the clearance of secretions without needing endotracheal intubation in all 3 of their patients. They also noted that HFPV accommodated volume distribution without overinflating compartments with low time constants thus potentially having a protective role against alveolar hyperinflation[164].

EVLP

Prior to EVLP, 4/5 of donor lungs expressed some degree of potential injury therefore not considered suitable for transplantation, limiting the donor pool[165]. Another major limitation of transplantation is prolonged cold storage during transport and its perceived effects on IRI[166]. Normothermic ex vivo lung perfusion is a novel way of organ preservation, evaluation, and potential reconditioning of donor lungs. EVLP allows for perfusion of the donor lungs using an ex vivo circuit (Figure 4).

There are currently 3 EVLP protocols that have been described, the Lund protocol, the Organ Care System protocol, and the Toronto protocol. The differences between the protocols are highlighted below in Table 5.

There are several EVLP kits available that differ in size, function, and portability. The specifics of these are outwith the remit of this review. EVLP was initially used by Steen *et al*[167] for the first human lung transplant using a DCD lung assessed by EVLP and the first successful lung transplant of an initially unacceptable donor lung reconditioned ex vivo in 2000. This proof of concept was then expanded to prolong the EVLP time up to 12 h[168] by the Toronto group. The usage of an acellular perfusate as per the Toronto Protocol is to mitigate the haemolysis of RBCs which may in itself precipitate IRI with the release of pro-inflammatory cytokines[169]. Haemolysis of RBCs also causes results in increased plasma volumes of AGEs (advanced glycation end-products), a finding noted in oxidative conditions and is associated with disease severity inflammatory conditions[170]. Since then, numerous trials have been conducted to show equivocal results to that of cold storage. This includes the NOVEL lung[171], HELP[165], and INSPIRE[172]. The HELP trial showed an increased rate of PGD at 72 h in lungs that underwent EVLP but this did not meet statistical significance (15% *vs* 30.1%; 95%CI: −2.6% to 32.8%; $P = 0.11$) although the study was not powered to calculate differences in PGD. Severe PGD rates were similar in both arms[165]. The NOVEL lung trial noted a higher number of severe PGD cases in the EVLP group [EVLP *vs* Control (21.4%, $n = 9$ *vs* 9.5%, $n = 4$), $P = 0.2$] although this study too was not powered for PGD outcomes[171]. Survival in both studies was similar between the groups. The UK-based DEVELOP-UK study indicated a higher rate of early severe PGD in the EVLP arm, but rates of PGD did not differ between groups after 72 h[173]. The requirement for ECMO support was higher in the EVLP arm than in the standard arm [(7/18, 38.8%) *vs* (6/184, 3.2%), $P < 0.001$][173]. The study however was concluded early and non-inferiority analysis of survival could not be performed. The EXPAND study was a single-arm trial that studied the role of EVLP using the Organ Care System Lung for procurement of extended-criteria donor lungs from brain-death donors, and donors after circulatory death, which are seldomly used for transplantation. The primary efficacy endpoint was a composite of patient survival at day 30 post-transplant and absence of primary graft dysfunction grade 3 (PGD3) within 72 h post-transplantation[174]. The authors chose a prespecified objective performance goal (OPG) of 65% based on a PGD3 within the initial 72 h post-transplant rate of 30.8% (95%CI: 28.2% to 33.3%) for standard-criteria donor lungs as noted by Diamond *et al*[9]. The primary effectiveness composite endpoint of patient survival at day 30 post-transplant and no PGD3 within the initial 72 h was achieved in 43/79 patients (54%) and did not meet the prespecified OPG[174]. When investigating this, they noted a perceptibly high rate of PGD3 of 44% (35/79 patients) within 72 h. At 72 h, post-transplantation, the severe PGD rate dropped to 6% (5/79) and moderate or severe PGD rate of 16% (13/79) which were comparable to the control group in INSPIRE[174]. These findings were also noted in the DEVELOP-UK study where the baseline severe PGD rate was 88.9% and dropped to 27.8% at 72 h [173].

There is a disproportionate number of severe PGD cases following DCD procurement and EVLP. This could be a result of the prolonged functional warm ischaemic time as described above. Another explanation could be the 48% rate of CPB usage in the EXPAND trial (38/79 recipients).

It should be noted that despite the rate PGD associated with EVLP at the time of writing, these were lungs that were unlikely to be used. Given the 98.7% (78/79 patients) 30-d survival rate of lungs transplanted in the EXPAND study, EVLP has a major role to play in expanding the donor pool for lung

Table 5 Differences between the *ex-vivo* lung perfusion protocols

Description	Lund	OCS	Toronto
Year	2001[176]	2011[222]	2008[177]
Perfusion parameters			
Perfusate	CellularSteen solution + RBCs	CellularOCS proprietary solution + RBCs	AcellularSteen solution
Target haematocrit	14%	15%-25%	N/A
Target flow	100% cardiac output	2.0-2.5 L/min	40% cardiac output
PA pressure	≤ 20 mmHg	≤ 20 mmHg	Flow dictated (usually < 15 mmHg)
Left atrium	Open	Open	Closed
Flow type	Continuous	Pulsatile	Continuous
Ventilation			
Initial temperature	32 °C	34 °C	32 °C
Tidal volume	5-7 mL/kg	6 mL/kg	7 mL/kg
Respiratory rate	20/min	10/min	7/min
FiO_2	50%	12%	21%
PEEP	5 cmH_2O	5-7 cmH_2O	5 cmH_2O

FiO2: Fraction of inspired oxygen; RBCs: Red blood cells; PEEP: Positive end-expiratory pressure; OCS: Organ Care System.

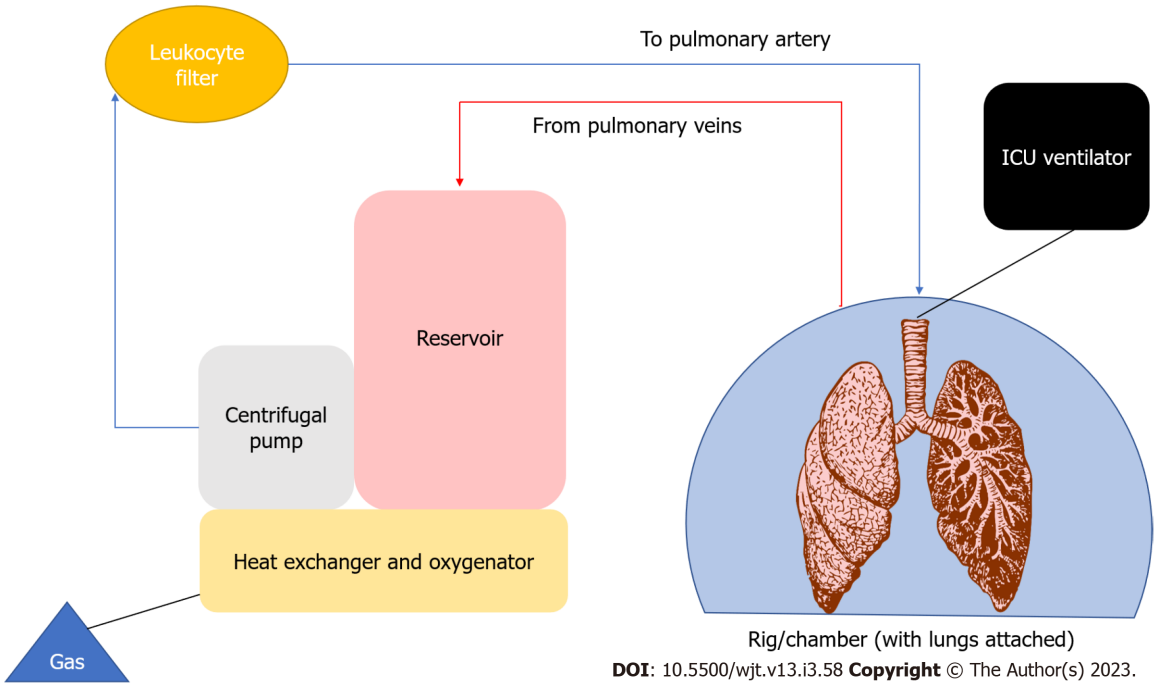

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Figure 4 Example of an *ex vivo* lung perfusion circuit. ICU: Intensive care unit.

transplantation[174]. It remains a viable avenue for studies on preconditioning, attenuation, and mitigation of IRI in the near future.

FUTURE HORIZONS

Given our current understanding of PGD and the role of IRI in its pathogenesis, several experimental studies have been conducted to attenuate these. The search for a biomarker however remains elusive. Several biomarkers have been suggested including RAGE, plasminogen activator inhibitor-1 (PAI-1)

[175], IL-8[176], endothelin-1 (ET-1)[177], ICAM-1[27], proadrenomedullin (proADM)[178], and several others have been mooted but none have made the transition to routine clinical practice. A list of studied biomarkers is available in Table 6.

Shah *et al*[179] utilised a panel of biomarkers to improve the predictive value for PGD and survival by using a combination of biomarkers derived from the alveolar epithelium (sRAGE, SP-D), coagulation cascade proteins (PAI-1 and protein C), and vascular endothelium (ICAM-1). Ongoing research is needed to improve discriminatory value for PGD to allow better resource provision for these patients in the intensive care setting.

Stem cell therapy

EVLP has allowed therapeutic interventions to donor lungs prior to implantation. Using IL-8 as a biomarker for inflammation, the Toronto group created an animal model using porcine lungs preserved for 18 h followed by 12 h of EVLP conditioning[180]. In the treatment arm, mesenchymal stromal cells were used in the pulmonary artery. They noted a significant reduction in IL-8 levels in the perfusate in the intervention arm compared to the control group. A similar study had also been conducted where by McAuley *et al*[181] whereby lungs that were rejected for transplantation were reconditioned using mesenchymal stromal cell administration into the perfusate in the intervention group increased alveolar fluid clearance in the experimental group compared to the control group. A more recent study also showed using amnion-derived mesenchymal stem cells added to Steen Solution during EVLP resulted in further attenuation of IRI effects thus improving the efficacy of EVLP[182]. Mesenchymal stromal cells also demonstrated IL-10 attenuating properties in an animal model on sepsis[183]. Whilst still at an experimental stage, stem cell therapy may provide tangible treatment options in the near future.

Ischaemic preconditioning

Ischaemic preconditioning (IPC) is an intervention whereby brief intermittent ischaemic episodes are induced interspersed with reperfusion either at the site of interest (IPC) or at a distance from the site of interest (remote ischemic preconditioning, RIPC)[184]. The evidence for IPC or RIPC has resulted in mixed outcomes with favourable results in some studies[185-188] but with little clinical benefit in others [189-191]. Many animal models however have shown a reduction in acute lung injury following IPC or RIPC[192-195]. The Dutch group performed a series of lung transplants using rabbits and a variety of IPC strategies and noted that the lungs that underwent increasing bouts of ischaemic preconditioning had less oedema[196]. The authors hinted at an additional benefit for repeated cycles of IPC[196]. Randomised studies on RIPC in lung resections have shown a decreased incidence of acute lung injury in the intervention group[185,197]. A randomised pilot study was performed by Lin *et al*[198] on 52 patients to study the effects of RIPC using a tourniquet on the lower limb of the recipient and noted no statistically significant differences in PaO_2/FiO_2 ratios or panel of inflammatory markers at different time points. They concluded that there was no significant benefit of RIPC although the incidence of IRI/PGD was lower than expected[198]. In their subsequent publication, the Australian group however noted that RIPC is feasible and despite not reaching statistical significance, they noted a trend to improvements in P/F ratio and PGD grade seen at virtually all time points during the first 72 h after lung transplantation[199]. Given the negligible cost of the intervention, a multicenter randomized study could well highlight whether RIPC has a role in lung transplantation.

Pharmacology

Pharmacological interventions to attenuate IRI have been suggested in recent times.

Adenosine A_2A receptor agonist - regadenoson is a drug that was intended for use for its coronary vasodilatory effects during stress testing in myocardial perfusion scans[200]. Animal models have shown success in using Adenosine A_2A agonists with EVLP in reducing IRI[201-203]. A recently completed Phase I study was also published with no dose-limiting toxicities observed and no mortalities reported[204].

α1-antitrypsin (AAT)- is a plasma proteinase inhibitor that has a protective function for proteolytic enzymes produced by inflammatory cells[205]. In a rat model, lungs primed in AAT had decreased weight and allograft necrosis compared to the control group (primed in albumin highlighting a potential role in ameliorating IRI[205]. When used in addition to lung preservation fluid, reduced the extent of primary graft dysfunction and early neutrophil responses after extended storage for 18 h at 4 ℃ and 4-h reperfusion in another rat model study[206]. Interestingly, there were similar findings in proteinase 3/neutrophil elastase (PR3/NE) double-deficient mice, highlighting a potential pathogenetic pathway[206].

C1-esterase inhibitor (C1-INH) - In ARDS, the blood coagulation contact system and the complement system are activated, leading to capillary leakage and the pathognomic sequalae. Activation of the contact as well as the complement system is regulated by a common inhibitor, C1-INH[207]. A canine model study indicated that C1-INH administration prevented hypoxemia, activation of the complement system, and decreased expression of leukocyte adhesion molecules alongside inflammatory cell infiltrate[208].

Table 6 List of biomarkers that have been used in primary graft dysfunction

Biomarker	Donor/recipient	Timing	Type
RAGE[179]	Donor	Retrieval	Alveolar epithelium
	Recipient	Intraoperative, post-transplant	
PAI-1[175]	Recipient	Post-transplant	Vascular endothelium
Protein C[179]	Recipient	Post-transplant	Vascular endothelium
IL-8[176]	Donor	EVLP	Inflammatory marker
	Recipient	Pre-transplant	
		Post-transplant	
ET-1[171]	Donor	EVLP	Inflammatory marker
ICAM-1[27]	Recipient	Post-transplant	Vascular endothelium
IL-6[135]	Recipient	Pre-transplant	Inflammatory marker
		Post-transplant	
IL-10[135]	Recipient	Pre-transplant	Inflammatory marker
		Post-transplant	
proADM[178]	Recipient	Post-transplant	Vascular endothelium
TNF-α[139]	Recipient	Post-transplant	Inflammatory marker
P-selectin[26]	Recipient	Post-transplant	Vascular endothelium
SP-D[179]	Recipient	Post-transplant	Alveolar epithelium

EVLP: Ex-vivo lung perfusion; proADM: Proadrenomedullin; RAGE: Receptor for advanced glycation endproducts; PAI-1: Plasminogen activator inhibitor-1; ET-1: Endothelin-1; ICAM-1: Intercellular adhesion molecule-1; TNF-α: Tumor necrosis factor-alpha; SP-D: Surfactant protein-D.

The Hannover group initially reported 2 cases whereby C1-INH was used to good effect[207]. They reported their experience in using it in PGD3 patients whereby it was administered in the operating theatre once PGD3 was suspected[209]. When comparing the 3 groups (control *vs* C1-INH *vs* PGD3) ICU stay was longest in the PGD3 cohort and prolonged in C1-INH patients compared with the control group [29 (2-70) *vs* 9 (2-83) *vs* 3 (1-166) d, $P = 0.002$]. The C1-INH-treated-group had a one-year survival of 82.5% which was better than the PGD3 cohort (71.4%)[209].

Gene therapy

The Toronto group described one of the earliest attempts at using adenovirus-mediated gene therapy in 1999[210]. They then successfully demonstrated that the adenoviral-mediated human IL-10 (hIL-10) gene to donor rat lungs 24 h before lung retrieval reduced IRI and improved post-transplant graft function[211]. Following the development of EVLP, they were able to administer the adenoviral-mediated hIL-10 gene intrabronchially with 12 h of EVLP and noted significantly better gas exchange, lower histologic inflammation score, and less interferon-gamma production when compared with non-treatment groups[212]. This will perhaps be an avenue clinical application of gene therapy to optimise donor lungs and improve outcomes post-lung transplantation.

CONCLUSION

PGD remains a life-threatening complication post-transplantation. The pathophysiology is not fully understood but ischaemic-reperfusion injury is almost certainly implicated. Diagnostic criteria make classification easier, however, it is still lacking an encompassing biomarker. Animal models and preclinical studies have played vital roles in helping us understand the pathophysiology and engineer therapeutic options which will hopefully translate to clinical benefits in the near future. The role of EVLP is still in its infancy with multiple conditioning, treatment, and assessment options available for research opportunities to guide our ongoing understanding of this condition.

FOOTNOTES

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REFERENCES

1 **Machuca TN**, Keshavjee S. Transplantation for lung cancer. *Curr Opin Organ Transplant* 2012; **17**: 479-484 [PMID: 22907541 DOI: 10.1097/MOT.0b013e328357fff6]
2 **Cooper JD**, Pearson FG, Patterson GA, Todd TR, Ginsberg RJ, Goldberg M, DeMajo WA. Technique of successful lung transplantation in humans. *J Thorac Cardiovasc Surg* 1987; **93**: 173-181 [PMID: 3543506 DOI: 10.1016/S0022-5223(19)36439-6]
3 **Chambers DC**, Cherikh WS, Harhay MO, Hayes D Jr, Hsich E, Khush KK, Meiser B, Potena L, Rossano JW, Toll AE, Singh TP, Sadavarte A, Zuckermann A, Stehlik J; International Society for Heart and Lung Transplantation. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-sixth adult lung and heart-lung transplantation Report-2019; Focus theme: Donor and recipient size match. *J Heart Lung Transplant* 2019; **38**: 1042-1055 [PMID: 31548030 DOI: 10.1016/j.healun.2019.08.001]
4 **Christie JD**, Bellamy S, Ware LB, Lederer D, Hadjiliadis D, Lee J, Robinson N, Localio AR, Wille K, Lama V, Palmer S, Orens J, Weinacker A, Crespo M, Demissie E, Kimmel SE, Kawut SM. Construct validity of the definition of primary graft dysfunction after lung transplantation. *J Heart Lung Transplant* 2010; **29**: 1231-1239 [PMID: 20655249 DOI: 10.1016/j.healun.2010.05.013]
5 **Christie JD**, Van Raemdonck D, de Perrot M, Barr M, Keshavjee S, Arcasoy S, Orens J; ISHLT Working Group on Primary Lung Graft Dysfunction. Report of the ISHLT Working Group on Primary Lung Graft Dysfunction part I: introduction and methods. *J Heart Lung Transplant* 2005; **24**: 1451-1453 [PMID: 16210115 DOI: 10.1016/j.healun.2005.03.004]
6 **Chatila WM**, Furukawa S, Gaughan JP, Criner GJ. Respiratory failure after lung transplantation. *Chest* 2003; **123**: 165-173 [PMID: 12527618 DOI: 10.1378/chest.123.1.165]
7 **Granton J**. Update of early respiratory failure in the lung transplant recipient. *Curr Opin Crit Care* 2006; **12**: 19-24 [PMID: 16394779 DOI: 10.1097/01.ccx.0000198995.44943.63]
8 **Diamond JM**, Arcasoy S, Kennedy CC, Eberlein M, Singer JP, Patterson GM, Edelman JD, Dhillon G, Pena T, Kawut SM, Lee JC, Girgis R, Dark J, Thabut G. Report of the International Society for Heart and Lung Transplantation Working Group on Primary Lung Graft Dysfunction, part II: Epidemiology, risk factors, and outcomes-A 2016 Consensus Group statement of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 2017; **36**: 1104-1113 [PMID: 28802530 DOI: 10.1016/j.healun.2017.07.020]
9 **Diamond JM**, Lee JC, Kawut SM, Shah RJ, Localio AR, Bellamy SL, Lederer DJ, Cantu E, Kohl BA, Lama VN, Bhorade SM, Crespo M, Demissie E, Sonett J, Wille K, Orens J, Shah AS, Weinacker A, Arcasoy S, Shah PD, Wilkes DS, Ware LB, Palmer SM, Christie JD; Lung Transplant Outcomes Group. Clinical risk factors for primary graft dysfunction after lung transplantation. *Am J Respir Crit Care Med* 2013; **187**: 527-534 [PMID: 23306540 DOI: 10.1164/rccm.201210-1865OC]
10 **Snell GI**, Yusen RD, Weill D, Strueber M, Garrity E, Reed A, Pelaez A, Whelan TP, Perch M, Bag R, Budev M, Corris PA, Crespo MM, Witt C, Cantu E, Christie JD. Report of the ISHLT Working Group on Primary Lung Graft Dysfunction, part I: Definition and grading-A 2016 Consensus Group statement of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 2017; **36**: 1097-1103 [PMID: 28942784 DOI: 10.1016/j.healun.2017.07.021]
11 **Oto T**, Griffiths AP, Levvey BJ, Pilcher DV, Williams TJ, Snell GI. Definitions of primary graft dysfunction after lung transplantation: differences between bilateral and single lung transplantation. *J Thorac Cardiovasc Surg* 2006; **132**: 140-147 [PMID: 16798314 DOI: 10.1016/j.jtcvs.2006.03.029]

12 **Van Raemdonck D**, Hartwig MG, Hertz MI, Davis RD, Cypel M, Hayes D Jr, Ivulich S, Kukreja J, Lease ED, Loor G, Mercier O, Paoletti L, Parmar J, Rampolla R, Wille K, Walia R, Keshavjee S. Report of the ISHLT Working Group on primary lung graft dysfunction Part IV: Prevention and treatment: A 2016 Consensus Group statement of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 2017; **36**: 1121-1136 [PMID: 28784325 DOI: 10.1016/j.healun.2017.07.013]

13 **Christie JD**, Kotloff RM, Ahya VN, Tino G, Pochettino A, Gaughan C, DeMissie E, Kimmel SE. The effect of primary graft dysfunction on survival after lung transplantation. *Am J Respir Crit Care Med* 2005; **171**: 1312-1316 [PMID: 15764726 DOI: 10.1164/rccm.200409-1243OC]

14 **Verleden GM**, Glanville AR, Lease ED, Fisher AJ, Calabrese F, Corris PA, Ensor CR, Gottlieb J, Hachem RR, Lama V, Martinu T, Neil DAH, Singer LG, Snell G, Vos R. Chronic lung allograft dysfunction: Definition, diagnostic criteria, and approaches to treatment-A consensus report from the Pulmonary Council of the ISHLT. *J Heart Lung Transplant* 2019; **38**: 493-503 [PMID: 30962148 DOI: 10.1016/j.healun.2019.03.009]

15 **den Hengst WA**, Gielis JF, Lin JY, Van Schil PE, De Windt LJ, Moens AL. Lung ischemia-reperfusion injury: a molecular and clinical view on a complex pathophysiological process. *Am J Physiol Heart Circ Physiol* 2010; **299**: H1283-H1299 [PMID: 20833966 DOI: 10.1152/ajpheart.00251.2010]

16 **Barman SA**, Ardell JL, Parker JC, Perry ML, Taylor AE. Pulmonary and systemic blood flow contributions to upper airways in canine lung. *Am J Physiol* 1988; **255**: H1130-H1135 [PMID: 3189574 DOI: 10.1152/ajpheart.1988.255.5.H1130]

17 **Frye CC**, Bery AI, Kreisel D, Kulkarni HS. Sterile inflammation in thoracic transplantation. *Cell Mol Life Sci* 2021; **78**: 581-601 [PMID: 32803398 DOI: 10.1007/s00018-020-03615-7]

18 **Weyker PD**, Webb CA, Kiamanesh D, Flynn BC. Lung ischemia reperfusion injury: a bench-to-bedside review. *Semin Cardiothorac Vasc Anesth* 2013; **17**: 28-43 [PMID: 23042205 DOI: 10.1177/1089253212458329]

19 **Wang X**, O'Brien ME, Yu J, Xu C, Zhang Q, Lu S, Liang L, An X, McDyer JF, Mallampalli RK. Prolonged Cold Ischemia Induces Necroptotic Cell Death in Ischemia-Reperfusion Injury and Contributes to Primary Graft Dysfunction after Lung Transplantation. *Am J Respir Cell Mol Biol* 2019; **61**: 244-256 [PMID: 30742487 DOI: 10.1165/rcmb.2018-0207OC]

20 **Kim H**, Zamel R, Bai XH, Lu C, Keshavjee S, Liu M. Ischemia-reperfusion induces death receptor-independent necroptosis *via* calpain-STAT3 activation in a lung transplant setting. *Am J Physiol Lung Cell Mol Physiol* 2018; **315**: L595-L608 [PMID: 30024306 DOI: 10.1152/ajplung.00069.2018]

21 **Gielis JF**, Beckers PAJ, Briedé JJ, Cos P, Van Schil PE. Oxidative and nitrosative stress during pulmonary ischemia-reperfusion injury: from the lab to the OR. *Ann Transl Med* 2017; **5**: 131 [PMID: 28462211 DOI: 10.21037/atm.2017.03.32]

22 **Ma J**, Yang L, Ren J, Yang J. Chapter 20 - Autophagy, Oxidative Stress, and Redox Regulation. In: Ren J, Sowers JR, Zhang Y, editors. Autophagy and Cardiometabolic Diseases. Academic Press; 2018: 237-251 [DOI: 10.1016/B978-0-12-805253-2.00020-1]

23 **de Perrot M**, Liu M, Waddell TK, Keshavjee S. Ischemia-reperfusion-induced lung injury. *Am J Respir Crit Care Med* 2003; **167**: 490-511 [PMID: 12588712 DOI: 10.1164/rccm.200207-670SO]

24 **Schnickel GT**, Ross DJ, Beygui R, Shefizadeh A, Laks H, Saggar R, Lynch JP 3rd, Ardehali A. Modified reperfusion in clinical lung transplantation: the results of 100 consecutive cases. *J Thorac Cardiovasc Surg* 2006; **131**: 218-223 [PMID: 16399315 DOI: 10.1016/j.jtcvs.2005.08.045]

25 **Christie JD**, Shah CV, Kawut SM, Mangalmurti N, Lederer DJ, Sonett JR, Ahya VN, Palmer SM, Wille K, Lama V, Shah PD, Shah A, Weinacker A, Deutschman CS, Kohl BA, Demissie E, Bellamy S, Ware LB; Lung Transplant Outcomes Group. Plasma levels of receptor for advanced glycation end products, blood transfusion, and risk of primary graft dysfunction. *Am J Respir Crit Care Med* 2009; **180**: 1010-1015 [PMID: 19661249 DOI: 10.1164/rccm.200901-0118OC]

26 **Kawut SM**, Okun J, Shimbo D, Lederer DJ, De Andrade J, Lama V, Shah A, Milstone A, Ware LB, Weinacker A, Demissie E, Christie JD; Lung Transplant Outcomes Group. Soluble p-selectin and the risk of primary graft dysfunction after lung transplantation. *Chest* 2009; **136**: 237-244 [PMID: 19255296 DOI: 10.1378/chest.08-2697]

27 **Covarrubias M**, Ware LB, Kawut SM, De Andrade J, Milstone A, Weinacker A, Orens J, Lama V, Wille K, Bellamy S, Shah C, Demissie E, Christie JD; Lung Transplant Outcomes Group. Plasma intercellular adhesion molecule-1 and von Willebrand factor in primary graft dysfunction after lung transplantation. *Am J Transplant* 2007; **7**: 2573-2578 [PMID: 17908278 DOI: 10.1111/j.1600-6143.2007.01981.x]

28 **Fang A**, Studer S, Kawut SM, Ahya VN, Lee J, Wille K, Lama V, Ware L, Orens J, Weinacker A, Palmer SM, Crespo M, Lederer DJ, Deutschman CS, Kohl BA, Bellamy S, Demissie E, Christie JD; Lung Transplant Outcomes Group. Elevated pulmonary artery pressure is a risk factor for primary graft dysfunction following lung transplantation for idiopathic pulmonary fibrosis. *Chest* 2011; **139**: 782-787 [PMID: 20864607 DOI: 10.1378/chest.09-2806]

29 **Monticelli LA**, Diamond JM, Saenz SA, Tait Wojno ED, Porteous MK, Cantu E, Artis D, Christie JD. Lung Innate Lymphoid Cell Composition Is Altered in Primary Graft Dysfunction. *Am J Respir Crit Care Med* 2020; **201**: 63-72 [PMID: 31394048 DOI: 10.1164/rccm.201906-1113OC]

30 **Porteous MK**, Ky B, Kirkpatrick JN, Shinohara R, Diamond JM, Shah RJ, Lee JC, Christie JD, Kawut SM. Diastolic Dysfunction Increases the Risk of Primary Graft Dysfunction after Lung Transplant. *Am J Respir Crit Care Med* 2016; **193**: 1392-1400 [PMID: 26745666 DOI: 10.1164/rccm.201508-1522OC]

31 **Li D**, Weinkauf J, Hirji A, Kapasi A, Lien D, Nagendran J, Kim D, Ezekowitz J, Halloran K. Elevated pre-transplant left ventricular end-diastolic pressure increases primary graft dysfunction risk in double lung transplant recipients. *J Heart Lung Transplant* 2019; **38**: 710-718 [PMID: 30850154 DOI: 10.1016/j.healun.2019.02.010]

32 **Avriel A**, Klement AH, Johnson SR, de Perrot M, Granton J. Impact of Left Ventricular Diastolic Dysfunction on Lung Transplantation Outcome in Patients With Pulmonary Arterial Hypertension. *Am J Transplant* 2017; **17**: 2705-2711 [PMID: 28508451 DOI: 10.1111/ajt.14352]

33 **Whitson BA**, Nath DS, Johnson AC, Walker AR, Prekker ME, Radosevich DM, Herrington CS, Dahlberg PS. Risk

factors for primary graft dysfunction after lung transplantation. *J Thorac Cardiovasc Surg* 2006; **131**: 73-80 [PMID: 16399297 DOI: 10.1016/j.jtcvs.2005.08.039]

34 **Bonser RS**, Taylor R, Collett D, Thomas HL, Dark JH, Neuberger J; Cardiothoracic Advisory Group to NHS Blood and Transplant and the Association of Lung Transplant Physicians (UK). Effect of donor smoking on survival after lung transplantation: a cohort study of a prospective registry. *Lancet* 2012; **380**: 747-755 [PMID: 22647758 DOI: 10.1016/S0140-6736(12)60160-3]

35 **Ware LB**, Lee JW, Wickersham N, Nguyen J, Matthay MA, Calfee CS; California Transplant Donor Network. Donor smoking is associated with pulmonary edema, inflammation and epithelial dysfunction in ex vivo human donor lungs. *Am J Transplant* 2014; **14**: 2295-2302 [PMID: 25146497 DOI: 10.1111/ajt.12853]

36 **Kuschner WG**, D'Alessandro A, Wong H, Blanc PD. Dose-dependent cigarette smoking-related inflammatory responses in healthy adults. *Eur Respir J* 1996; **9**: 1989-1994 [PMID: 8902455 DOI: 10.1183/09031936.96.09101989]

37 **Diamond JM**, Porteous MK, Roberts LJ 2nd, Wickersham N, Rushefski M, Kawut SM, Shah RJ, Cantu E 3rd, Lederer DJ, Chatterjee S, Lama VN, Bhorade S, Crespo M, McDyer J, Wille K, Orens J, Weinacker A, Arcasoy S, Shah PD, Wilkes DS, Hage C, Palmer SM, Snyder L, Calfee CS, Ware LB, Christie JD; Lung Transplant Outcomes Group. The relationship between plasma lipid peroxidation products and primary graft dysfunction after lung transplantation is modified by donor smoking and reperfusion hyperoxia. *J Heart Lung Transplant* 2016; **35**: 500-507 [PMID: 26856667 DOI: 10.1016/j.healun.2015.12.012]

38 **Ayala A**, Muñoz MF, Argüelles S. Lipid peroxidation: production, metabolism, and signaling mechanisms of malondialdehyde and 4-hydroxy-2-nonenal. *Oxid Med Cell Longev* 2014; **2014**: 360438 [PMID: 24999379 DOI: 10.1155/2014/360438]

39 **Morrison D**, Rahman I, Lannan S, MacNee W. Epithelial permeability, inflammation, and oxidant stress in the air spaces of smokers. *Am J Respir Crit Care Med* 1999; **159**: 473-479 [PMID: 9927360 DOI: 10.1164/ajrccm.159.2.9804080]

40 **Simou E**, Leonardi-Bee J, Britton J. The Effect of Alcohol Consumption on the Risk of ARDS: A Systematic Review and Meta-Analysis. *Chest* 2018; **154**: 58-68 [PMID: 29288645 DOI: 10.1016/j.chest.2017.11.041]

41 **Lowery EM**, Kuhlmann EA, Mahoney EL, Dilling DF, Kliethermes SA, Kovacs EJ. Heavy alcohol use in lung donors increases the risk for primary graft dysfunction. *Alcohol Clin Exp Res* 2014; **38**: 2853-2861 [PMID: 25421520 DOI: 10.1111/acer.12553]

42 **Pelaez A**, Mitchell PO, Shah NS, Force SD, Elon L, Brown LA, Guidot DM. The role of donor chronic alcohol abuse in the development of primary graft dysfunction in lung transplant recipients. *Am J Med Sci* 2015; **349**: 117-123 [PMID: 25310510 DOI: 10.1097/MAJ.0000000000000361]

43 **Valencia-Martín JL**, Galán I, Rodríguez-Artalejo F. The joint association of average volume of alcohol and binge drinking with hazardous driving behaviour and traffic crashes. *Addiction* 2008; **103**: 749-757 [PMID: 18412753 DOI: 10.1111/j.1360-0443.2008.02165.x]

44 **Poulose B**, Srinivasan K. High risk behaviours following alcohol use in alcohol dependent men. *Indian J Med Res* 2009; **129**: 376-381 [PMID: 19535831]

45 **Pompili M**, Serafini G, Innamorati M, Dominici G, Ferracuti S, Kotzalidis GD, Serra G, Girardi P, Janiri L, Tatarelli R, Sher L, Lester D. Suicidal behavior and alcohol abuse. *Int J Environ Res Public Health* 2010; **7**: 1392-1431 [PMID: 20617037 DOI: 10.3390/ijerph7041392]

46 **Guidot DM**, Brown LA. Mitochondrial glutathione replacement restores surfactant synthesis and secretion in alveolar epithelial cells of ethanol-fed rats. *Alcohol Clin Exp Res* 2000; **24**: 1070-1076 [PMID: 10924012 DOI: 10.1111/j.1530-0277.2000.tb04652.x]

47 **Moss M**, Guidot DM, Wong-Lambertina M, Ten Hoor T, Perez RL, Brown LA. The effects of chronic alcohol abuse on pulmonary glutathione homeostasis. *Am J Respir Crit Care Med* 2000; **161**: 414-419 [PMID: 10673179 DOI: 10.1164/ajrccm.161.2.9905002]

48 **Mitchell PO**, Jensen JS, Ritzenthaler JD, Roman J, Pelaez A, Guidot DM. Alcohol primes the airway for increased interleukin-13 signaling. *Alcohol Clin Exp Res* 2009; **33**: 505-513 [PMID: 19120067 DOI: 10.1111/j.1530-0277.2008.00863.x]

49 **Singh SSA**, Dalzell JR, Berry C, Al-Attar N. Primary graft dysfunction after heart transplantation: a thorn amongst the roses. *Heart Fail Rev* 2019; **24**: 805-820 [PMID: 31020451 DOI: 10.1007/s10741-019-09794-1]

50 **Dayoub JC**, Cortese F, Anžič A, Grum T, de Magalhães JP. The effects of donor age on organ transplants: A review and implications for aging research. *Exp Gerontol* 2018; **110**: 230-240 [PMID: 29935294 DOI: 10.1016/j.exger.2018.06.019]

51 **Baldwin MR**, Peterson ER, Easthausen I, Quintanilla I, Colago E, Sonett JR, D'Ovidio F, Costa J, Diamond JM, Christie JD, Arcasoy SM, Lederer DJ. Donor age and early graft failure after lung transplantation: a cohort study. *Am J Transplant* 2013; **13**: 2685-2695 [PMID: 24034167 DOI: 10.1111/ajt.12428]

52 **De Perrot M**, Waddell TK, Shargall Y, Pierre AF, Fadel E, Uy K, Chaparro C, Hutcheon M, Singer LG, Keshavjee S. Impact of donors aged 60 years or more on outcome after lung transplantation: results of an 11-year single-center experience. *J Thorac Cardiovasc Surg* 2007; **133**: 525-531 [PMID: 17258592 DOI: 10.1016/j.jtcvs.2006.09.054]

53 **Shigemura N**, Horai T, Bhama JK, D'Cunha J, Zaldonis D, Toyoda Y, Pilewski JM, Luketich JD, Bermudez CA. Lung transplantation with lungs from older donors: recipient and surgical factors affect outcomes. *Transplantation* 2014; **98**: 903-908 [PMID: 24825527 DOI: 10.1097/TP.0000000000000134]

54 **Fischer S**, Gohrbandt B, Struckmeier P, Niedermeyer J, Simon A, Hagl C, Kallenbach K, Haverich A, Strüber M. Lung transplantation with lungs from donors fifty years of age and older. *J Thorac Cardiovasc Surg* 2005; **129**: 919-925 [PMID: 15821664 DOI: 10.1016/j.jtcvs.2004.07.053]

55 **Waller DA**, Bennett MK, Corris PA, Dark JH. Donor-acquired fat embolism causing primary organ failure after lung transplantation. *Ann Thorac Surg* 1995; **59**: 1565-1566 [PMID: 7771844 DOI: 10.1016/0003-4975(94)00909-Q]

56 **Rosendale BE**, Keenan RJ, Duncan SR, Hardesty RL, Armitage JA, Griffith BP, Yousem SA. Donor cerebral emboli as a cause of acute graft dysfunction in lung transplantation. *J Heart Lung Transplant* 1992; **11**: 72-76 [PMID: 1540614]

57 **Oto T**, Excell L, Griffiths AP, Levvey BJ, Snell GI. The implications of pulmonary embolism in a multiorgan donor for subsequent pulmonary, renal, and cardiac transplantation. *J Heart Lung Transplant* 2008; **27**: 78-85 [PMID: 18187091

DOI: 10.1016/j.healun.2007.10.001]
58 **Oto T**, Rabinov M, Griffiths AP, Whitford H, Levvey BJ, Esmore DS, Williams TJ, Snell GI. Unexpected donor pulmonary embolism affects early outcomes after lung transplantation: a major mechanism of primary graft failure? *J Thorac Cardiovasc Surg* 2005; **130**: 1446 [PMID: 16256801 DOI: 10.1016/j.jtcvs.2005.07.025]
59 **Ciccone AM**, Stewart KC, Meyers BF, Guthrie TJ, Battafarano RJ, Trulock EP, Cooper JD, Patterson GA. Does donor cause of death affect the outcome of lung transplantation? *J Thorac Cardiovasc Surg* 2002; **123**: 429-434; discussion 434 [PMID: 11882812 DOI: 10.1067/mtc.2002.120732]
60 **Eberlein M**, Reed RM, Bolukbas S, Diamond JM, Wille KM, Orens JB, Brower RG, Christie JD; Lung Transplant Outcomes Group. Lung size mismatch and primary graft dysfunction after bilateral lung transplantation. *J Heart Lung Transplant* 2015; **34**: 233-240 [PMID: 25447586 DOI: 10.1016/j.healun.2014.09.030]
61 **Riddell P**, Ma J, Dunne B, Binnie M, Cypel M, Donahoe L, de Perrot M, Pierre A, Waddell TK, Yeung J, Yasufuku K, Tomlinson G, Singer LG, Keshavjee S. A simplified strategy for donor-recipient size-matching in lung transplant for interstitial lung disease. *J Heart Lung Transplant* 2021; **40**: 1422-1430 [PMID: 34301464 DOI: 10.1016/j.healun.2021.06.013]
62 **Liu Y**, Liu Y, Su L, Jiang SJ. Recipient-related clinical risk factors for primary graft dysfunction after lung transplantation: a systematic review and meta-analysis. *PLoS One* 2014; **9**: e92773 [PMID: 24658073 DOI: 10.1371/journal.pone.0092773]
63 **Wahidi MM**, Ravenel J, Palmer SM, McAdams HP. Progression of idiopathic pulmonary fibrosis in native lungs after single lung transplantation. *Chest* 2002; **121**: 2072-2076 [PMID: 12065382 DOI: 10.1378/chest.121.6.2072]
64 **Khalil N**, O'Connor R. Idiopathic pulmonary fibrosis: current understanding of the pathogenesis and the status of treatment. *CMAJ* 2004; **171**: 153-160 [PMID: 15262886 DOI: 10.1503/cmaj.1030055]
65 **Mason DP**, Brizzio ME, Alster JM, McNeill AM, Murthy SC, Budev MM, Mehta AC, Minai OA, Pettersson GB, Blackstone EH. Lung transplantation for idiopathic pulmonary fibrosis. *Ann Thorac Surg* 2007; **84**: 1121-1128 [PMID: 17888957 DOI: 10.1016/j.athoracsur.2007.04.096]
66 **Kanasky WF Jr**, Anton SD, Rodrigue JR, Perri MG, Szwed T, Baz MA. Impact of body weight on long-term survival after lung transplantation. *Chest* 2002; **121**: 401-406 [PMID: 11834649 DOI: 10.1378/chest.121.2.401]
67 **Madill J**, Gutierrez C, Grossman J, Allard J, Chan C, Hutcheon M, Keshavjee SH; Toronto Lung Transplant Program. Nutritional assessment of the lung transplant patient: body mass index as a predictor of 90-day mortality following transplantation. *J Heart Lung Transplant* 2001; **20**: 288-296 [PMID: 11257554 DOI: 10.1016/S1053-2498(00)00315-6]
68 **Zhang Y**, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. *Nature* 1994; **372**: 425-432 [PMID: 7984236 DOI: 10.1038/372425a0]
69 **Friedman JM**. Modern science versus the stigma of obesity. *Nat Med* 2004; **10**: 563-569 [PMID: 15170194 DOI: 10.1038/nm0604-563]
70 **Fantuzzi G**, Faggioni R. Leptin in the regulation of immunity, inflammation, and hematopoiesis. *J Leukoc Biol* 2000; **68**: 437-446 [PMID: 11037963 DOI: 10.1189/jlb.68.4.437]
71 **Jain M**, Budinger GR, Lo A, Urich D, Rivera SE, Ghosh AK, Gonzalez A, Chiarella SE, Marks K, Donnelly HK, Soberanes S, Varga J, Radigan KA, Chandel NS, Mutlu GM. Leptin promotes fibroproliferative acute respiratory distress syndrome by inhibiting peroxisome proliferator-activated receptor-γ. *Am J Respir Crit Care Med* 2011; **183**: 1490-1498 [PMID: 21317313 DOI: 10.1164/rccm.201009-1409OC]
72 **Lederer DJ**, Kawut SM, Wickersham N, Winterbottom C, Bhorade S, Palmer SM, Lee J, Diamond JM, Wille KM, Weinacker A, Lama VN, Crespo M, Orens JB, Sonett JR, Arcasoy SM, Ware LB, Christie JD; Lung Transplant Outcomes Group. Obesity and primary graft dysfunction after lung transplantation: the Lung Transplant Outcomes Group Obesity Study. *Am J Respir Crit Care Med* 2011; **184**: 1055-1061 [PMID: 21799077 DOI: 10.1164/rccm.201104-0728OC]
73 **Medoff BD**, Okamoto Y, Leyton P, Weng M, Sandall BP, Raher MJ, Kihara S, Bloch KD, Libby P, Luster AD. Adiponectin deficiency increases allergic airway inflammation and pulmonary vascular remodeling. *Am J Respir Cell Mol Biol* 2009; **41**: 397-406 [PMID: 19168697 DOI: 10.1165/rcmb.2008-0415OC]
74 **Charalampidis C**, Youroukou A, Lazaridis G, Baka S, Mpoukovinas I, Karavasilis V, Kioumis I, Pitsiou G, Papaiwannou A, Karavergou A, Tsakiridis K, Katsikogiannis N, Sarika E, Kapanidis K, Sakkas L, Korantzis I, Lampaki S, Zarogoulidis K, Zarogoulidis P. Pleura space anatomy. *J Thorac Dis* 2015; **7**: S27-S32 [PMID: 25774304 DOI: 10.3978/j.issn.2072-1439.2015.01.48]
75 **Shigemura N**, Bhama J, Gries CJ, Kawamura T, Crespo M, Johnson B, Zaldonis D, Pilewski J, Toyoda Y, Bermudez C. Lung transplantation in patients with prior cardiothoracic surgical procedures. *Am J Transplant* 2012; **12**: 1249-1255 [PMID: 22300103 DOI: 10.1111/j.1600-6143.2011.03946.x]
76 **Soresi S**, Zeriouh M, Sabashnikov A, Sarang Z, Mohite PN, Patil NP, Mansur A, Weymann A, Wippermann J, Wahlers T, Reed A, Carby M, Simon AR, Popov AF. Extended Recipient Criteria in Lung Transplantation: Impact of Pleural Abnormalities on Primary Graft Dysfunction. *Ann Thorac Surg* 2016; **101**: 2112-2119 [PMID: 26916718 DOI: 10.1016/j.athoracsur.2015.11.068]
77 **Toyoda Y**, Bhama JK, Shigemura N, Zaldonis D, Pilewski J, Crespo M, Bermudez C. Efficacy of extracorporeal membrane oxygenation as a bridge to lung transplantation. *J Thorac Cardiovasc Surg* 2013; **145**: 1065-1071 [PMID: 23332185 DOI: 10.1016/j.jtcvs.2012.12.067]
78 **Moon S**, Park MS, Lee JG, Jung JY, Kang YA, Kim YS, Kim SK, Chang J, Paik HC, Kim SY. Risk factors and outcome of primary graft dysfunction after lung transplantation in Korea. *J Thorac Dis* 2016; **8**: 3275-3282 [PMID: 28066607 DOI: 10.21037/jtd.2016.11.48]
79 **Gulack BC**, Hirji SA, Hartwig MG. Bridge to lung transplantation and rescue post-transplant: the expanding role of extracorporeal membrane oxygenation. *J Thorac Dis* 2014; **6**: 1070-1079 [PMID: 25132974 DOI: 10.3978/j.issn.2072-1439.2014.06.04]
80 **George TJ**, Beaty CA, Kilic A, Shah PD, Merlo CA, Shah AS. Outcomes and temporal trends among high-risk patients after lung transplantation in the United States. *J Heart Lung Transplant* 2012; **31**: 1182-1191 [PMID: 22885156 DOI: 10.1016/j.healun.2012.07.001]

81 **Mason DP**, Thuita L, Nowicki ER, Murthy SC, Pettersson GB, Blackstone EH. Should lung transplantation be performed for patients on mechanical respiratory support? *J Thorac Cardiovasc Surg* 2010; **139**: 765-773.e1 [PMID: 19931096 DOI: 10.1016/j.jtcvs.2009.09.031]

82 **Sharma NS**, Hartwig MG, Hayes D Jr. Extracorporeal membrane oxygenation in the pre and post lung transplant period. *Ann Transl Med* 2017; **5**: 74 [PMID: 28275619 DOI: 10.21037/atm.2017.02.09]

83 **Hämmäinen P**, Schersten H, Lemström K, Riise GC, Kukkonen S, Swärd K, Sipponen J, Silverborn M, Dellgren G. Usefulness of extracorporeal membrane oxygenation as a bridge to lung transplantation: a descriptive study. *J Heart Lung Transplant* 2011; **30**: 103-107 [PMID: 20934887 DOI: 10.1016/j.healun.2010.08.017]

84 **Hayanga JW**, Lira A, Aboagye JK, Hayanga HK, D'Cunha J. Extracorporeal membrane oxygenation as a bridge to lung transplantation: what lessons might we learn from volume and expertise? *Interact Cardiovasc Thorac Surg* 2016; **22**: 406-410 [PMID: 26769730 DOI: 10.1093/icvts/ivv379]

85 **Shafii AE**, Mason DP, Brown CR, Vakil N, Johnston DR, McCurry KR, Pettersson GB, Murthy SC. Growing experience with extracorporeal membrane oxygenation as a bridge to lung transplantation. *ASAIO J* 2012; **58**: 526-529 [PMID: 22929896 DOI: 10.1097/MAT.0b013e31826417d8]

86 **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 [PMID: 28918471 DOI: 10.1007/s11748-017-0836-3]

87 **Bermudez CA**, Shiose A, Esper SA, Shigemura N, D'Cunha J, Bhama JK, Richards TJ, Arlia P, Crespo MM, Pilewski JM. Outcomes of intraoperative venoarterial extracorporeal membrane oxygenation versus cardiopulmonary bypass during lung transplantation. *Ann Thorac Surg* 2014; **98**: 1936-42; discussion 1942 [PMID: 25443002 DOI: 10.1016/j.athoracsur.2014.06.072]

88 **Hoetzenecker K**, Donahoe L, Yeung JC, Azad S, Fan E, Ferguson ND, Del Sorbo L, de Perrot M, Pierre A, Yasufuku K, Singer L, Waddell TK, Keshavjee S, Cypel M. Extracorporeal life support as a bridge to lung transplantation-experience of a high-volume transplant center. *J Thorac Cardiovasc Surg* 2018; **155**: 1316-1328.e1 [PMID: 29248282 DOI: 10.1016/j.jtcvs.2017.09.161]

89 **Avtaar Singh SS**, DAS DE S, Rushton S, Berry C, Al-Attar N. PREDICTA: A Model to Predict Primary Graft Dysfunction After Adult Heart Transplantation in the United Kingdom. *J Card Fail* 2019; **25**: 971-977 [PMID: 31330297 DOI: 10.1016/j.cardfail.2019.07.009]

90 **Khan TFT**, Ahmad N, Serageldeen AS, Fourtounas K. Implantation Warm Ischemia Time in Kidney Transplant Recipients: Defining Its Limits and Impact on Early Graft Function. *Ann Transplant* 2019; **24**: 432-438 [PMID: 31332156 DOI: 10.12659/AOT.916012]

91 **Lozanovski VJ**, Döhler B, Weiss KH, Mehrabi A, Süsal C. The Differential Influence of Cold Ischemia Time on Outcome After Liver Transplantation for Different Indications-Who Is at Risk? *Front Immunol* 2020; **11**: 892 [PMID: 32477362 DOI: 10.3389/fimmu.2020.00892]

92 **Thabut G**, Vinatier I, Brugière O, Lesèche G, Loirat P, Bisson A, Marty J, Fournier M, Mal H. Influence of preservation solution on early graft failure in clinical lung transplantation. *Am J Respir Crit Care Med* 2001; **164**: 1204-1208 [PMID: 11673210 DOI: 10.1164/ajrccm.164.7.2012135]

93 **Novick RJ**, Bennett LE, Meyer DM, Hosenpud JD. Influence of graft ischemic time and donor age on survival after lung transplantation. *J Heart Lung Transplant* 1999; **18**: 425-431 [PMID: 10363686 DOI: 10.1016/S1053-2498(98)00057-6]

94 **Bund M**, Strüber M, Heine J, Jaeger K, Wahlers T, Haverich A, Piepenbrock S. Effect of lung allograft ischaemia duration on postreperfusion graft function and postoperative course. *Thorac Cardiovasc Surg* 1998; **46**: 93-96 [PMID: 9618811 DOI: 10.1055/s-2007-1010197]

95 **Grimm JC**, Valero V 3rd, Kilic A, Magruder JT, Merlo CA, Shah PD, Shah AS. Association Between Prolonged Graft Ischemia and Primary Graft Failure or Survival Following Lung Transplantation. *JAMA Surg* 2015; **150**: 547-553 [PMID: 25874575 DOI: 10.1001/jamasurg.2015.12]

96 **Chambers DC**, Yusen RD, Cherikh WS, Goldfarb SB, Kucheryavaya AY, Khusch K, Levvey BJ, Lund LH, Meiser B, Rossano JW, Stehlik J; International Society for Heart and Lung Transplantation. The Registry of the International Society for Heart and Lung Transplantation: Thirty-fourth Adult Lung And Heart-Lung Transplantation Report-2017; Focus Theme: Allograft ischemic time. *J Heart Lung Transplant* 2017; **36**: 1047-1059 [PMID: 28784324 DOI: 10.1016/j.healun.2017.07.016]

97 **Snell GI**, Rabinov M, Griffiths A, Williams T, Ugoni A, Salamonsson R, Esmore D. Pulmonary allograft ischemic time: an important predictor of survival after lung transplantation. *J Heart Lung Transplant* 1996; **15**: 160-168 [PMID: 8672519]

98 **Gammie JS**, Stukus DR, Pham SM, Hattler BG, McGrath MF, McCurry KR, Griffith BP, Keenan RJ. Effect of ischemic time on survival in clinical lung transplantation. *Ann Thorac Surg* 1999; **68**: 2015-9; discussion 2019 [PMID: 10616969 DOI: 10.1016/S0003-4975(99)00903-0]

99 **Ghaidan H**, Fakhro M, Lindstedt S. Impact of allograft ischemic time on long-term survival in lung transplantation: a Swedish monocentric study. *Scand Cardiovasc J* 2020; **54**: 322-329 [PMID: 32573283 DOI: 10.1080/14017431.2020.1781240]

100 **Sandoval E**, Fernández-Cisneros A, Boada M. DCD lungs: is it all the same? *Ann Cardiothorac Surg* 2020; **9**: 54-55 [PMID: 32175241 DOI: 10.21037/acs.2019.11.07]

101 **Halazun KJ**, Al-Mukhtar A, Aldouri A, Willis S, Ahmad N. Warm ischemia in transplantation: search for a consensus definition. *Transplant Proc* 2007; **39**: 1329-1331 [PMID: 17580133 DOI: 10.1016/j.transproceed.2007.02.061]

102 **Manara AR**, Murphy PG, O'Callaghan G. Donation after circulatory death. *Br J Anaesth* 2012; **108** Suppl 1: i108-i121 [PMID: 22194426 DOI: 10.1093/bja/aer357]

103 **Kayano K**, Toda K, Naka Y, Pinsky DJ. Identification of optimal conditions for lung graft storage with Euro-Collins solution by use of a rat orthotopic lung transplant model. *Circulation* 1999; **100**: II257-II261 [PMID: 10567313 DOI: 10.1161/01.CIR.100.suppl_2.II-257]

104 **DeCampos KN**, Keshavjee S, Liu M, Slutsky AS. Optimal inflation volume for hypothermic preservation of rat lungs. *J*

Heart Lung Transplant 1998; **17**: 599-607 [PMID: 9662096]

105 **Healey A**, Watanabe Y, Mills C, Stoncius M, Lavery S, Johnson K, Sanderson R, Humar A, Yeung J, Donahoe L, Pierre A, de Perrot M, Yasufuku K, Waddell TK, Keshavjee S, Cypel M. Initial lung transplantation experience with uncontrolled donation after cardiac death in North America. *Am J Transplant* 2020; **20**: 1574-1581 [PMID: 31995660 DOI: 10.1111/ajt.15795]

106 **Villavicencio MA**, Axtell AL, Spencer PJ, Heng EE, Kilmarx S, Dalpozzal N, Funamoto M, Roy N, Osho A, Melnitchouk S, D'Alessandro DA, Tolis G, Astor T. Lung Transplantation From Donation After Circulatory Death: United States and Single-Center Experience. *Ann Thorac Surg* 2018; **106**: 1619-1627 [PMID: 30205113 DOI: 10.1016/j.athoracsur.2018.07.024]

107 **Sabashnikov A**, Patil NP, Popov AF, Soresi S, Zych B, Weymann A, Mohite PN, García Sáez D, Zeriouh M, Wahlers T, Choi YH, Wippermann J, Wittwer T, De Robertis F, Bahrami T, Amrani M, Simon AR. Long-term results after lung transplantation using organs from circulatory death donors: a propensity score-matched analysis†. *Eur J Cardiothorac Surg* 2016; **49**: 46-53 [PMID: 25777057 DOI: 10.1093/ejcts/ezv051]

108 **Erasmus ME**, van Raemdonck D, Akhtar MZ, Neyrinck A, de Antonio DG, Varela A, Dark J. DCD lung donation: donor criteria, procedural criteria, pulmonary graft function validation, and preservation. *Transpl Int* 2016; **29**: 790-797 [PMID: 26718316 DOI: 10.1111/tri.12738]

109 **Krutsinger D**, Reed RM, Blevins A, Puri V, De Oliveira NC, Zych B, Bolukbas S, Van Raemdonck D, Snell GI, Eberlein M. Lung transplantation from donation after cardiocirculatory death: a systematic review and meta-analysis. *J Heart Lung Transplant* 2015; **34**: 675-684 [PMID: 25638297 DOI: 10.1016/j.healun.2014.11.009]

110 **Copeland H**, Hayanga JWA, Neyrinck A, MacDonald P, Dellgren G, Bertolotti A, Khuu T, Burrows F, Copeland JG, Gooch D, Hackmann A, Hormuth D, Kirk C, Linacre V, Lyster H, Marasco S, McGiffin D, Nair P, Rahmel A, Sasevich M, Schweiger M, Siddique A, Snyder TJ, Stansfield W, Tsui S, Orr Y, Uber P, Venkateswaran R, Kukreja J, Mulligan M. Donor heart and lung procurement: A consensus statement. *J Heart Lung Transplant* 2020; **39**: 501-517 [PMID: 32503726 DOI: 10.1016/j.healun.2020.03.020]

111 **Oechslin P**, Zalunardo MP, Inci I, Schlaepfer M, Grande B. Established and potential predictors of blood loss during lung transplant surgery. *J Thorac Dis* 2018; **10**: 3845-3848 [PMID: 30069385 DOI: 10.21037/jtd.2018.05.165]

112 **Semple JW**, Rebetz J, Kapur R. Transfusion-associated circulatory overload and transfusion-related acute lung injury. *Blood* 2019; **133**: 1840-1853 [PMID: 30808638 DOI: 10.1182/blood-2018-10-860809]

113 **Weber D**, Cottini SR, Locher P, Wenger U, Stehberger PA, Fasshauer M, Schuepbach RA, Béchir M. Association of intraoperative transfusion of blood products with mortality in lung transplant recipients. *Perioper Med (Lond)* 2013; **2**: 20 [PMID: 24472535 DOI: 10.1186/2047-0525-2-20]

114 **Björkbom E**, Hämmäinen P, Schramko A. Effects of Perioperative Fluid Replacement Therapy in Lung Transplant Patients. *Exp Clin Transplant* 2017; **15**: 78-81 [PMID: 27855591 DOI: 10.6002/ect.2016.0033]

115 **Cunningham PS**, Maidstone R, Durrington HJ, Venkateswaran RV, Cypel M, Keshavjee S, Gibbs JE, Loudon AS, Chow CW, Ray DW, Blaikley JF. Incidence of primary graft dysfunction after lung transplantation is altered by timing of allograft implantation. *Thorax* 2019; **74**: 413-416 [PMID: 30301818 DOI: 10.1136/thoraxjnl-2018-212021]

116 **Griffin P**, Dimitry JM, Sheehan PW, Lananna BV, Guo C, Robinette ML, Hayes ME, Cedeño MR, Nadarajah CJ, Ezerskiy LA, Colonna M, Zhang J, Bauer AQ, Burris TP, Musiek ES. Circadian clock protein Rev-erbα regulates neuroinflammation. *Proc Natl Acad Sci USA* 2019; **116**: 5102-5107 [PMID: 30792350 DOI: 10.1073/pnas.1812405116]

117 **Montaigne D**, Marechal X, Modine T, Coisne A, Mouton S, Fayad G, Ninni S, Klein C, Ortmans S, Seunes C, Potelle C, Berthier A, Gheeraert C, Piveteau C, Deprez R, Eeckhoute J, Duez H, Lacroix D, Deprez B, Jegou B, Koussa M, Edme JL, Lefebvre P, Staels B. Daytime variation of perioperative myocardial injury in cardiac surgery and its prevention by Rev-Erbα antagonism: a single-centre propensity-matched cohort study and a randomised study. *Lancet* 2018; **391**: 59-69 [PMID: 29107324 DOI: 10.1016/S0140-6736(17)32132-3]

118 **Ikeda R**, Tsuchiya Y, Koike N, Umemura Y, Inokawa H, Ono R, Inoue M, Sasawaki Y, Grieten T, Okubo N, Ikoma K, Fujiwara H, Kubo T, Yagita K. REV-ERBα and REV-ERBβ function as key factors regulating Mammalian Circadian Output. *Sci Rep* 2019; **9**: 10171 [PMID: 31308426 DOI: 10.1038/s41598-019-46656-0]

119 **Ren D**, Kaleekal TS, Graviss EA, Nguyen DT, Sinha N, Goodarzi A, Agboli I, Suarez EE, Loebe M, Scheinin SA, Bruckner BA. Retransplantation Outcomes at a Large Lung Transplantation Program. *Transplant Direct* 2018; **4**: e404 [PMID: 30534595 DOI: 10.1097/TXD.0000000000000844]

120 **Wallinder A**, Danielsson C, Magnusson J, Riise GC, Dellgren G. Outcomes and Long-term Survival After Pulmonary Retransplantation: A Single-Center Experience. *Ann Thorac Surg* 2019; **108**: 1037-1044 [PMID: 31121129 DOI: 10.1016/j.athoracsur.2019.04.028]

121 **Osaki S**, Maloney JD, Meyer KC, Cornwell RD, Edwards NM, De Oliveira NC. Redo lung transplantation for acute and chronic lung allograft failure: long-term follow-up in a single center. *Eur J Cardiothorac Surg* 2008; **34**: 1191-1197 [PMID: 18774303 DOI: 10.1016/j.ejcts.2008.07.052]

122 **Aigner C**, Jaksch P, Taghavi S, Lang G, Reza-Hoda MA, Wisser W, Klepetko W. Pulmonary retransplantation: is it worth the effort? *J Heart Lung Transplant* 2008; **27**: 60-65 [PMID: 18187088 DOI: 10.1016/j.healun.2007.09.023]

123 **Schumer EM**, Rice JD, Kistler AM, Trivedi JR, Black MC, Bousamra M 2nd, van Berkel V. Single Versus Double Lung Retransplantation Does Not Affect Survival Based on Previous Transplant Type. *Ann Thorac Surg* 2017; **103**: 236-240 [PMID: 27677564 DOI: 10.1016/j.athoracsur.2016.07.012]

124 **Acute Respiratory Distress Syndrome Network**, Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; **342**: 1301-1308 [PMID: 10793162 DOI: 10.1056/NEJM200005043421801]

125 **Barnes L**, Reed RM, Parekh KR, Bhama JK, Pena T, Rajagopal S, Schmidt GA, Klesney-Tait JA, Eberlein M. Mechanical ventilation for the lung transplant recipient. *Curr Pulmonol Rep* 2015; **4**: 88-96 [PMID: 26495241 DOI: 10.1007/s13665-015-0114-8]

126 **Petrucci N**, De Feo C. Lung protective ventilation strategy for the acute respiratory distress syndrome. *Cochrane*

Database Syst Rev 2013; **2013**: CD003844 [PMID: 23450544 DOI: 10.1002/14651858.CD003844.pub4]

127 **Chacko B**, Peter JV, Tharyan P, John G, Jeyaseelan L. Pressure-controlled versus volume-controlled ventilation for acute respiratory failure due to acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). *Cochrane Database Syst Rev* 2015; **1**: CD008807 [PMID: 25586462 DOI: 10.1002/14651858.CD008807.pub2]

128 **Tague LK**, Bedair B, Witt C, Byers DE, Vazquez-Guillamet R, Kulkarni H, Alexander-Brett J, Nava R, Puri V, Kreisel D, Trulock EP, Gelman A, Hachem RR. Lung protective ventilation based on donor size is associated with a lower risk of severe primary graft dysfunction after lung transplantation. *J Heart Lung Transplant* 2021; **40**: 1212-1222 [PMID: 34353713 DOI: 10.1016/j.healun.2021.06.016]

129 **Pierre AF**, DeCampos KN, Liu M, Edwards V, Cutz E, Slutsky AS, Keshavjee SH. Rapid reperfusion causes stress failure in ischemic rat lungs. *J Thorac Cardiovasc Surg* 1998; **116**: 932-942 [PMID: 9832683 DOI: 10.1016/S0022-5223(98)70043-1]

130 **Ardehali A**, Laks H, Russell H, Levine M, Shpiner R, Lackey S, Ross D. Modified reperfusion and ischemia-reperfusion injury in human lung transplantation. *J Thorac Cardiovasc Surg* 2003; **126**: 1929-1934 [PMID: 14688708 DOI: 10.1016/S0022-5223(03)00976-0]

131 **Kagawa H**, Morita K, Nagahori R, Shinohara G, Kinouchi K, Hashimoto K. Prevention of ischemia/reperfusion-induced pulmonary dysfunction after cardiopulmonary bypass with terminal leukocyte-depleted lung reperfusion. *J Thorac Cardiovasc Surg* 2010; **139**: 174-180 [PMID: 19919867 DOI: 10.1016/j.jtcvs.2009.08.036]

132 **Noda K**, Tane S, Haam SJ, D'Cunha J, Hayanga AJ, Luketich JD, Shigemura N. Targeting Circulating Leukocytes and Pyroptosis During Ex Vivo Lung Perfusion Improves Lung Preservation. *Transplantation* 2017; **101**: 2841-2849 [PMID: 28452921 DOI: 10.1097/TP.0000000000001798]

133 **Date H**, Triantafillou AN, Trulock EP, Pohl MS, Cooper JD, Patterson GA. Inhaled nitric oxide reduces human lung allograft dysfunction. *J Thorac Cardiovasc Surg* 1996; **111**: 913-919 [PMID: 8622313 DOI: 10.1016/S0022-5223(96)70364-1]

134 **Gebistorf F**, Karam O, Wetterslev J, Afshari A. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) in children and adults. *Cochrane Database Syst Rev* 2016; **2016**: CD002787 [PMID: 27347773 DOI: 10.1002/14651858.CD002787.pub3]

135 **Moreno I**, Vicente R, Mir A, León I, Ramos F, Vicente JL, Barbera M. Effects of inhaled nitric oxide on primary graft dysfunction in lung transplantation. *Transplant Proc* 2009; **41**: 2210-2212 [PMID: 19715875 DOI: 10.1016/j.transproceed.2009.05.019]

136 **Yerebakan C**, Ugurlucan M, Bayraktar S, Bethea BT, Conte JV. Effects of inhaled nitric oxide following lung transplantation. *J Card Surg* 2009; **24**: 269-274 [PMID: 19438780 DOI: 10.1111/j.1540-8191.2009.00833.x]

137 **Bhandary S**, Stoicea N, Joseph N, Whitson B, Essandoh M. Pro: Inhaled Pulmonary Vasodilators Should Be Used Routinely in the Management of Patients Undergoing Lung Transplantation. *J Cardiothorac Vasc Anesth* 2017; **31**: 1123-1126 [PMID: 27863877 DOI: 10.1053/j.jvca.2016.08.036]

138 **Shargall Y**, Guenther G, Ahya VN, Ardehali A, Singhal A, Keshavjee S; ISHLT Working Group on Primary Lung Graft Dysfunction. Report of the ISHLT Working Group on Primary Lung Graft Dysfunction part VI: treatment. *J Heart Lung Transplant* 2005; **24**: 1489-1500 [PMID: 16210120 DOI: 10.1016/j.healun.2005.03.011]

139 **de Perrot M**, Fischer S, Liu M, Jin R, Bai XH, Waddell TK, Keshavjee S. Prostaglandin E1 protects lung transplants from ischemia-reperfusion injury: a shift from pro- to anti-inflammatory cytokines. *Transplantation* 2001; **72**: 1505-1512 [PMID: 11707737 DOI: 10.1097/00007890-200111150-00006]

140 **Toyoda Y**, Thacker J, Santos R, Nguyen D, Bhama J, Bermudez C, Kormos R, Johnson B, Crespo M, Pilewski J, Teuteberg J, Alvarez R, Mathier M, McNamara D, McCurry K, Zenati M, Hattler B. Long-term outcome of lung and heart-lung transplantation for idiopathic pulmonary arterial hypertension. *Ann Thorac Surg* 2008; **86**: 1116-1122 [PMID: 18805144 DOI: 10.1016/j.athoracsur.2008.05.049]

141 **Chiang CH**, Wu K, Yu CP, Yan HC, Perng WC, Wu CP. Hypothermia and prostaglandin E(1) produce synergistic attenuation of ischemia-reperfusion lung injury. *Am J Respir Crit Care Med* 1999; **160**: 1319-1323 [PMID: 10508824 DOI: 10.1164/ajrccm.160.4.9811079]

142 **Riva CM**, Morganroth ML, Ljungman AG, Schoeneich SO, Marks RM, Todd RF 3rd, Ward PA, Boxer LA. Iloprost inhibits neutrophil-induced lung injury and neutrophil adherence to endothelial monolayers. *Am J Respir Cell Mol Biol* 1990; **3**: 301-309 [PMID: 1698399 DOI: 10.1165/ajrcmb/3.4.301]

143 **Lee SH**, Lee JG, Lee CY, Kim N, Chang MY, You YC, Kim HJ, Paik HC, Oh YJ. Effects of intraoperative inhaled iloprost on primary graft dysfunction after lung transplantation: A retrospective single center study. *Medicine (Baltimore)* 2016; **95**: e3975 [PMID: 27399072 DOI: 10.1097/MD.0000000000003975]

144 **Kawashima M**, Nakamura T, Schneider S, Vollmar B, Lausberg HF, Bauer M, Menger MD, Schäfers HJ. Iloprost ameliorates post-ischemic lung reperfusion injury and maintains an appropriate pulmonary ET-1 balance. *J Heart Lung Transplant* 2003; **22**: 794-801 [PMID: 12873548 DOI: 10.1016/S1053-2498(02)00646-0]

145 **Koksel O**, Ozdulger A, Aytacoglu B, Tamer L, Polat A, Sucu N, Yildirim C, Degirmenci U, Kanik A. The influence of iloprost on acute lung injury induced by hind limb ischemia-reperfusion in rats. *Pulm Pharmacol Ther* 2005; **18**: 235-241 [PMID: 15777606 DOI: 10.1016/j.pupt.2004.12.005]

146 **Amital A**, Shitrit D, Raviv Y, Saute M, Medalion B, Bakal L, Kramer MR. The use of surfactant in lung transplantation. *Transplantation* 2008; **86**: 1554-1559 [PMID: 19077889 DOI: 10.1097/TP.0b013e31818a8418]

147 **Amital A**, Shitrit D, Raviv Y, Saute M, Bakal I, Medalion B, Kramer MR. Surfactant as salvage therapy in life threatening primary graft dysfunction in lung transplantation. *Eur J Cardiothorac Surg* 2009; **35**: 299-303 [PMID: 18996711 DOI: 10.1016/j.ejcts.2008.09.039]

148 **Wigfield CH**, Lindsey JD, Steffens TG, Edwards NM, Love RB. Early institution of extracorporeal membrane oxygenation for primary graft dysfunction after lung transplantation improves outcome. *J Heart Lung Transplant* 2007; **26**: 331-338 [PMID: 17403473 DOI: 10.1016/j.healun.2006.12.010]

149 **Bermudez CA**, Adusumilli PS, McCurry KR, Zaldonis D, Crespo MM, Pilewski JM, Toyoda Y. Extracorporeal membrane oxygenation for primary graft dysfunction after lung transplantation: long-term survival. *Ann Thorac Surg*

2009; **87**: 854-860 [PMID: 19231405 DOI: 10.1016/j.athoracsur.2008.11.036]
150 **Hartwig MG**, Appel JZ 3rd, Cantu E 3rd, Simsir S, Lin SS, Hsieh CC, Walczak R, Palmer SM, Davis RD Jr. Improved results treating lung allograft failure with venovenous extracorporeal membrane oxygenation. *Ann Thorac Surg* 2005; **80**: 1872-1879; discussion 1879 [PMID: 16242472 DOI: 10.1016/j.athoracsur.2005.04.063]
151 **Hartwig MG**, Walczak R, Lin SS, Davis RD. Improved survival but marginal allograft function in patients treated with extracorporeal membrane oxygenation after lung transplantation. *Ann Thorac Surg* 2012; **93**: 366-371 [PMID: 21962264 DOI: 10.1016/j.athoracsur.2011.05.017]
152 **Cheng R**, Hachamovitch R, Kittleson M, Patel J, Arabia F, Moriguchi J, Esmailian F, Azarbal B. Complications of extracorporeal membrane oxygenation for treatment of cardiogenic shock and cardiac arrest: a meta-analysis of 1,866 adult patients. *Ann Thorac Surg* 2014; **97**: 610-616 [PMID: 24210621 DOI: 10.1016/j.athoracsur.2013.09.008]
153 **Force SD**, Miller DL, Pelaez A, Ramirez AM, Vega D, Barden B, Lawrence EC. Outcomes of delayed chest closure after bilateral lung transplantation. *Ann Thorac Surg* 2006; **81**: 2020-2024; discussion 2024 [PMID: 16731123 DOI: 10.1016/j.athoracsur.2006.01.050]
154 **Shigemura N**, Orhan Y, Bhama JK, D'Cunha J, Zaldonis D, Pilewski JM, Luketich JD, Bermudez CA. Delayed chest closure after lung transplantation: techniques, outcomes, and strategies. *J Heart Lung Transplant* 2014; **33**: 741-748 [PMID: 24726683 DOI: 10.1016/j.healun.2014.03.003]
155 **Shimoyama T**, Tabuchi N, Kojima K, Akamatsu H, Arai H, Tanaka H, Sunamori M. Aprotinin attenuated ischemia-reperfusion injury in an isolated rat lung model after 18-hours preservation. *Eur J Cardiothorac Surg* 2005; **28**: 581-587 [PMID: 16125404 DOI: 10.1016/j.ejcts.2005.06.038]
156 **Eren S**, Esme H, Balci AE, Cakir O, Buyukbayram H, Eren MN, Erdinc L, Satici O. The effect of aprotinin on ischemia-reperfusion injury in an in situ normothermic ischemic lung model. *Eur J Cardiothorac Surg* 2003; **23**: 60-65 [PMID: 12493506 DOI: 10.1016/S1010-7940(02)00623-1]
157 **Roberts RF**, Nishanian GP, Carey JN, Darbinian SH, Kim JD, Sakamaki Y, Chang JY, Starnes VA, Barr ML. Addition of aprotinin to organ preservation solutions decreases lung reperfusion injury. *Ann Thorac Surg* 1998; **66**: 225-230 [PMID: 9692469 DOI: 10.1016/S0003-4975(98)00323-3]
158 **Mathias MA**, Tribble CG, Dietz JF, Nguyen RP, Shockey KS, Kern JA, Kron IL. Aprotinin improves pulmonary function during reperfusion in an isolated lung model. *Ann Thorac Surg* 2000; **70**: 1671-1674 [PMID: 11093508 DOI: 10.1016/S0003-4975(00)01767-7]
159 **Bittner HB**, Richter M, Kuntze T, Rahmel A, Dahlberg P, Hertz M, Mohr FW. Aprotinin decreases reperfusion injury and allograft dysfunction in clinical lung transplantation. *Eur J Cardiothorac Surg* 2006; **29**: 210-215 [PMID: 16386921 DOI: 10.1016/j.ejcts.2005.12.001]
160 **Scholten EL**, Beitler JR, Prisk GK, Malhotra A. Treatment of ARDS With Prone Positioning. *Chest* 2017; **151**: 215-224 [PMID: 27400909 DOI: 10.1016/j.chest.2016.06.032]
161 **Lai-Fook SJ**, Rodarte JR. Pleural pressure distribution and its relationship to lung volume and interstitial pressure. *J Appl Physiol (1985)* 1991; **70**: 967-978 [PMID: 2033012 DOI: 10.1152/jappl.1991.70.3.967]
162 **Gattinoni L**, Chiumello D, Rossi S. COVID-19 pneumonia: ARDS or not? *Crit Care* 2020; **24**: 154 [PMID: 32299472 DOI: 10.1186/s13054-020-02880-z]
163 **Petrone P**, Brathwaite CEM, Joseph DK. Prone ventilation as treatment of acute respiratory distress syndrome related to COVID-19. *Eur J Trauma Emerg Surg* 2021; **47**: 1017-1022 [PMID: 33201268 DOI: 10.1007/s00068-020-01542-7]
164 **Feltracco P**, Serra E, Barbieri S, Milevoj M, Michieletto E, Carollo C, Rea F, Zanus G, Boetto R, Ori C. Noninvasive high-frequency percussive ventilation in the prone position after lung transplantation. *Transplant Proc* 2012; **44**: 2016-2021 [PMID: 22974896 DOI: 10.1016/j.transproceed.2012.05.062]
165 **Cypel M**, Yeung JC, Liu M, Anraku M, Chen F, Karolak W, Sato M, Laratta J, Azad S, Madonik M, Chow CW, Chaparro C, Hutcheon M, Singer LG, Slutsky AS, Yasufuku K, de Perrot M, Pierre AF, Waddell TK, Keshavjee S. Normothermic ex vivo lung perfusion in clinical lung transplantation. *N Engl J Med* 2011; **364**: 1431-1440 [PMID: 21488765 DOI: 10.1056/NEJMoa1014597]
166 **Moreno Garijo J**, Roscoe A. Ex-vivo lung perfusion. *Curr Opin Anaesthesiol* 2020; **33**: 50-54 [PMID: 31688085 DOI: 10.1097/ACO.0000000000000804]
167 **Steen S**, Sjöberg T, Pierre L, Liao Q, Eriksson L, Algotsson L. Transplantation of lungs from a non-heart-beating donor. *Lancet* 2001; **357**: 825-829 [PMID: 11265950 DOI: 10.1016/S0140-6736(00)04195-7]
168 **Cypel M**, Yeung JC, Hirayama S, Rubacha M, Fischer S, Anraku M, Sato M, Harwood S, Pierre A, Waddell TK, de Perrot M, Liu M, Keshavjee S. Technique for prolonged normothermic ex vivo lung perfusion. *J Heart Lung Transplant* 2008; **27**: 1319-1325 [PMID: 19059112 DOI: 10.1016/j.healun.2008.09.003]
169 **Andreasson AS**, Dark JH, Fisher AJ. Ex vivo lung perfusion in clinical lung transplantation--state of the art. *Eur J Cardiothorac Surg* 2014; **46**: 779-788 [PMID: 25061215 DOI: 10.1093/ejcts/ezu228]
170 **Nur E**, Brandjes DP, Schnog JJ, Otten HM, Fijnvandraat K, Schalkwijk CG, Biemond BJ; CURAMA Study Group. Plasma levels of advanced glycation end products are associated with haemolysis-related organ complications in sickle cell patients. *Br J Haematol* 2010; **151**: 62-69 [PMID: 20678158 DOI: 10.1111/j.1365-2141.2010.08320.x]
171 **Sanchez PG**, Davis RD, D'Ovidio F, Cantu E, Weyant M, Camp P, Griffith B. The NOVEL Lung Trial One-Year Outcomes. *J Heart Lung Transplant* 2014; 33: S71-S72 [DOI: 10.1016/j.healun.2014.01.226]
172 **Warnecke G**, Van Raemdonck D, Smith MA, Massard G, Kukreja J, Rea F, Loor G, De Robertis F, Nagendran J, Dhital KK, Moradiellos Díez FJ, Knosalla C, Bermudez CA, Tsui S, McCurry K, Wang IW, Deuse T, Lesèche G, Thomas P, Tudorache I, Kühn C, Avsar M, Wiegmann B, Sommer W, Neyrinck A, Schiavon M, Calabrese F, Santelmo N, Olland A, Falcoz PE, Simon AR, Varela A, Madsen JC, Hertz M, Haverich A, Ardehali A. Normothermic ex-vivo preservation with the portable Organ Care System Lung device for bilateral lung transplantation (INSPIRE): a randomised, open-label, non-inferiority, phase 3 study. *Lancet Respir Med* 2018; **6**: 357-367 [PMID: 29650408 DOI: 10.1016/S2213-2600(18)30136-X]
173 **Fisher A**, Andreasson A, Chrysos A, Lally J, Mamasoula C, Exley C, Wilkinson J, Qian J, Watson G, Lewington O, Chadwick T, McColl E, Pearce M, Mann K, McMeekin N, Vale L, Tsui S, Yonan N, Simon A, Marczin N, Mascaro J,

Dark J. An observational study of Donor Ex Vivo Lung Perfusion in UK lung transplantation: DEVELOP-UK. *Health Technol Assess* 2016; **20**: 1-276 [PMID: 27897967 DOI: 10.3310/hta20850]

174 **Loor G**, Warnecke G, Villavicencio MA, Smith MA, Kukreja J, Ardehali A, Hartwig M, Daneshmand MA, Hertz MI, Huddleston S, Haverich A, Madsen JC, Van Raemdonck D. Portable normothermic ex-vivo lung perfusion, ventilation, and functional assessment with the Organ Care System on donor lung use for transplantation from extended-criteria donors (EXPAND): a single-arm, pivotal trial. *Lancet Respir Med* 2019; **7**: 975-984 [PMID: 31378427 DOI: 10.1016/S2213-2600(19)30200-0]

175 **Hamilton BCS**, Dincheva GR, Zhuo H, Golden JA, Brzezinski M, Singer JP, Matthay MA, Kukreja J. Elevated donor plasminogen activator inhibitor-1 levels and the risk of primary graft dysfunction. *Clin Transplant* 2018; **32**: e13210 [PMID: 29377268 DOI: 10.1111/ctr.13210]

176 **Fisher AJ**, Donnelly SC, Hirani N, Haslett C, Strieter RM, Dark JH, Corris PA. Elevated levels of interleukin-8 in donor lungs is associated with early graft failure after lung transplantation. *Am J Respir Crit Care Med* 2001; **163**: 259-265 [PMID: 11208654 DOI: 10.1164/ajrccm.163.1.2005093]

177 **Salama M**, Andrukhova O, Hoda MA, Taghavi S, Jaksch P, Heinze G, Klepetko W, Aharinejad S. Concomitant endothelin-1 overexpression in lung transplant donors and recipients predicts primary graft dysfunction. *Am J Transplant* 2010; **10**: 628-636 [PMID: 20055806 DOI: 10.1111/j.1600-6143.2009.02957.x]

178 **Riera J**, Senna A, Cubero M, Roman A, Rello J; Vall d'Hebron Lung Transplant Study Group Investigators. Primary Graft Dysfunction and Mortality Following Lung Transplantation: A Role for Proadrenomedullin Plasma Levels. *Am J Transplant* 2016; **16**: 634-639 [PMID: 26461449 DOI: 10.1111/ajt.13478]

179 **Shah RJ**, Bellamy SL, Localio AR, Wickersham N, Diamond JM, Weinacker A, Lama VN, Bhorade S, Belperio JA, Crespo M, Demissie E, Kawut SM, Wille KM, Lederer DJ, Lee JC, Palmer SM, Orens J, Reynolds J, Shah A, Wilkes DS, Ware LB, Christie JD. A panel of lung injury biomarkers enhances the definition of primary graft dysfunction (PGD) after lung transplantation. *J Heart Lung Transplant* 2012; **31**: 942-949 [PMID: 22694851 DOI: 10.1016/j.healun.2012.05.001]

180 **Mordant P**, Nakajima D, Kalaf R, Iskender I, Maahs L, Behrens P, Coutinho R, Iyer RK, Davies JE, Cypel M, Liu M, Waddell TK, Keshavjee S. Mesenchymal stem cell treatment is associated with decreased perfusate concentration of interleukin-8 during ex vivo perfusion of donor lungs after 18-hour preservation. *J Heart Lung Transplant* 2016; **35**: 1245-1254 [PMID: 27444694 DOI: 10.1016/j.healun.2016.04.017]

181 **McAuley DF**, Curley GF, Hamid UI, Laffey JG, Abbott J, McKenna DH, Fang X, Matthay MA, Lee JW. Clinical grade allogeneic human mesenchymal stem cells restore alveolar fluid clearance in human lungs rejected for transplantation. *Am J Physiol Lung Cell Mol Physiol* 2014; **306**: L809-L815 [PMID: 24532289 DOI: 10.1152/ajplung.00358.2013]

182 **Miceli V**, Bertani A, Chinnici CM, Bulati M, Pampalone M, Amico G, Carcione C, Schmelzer E, Gerlach JC, Conaldi PG. Conditioned Medium from Human Amnion-Derived Mesenchymal Stromal/Stem Cells Attenuating the Effects of Cold Ischemia-Reperfusion Injury in an In Vitro Model Using Human Alveolar Epithelial Cells. *Int J Mol Sci* 2021; **22** [PMID: 33419219 DOI: 10.3390/ijms22020510]

183 **Németh K**, Leelahavanichkul A, Yuen PS, Mayer B, Parmelee A, Doi K, Robey PG, Leelahavanichkul K, Koller BH, Brown JM, Hu X, Jelinek I, Star RA, Mezey E. Bone marrow stromal cells attenuate sepsis *via* prostaglandin E(2)-dependent reprogramming of host macrophages to increase their interleukin-10 production. *Nat Med* 2009; **15**: 42-49 [PMID: 19098906 DOI: 10.1038/nm.1905]

184 **Cocking S**, Jones H, Cable NT, Thijssen DH. Chapter 19 - Enhancing Sports Performance Through Ischemic Preconditioning: Moderating Factors and Potential Mechanisms. In: Rattan SIS, Kyriazis M, editors. The Science of Hormesis in Health and Longevity. Academic Press; 2019: 213-222 [DOI: 10.1016/B978-0-12-814253-0.00019-X]

185 **Li C**, Xu M, Wu Y, Li YS, Huang WQ, Liu KX. Limb remote ischemic preconditioning attenuates lung injury after pulmonary resection under propofol-remifentanil anesthesia: a randomized controlled study. *Anesthesiology* 2014; **121**: 249-259 [PMID: 24743579 DOI: 10.1097/ALN.0000000000000266]

186 **Li C**, Li YS, Xu M, Wen SH, Yao X, Wu Y, Huang CY, Huang WQ, Liu KX. Limb remote ischemic preconditioning for intestinal and pulmonary protection during elective open infrarenal abdominal aortic aneurysm repair: a randomized controlled trial. *Anesthesiology* 2013; **118**: 842-852 [PMID: 23353795 DOI: 10.1097/ALN.0b013e3182850da5]

187 **Jensen HA**, Loukogeorgakis S, Yannopoulos F, Rimpiläinen E, Petzold A, Tuominen H, Lepola P, Macallister RJ, Deanfield JE, Mäkelä T, Alestalo K, Kiviluoma K, Anttila V, Tsang V, Juvonen T. Remote ischemic preconditioning protects the brain against injury after hypothermic circulatory arrest. *Circulation* 2011; **123**: 714-721 [PMID: 21300953 DOI: 10.1161/CIRCULATIONAHA.110.986497]

188 **Hausenloy DJ**, Mwamure PK, Venugopal V, Harris J, Barnard M, Grundy E, Ashley E, Vichare S, Di Salvo C, Kolvekar S, Hayward M, Keogh B, MacAllister RJ, Yellon DM. Effect of remote ischaemic preconditioning on myocardial injury in patients undergoing coronary artery bypass graft surgery: a randomised controlled trial. *Lancet* 2007; **370**: 575-579 [PMID: 17707752 DOI: 10.1016/S0140-6736(07)61296-3]

189 **Kim JC**, Shim JK, Lee S, Yoo YC, Yang SY, Kwak YL. Effect of combined remote ischemic preconditioning and postconditioning on pulmonary function in valvular heart surgery. *Chest* 2012; **142**: 467-475 [PMID: 22281799 DOI: 10.1378/chest.11-2246]

190 **Hausenloy DJ**, Candilio L, Evans R, Ariti C, Jenkins DP, Kolvekar S, Knight R, Kunst G, Laing C, Nicholas J, Pepper J, Robertson S, Xenou M, Clayton T, Yellon DM; ERICCA Trial Investigators. Remote Ischemic Preconditioning and Outcomes of Cardiac Surgery. *N Engl J Med* 2015; **373**: 1408-1417 [PMID: 26436207 DOI: 10.1056/NEJMoa1413534]

191 **Meybohm P**, Bein B, Brosteanu O, Cremer J, Gruenewald M, Stoppe C, Coburn M, Schaelte G, Böning A, Niemann B, Roesner J, Kletzin F, Strouhal U, Reyher C, Laufenberg-Feldmann R, Ferner M, Brandes IF, Bauer M, Stehr SN, Kortgen A, Wittmann M, Baumgarten G, Meyer-Treschan T, Kienbaum P, Heringlake M, Schön J, Sander M, Treskatsch S, Smul T, Wolwender E, Schilling T, Fuernau G, Hasenclever D, Zacharowski K; RIPHeart Study Collaborators. A Multicenter Trial of Remote Ischemic Preconditioning for Heart Surgery. *N Engl J Med* 2015; **373**: 1397-1407 [PMID: 26436208 DOI: 10.1056/NEJMoa1413579]

192 **Liu Q**, Rehman H, Krishnasamy Y, Lemasters JJ, Zhong Z. Ischemic preconditioning attenuates acute lung injury after partial liver transplantation. *Int J Physiol Pathophysiol Pharmacol* 2018; **10**: 83-94 [PMID: 29755641]

193 **Olguner C**, Koca U, Kar A, Karci A, Işlekel H, Canyilmaz M, Mavioğlu O, Kizildağ S, Unlü G, Elar Z. Ischemic preconditioning attenuates the lipid peroxidation and remote lung injury in the rat model of unilateral lower limb ischemia reperfusion. *Acta Anaesthesiol Scand* 2006; **50**: 150-155 [PMID: 16430534 DOI: 10.1111/j.1399-6576.2006.00938.x]

194 **Jan WC**, Chen CH, Tsai PS, Huang CJ. Limb ischemic preconditioning mitigates lung injury induced by haemorrhagic shock/resuscitation in rats. *Resuscitation* 2011; **82**: 760-766 [PMID: 21398019 DOI: 10.1016/j.resuscitation.2011.02.010]

195 **Luo N**, Liu J, Chen Y, Li H, Hu Z, Abbott GW. Remote ischemic preconditioning STAT3-dependently ameliorates pulmonary ischemia/reperfusion injury. *PLoS One* 2018; **13**: e0196186 [PMID: 29768493 DOI: 10.1371/journal.pone.0196186]

196 **Gasparri RI**, Jannis NC, Flameng WJ, Lerut TE, Van Raemdonck DE. Ischemic preconditioning enhances donor lung preservation in the rabbit. *Eur J Cardiothorac Surg* 1999; **16**: 639-646 [PMID: 10647834 DOI: 10.1016/S1010-7940(99)00335-8]

197 **García-de-la-Asunción J**, Bruno L, Perez-Griera J, Galan G, Morcillo A, Wins R, García-Del-Olmo E, Guijarro R, Sarriá B, Martí F, Soro M, Belda FJ. Remote Ischemic Preconditioning Decreases Oxidative Lung Damage After Pulmonary Lobectomy: A Single-Center Randomized, Double-Blind, Controlled Trial. *Anesth Analg* 2017; **125**: 499-506 [PMID: 28504995 DOI: 10.1213/ANE.0000000000002065]

198 **Lin E**, Snell GI, Levvey BJ, Mitchell LE, Marasco S, Kotsimbos T, Mifsud NA, Sharland AF, Myles P. 532 Remote Ischemic Pre-Conditioning (RIPC) To Improve Lung Transplant (LTx) Outcomes: A Randomized, Placebo-Controlled, Clinical and Mechanistic Trial. *J Heart Lung Transplant* 2012; **31**: S184-S185 [DOI: 10.1016/j.healun.2012.01.544]

199 **Lin E**, Snell GI, Levvey BJ, Mifsud N, Paul M, Buckland MR, Gooi J, Marasco S, Sharland AF, Myles PS. Safety, feasibility, and effect of remote ischemic conditioning in patients undergoing lung transplantation. *J Heart Lung Transplant* 2014; **33**: 1139-1148 [PMID: 25016922 DOI: 10.1016/j.healun.2014.04.022]

200 **Seto AH**. 3 - Interventional Pharmacology. In: Kern MJ, Sorajja P, Lim MJ, editors. The Interventional Cardiac Catheterization Handbook (Fourth Edition): Elsevier. 2018: 88-106 [DOI: 10.1016/B978-0-323-47671-3.00003-X]

201 **Emaminia A**, Lapar DJ, Zhao Y, Steidle JF, Harris DA, Laubach VE, Linden J, Kron IL, Lau CL. Adenosine A_2A agonist improves lung function during ex vivo lung perfusion. *Ann Thorac Surg* 2011; **92**: 1840-1846 [PMID: 22051279 DOI: 10.1016/j.athoracsur.2011.06.062]

202 **Wagner CE**, Pope NH, Charles EJ, Huerter ME, Sharma AK, Salmon MD, Carter BT, Stoler MH, Lau CL, Laubach VE, Kron IL. Ex vivo lung perfusion with adenosine A2A receptor agonist allows prolonged cold preservation of lungs donated after cardiac death. *J Thorac Cardiovasc Surg* 2016; **151**: 538-545 [PMID: 26323621 DOI: 10.1016/j.jtcvs.2015.07.075]

203 **Gazoni LM**, Laubach VE, Mulloy DP, Bellizzi A, Unger EB, Linden J, Ellman PI, Lisle TC, Kron IL. Additive protection against lung ischemia-reperfusion injury by adenosine A2A receptor activation before procurement and during reperfusion. *J Thorac Cardiovasc Surg* 2008; **135**: 156-165 [PMID: 18179933 DOI: 10.1016/j.jtcvs.2007.08.041]

204 **Lau CL**, Beller JP, Boys JA, Zhao Y, Phillips J, Cosner M, Conaway MR, Petroni G, Charles EJ, Mehaffey JH, Mannem HC, Kron IL, Krupnick AS, Linden J. Adenosine A2A receptor agonist (regadenoson) in human lung transplantation. *J Heart Lung Transplant* 2020; **39**: 563-570 [PMID: 32503727 DOI: 10.1016/j.healun.2020.02.003]

205 **Emtiazjoo AM**, Hu H, Lu L, Brantly ML. Alpha-1 Antitrypsin Attenuates Acute Lung Allograft Injury in a Rat Lung Transplant Model. *Transplant Direct* 2019; **5**: e458 [PMID: 31723592 DOI: 10.1097/TXD.0000000000000898]

206 **Götzfried J**, Smirnova NF, Morrone C, Korkmaz B, Yildirim AÖ, Eickelberg O, Jenne DE. Preservation with α(1)-antitrypsin improves primary graft function of murine lung transplants. *J Heart Lung Transplant* 2018; **37**: 1021-1028 [PMID: 29776812 DOI: 10.1016/j.healun.2018.03.015]

207 **Strüber M**, Hagl C, Hirt SW, Cremer J, Harringer W, Haverich A. C1-esterase inhibitor in graft failure after lung transplantation. *Intensive Care Med* 1999; **25**: 1315-1318 [PMID: 10654221 DOI: 10.1007/s001340051065]

208 **Salvatierra A**, Velasco F, Rodriguez M, Alvarez A, Lopez-Pedrera R, Ramirez R, Carracedo J, Lopez-Rubio F, Lopez-Pujol J, Guerrero R. C1-esterase inhibitor prevents early pulmonary dysfunction after lung transplantation in the dog. *Am J Respir Crit Care Med* 1997; **155**: 1147-1154 [PMID: 9117001 DOI: 10.1164/ajrccm.155.3.9117001]

209 **Sommer W**, Tudorache I, Kühn C, Avsar M, Salman J, Ius F, Gras C, Weber P, Welte T, Gottlieb J, Haverich A, Warnecke G. C1-esterase-inhibitor for primary graft dysfunction in lung transplantation. *Transplantation* 2014; **97**: 1185-1191 [PMID: 24573112 DOI: 10.1097/TP.0000000000000034]

210 **Cassivi SD**, Liu M, Boehler A, Tanswell AK, Slutsky AS, Keshavjee S, Todd STRJ. Transgene expression after adenovirus-mediated retransfection of rat lungs is increased and prolonged by transplant immunosuppression. *J Thorac Cardiovasc Surg* 1999; **117**: 1-7 [PMID: 9869751 DOI: 10.1016/S0022-5223(99)70462-9]

211 **Fischer S**, Liu M, MacLean AA, de Perrot M, Ho M, Cardella JA, Zhang XM, Bai XH, Suga M, Imai Y, Keshavjee S. In vivo transtracheal adenovirus-mediated transfer of human interleukin-10 gene to donor lungs ameliorates ischemia-reperfusion injury and improves early posttransplant graft function in the rat. *Hum Gene Ther* 2001; **12**: 1513-1526 [PMID: 11506694 DOI: 10.1089/10430340152480249]

212 **Machuca TN**, Cypel M, Bonato R, Yeung JC, Chun YM, Juvet S, Guan Z, Hwang DM, Chen M, Saito T, Harmantas C, Davidson BL, Waddell TK, Liu M, Keshavjee S. Safety and Efficacy of Ex Vivo Donor Lung Adenoviral IL-10 Gene Therapy in a Large Animal Lung Transplant Survival Model. *Hum Gene Ther* 2017; **28**: 757-765 [PMID: 28052693 DOI: 10.1089/hum.2016.070]

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MINIREVIEWS

Transitioning of renal transplant pathology from allograft to xenograft and tissue engineering pathology: Are we prepared?

Muhammed Mubarak

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Abstract

Currently, the most feasible and widely practiced option for patients with end-stage organ failure is the transplantation of part of or whole organs, either from deceased or living donors. However, organ shortage has posed and is still posing a big challenge in this field. Newer options being explored are xenografts and engineered/bioengineered tissues/organs. Already small steps have been taken in this direction and sooner or later, these will become a norm in this field. However, these developments will pose different challenges for the diagnosis and management of problems as compared with traditional allografts. The approach to pathologic diagnosis of dysfunction in these settings will likely be significantly different. Thus, there is a need to increase awareness and prepare transplant diagnosticians to meet this future challenge in the field of xenotransplantation/regenerative medicine. This review will focus on the current status of transplant pathology and how it will be changed in the future with the emerging scenario of routine xenotransplantation.

Key Words: Xenotransplantation; Bioengineered tissues; Pathology; Allograft; Xenograft

Core Tip: End-stage organ failure is a significant public health problem worldwide. Currently, treatment options are limited and organ shortage for allotransplantation is one of the biggest challenges. Alternative options being explored are xenografts and engineered/bioengineered tissues/organs. These developments will pose different challenges for the diagnosis and management of transplant pathologies as compared with traditional allografts. The approach to pathologic diagnosis of dysfunction in these settings will likely be significantly different. Thus, there is a need to increase awareness and prepare transplant pathologists to meet this imminent challenge in the field of xenotransplantation/regenerative medicine.

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INTRODUCTION

End-stage organ failure of vital organs is one of the leading causes of morbidity and mortality worldwide. Currently, the only treatment or in the case of some organs, the treatment of choice for these patients is the transplantation of those organs. In the United States of America alone, more than 1.2 million people need transplantation for end-stage organ failure; the vast majority of these await kidney transplants. Currently, less than one-third of these succeed in getting transplants with varying rates in different countries, as shown in Figure 1[1-3].

The remarkable success in the progress of solid-organ transplantation in the last few decades of the preceding century is rightly considered a milestone in the history of modern medicine. However, it has not completely met the goals. Many challenges remain to be surpassed and unmet needs to be fulfilled. Currently, the main limitations to the field of transplantation include complications related to lifelong immunosuppression, chronic rejection, and shortage of organs. Among these, the latter is one of the biggest challenges facing the transplant community worldwide. The rejection of transplanted organs, particularly chronic rejection, represents another formidable challenge. Fortunately, the rate of acute rejection has been reduced drastically over the past few decades due chiefly to the development of more potent immunosuppressive agents. However, chronic rejection still poses a big challenge and it remains the leading cause of graft failure worldwide and the dominant indication for second or third transplants. Efforts to prevent or treat it effectively have not been successful till date[4,5].

Against the backdrop of the above facts and challenges, the scientific community has been striving hard to find alternative solutions. The use of animal cells or tissues (xenogeneic) is one of such solutions that could easily reduce the ever-increasing gap between the demand of organs and their supply[6-10]. Although non-human primates are closely related to humans phylogenetically, it is the pig that has been identified as the optimum donor species for xenotransplantation (XenoTx) into humans. The pig kidneys are suited for transplantation in humans on both anatomical and physiological grounds[11,12]. Pig breeding is easy and does not pose major ethical issues, and considerable progress has been made in genetically modifying the animal to improve the acceptance of swine organs. Xenografts from genetically modified pigs have become one of the most promising solutions to the shortage of human organs available for transplantation. The use of organs from such modified pigs together with different methods of inducing tolerance has paved the way to prolonged survival of xenografts, removing the early obstacles that cause hyperacute rejection (HAR) and immediate graft loss[13-17]. Transgenic modifications including knockout of carbohydrate epitopes and additions of the complement cascade and coagulation cascade regulatory proteins have extended the xenograft survival in pig-to-non-human primate transplants of kidneys, hearts, and livers. In addition, improvements in immunosuppressive drugs such as the introduction of mammalian target of rapamycin inhibitors and blockers of co-stimulatory pathways have resulted in better outcomes. However, delayed antibody-mediated rejection and thrombotic microangiopathy (TMA) continue to be the major challenges in the field and need further focused research[18-20].

Regenerative medicine/tissue engineering is another promising field to bridge the existing gaps in transplantation. It can be used to lengthen the lifespan and improve the function of suboptimal donor organs, thereby greatly augmenting the existing donor organ pool, and has the capability to save the remaining vast majority of patients waiting for transplants, by generating or repairing organs. The discipline of regenerative science is older than that of organ transplantation. The first textbook on regenerative medicine was written in 1901. Similarly, a major regenerative science conference was held in 1988, while first Banff renal transplant pathology meeting was held three years later[21]. Contrary to this, the subject of regenerative medicine/tissue engineering pathology (TEP) never received much attention till the recent past[21-25]. In the near future, the discipline of transplantation will expand manifold, through a combination of tissue engineering with the prevalent approaches to decrease the

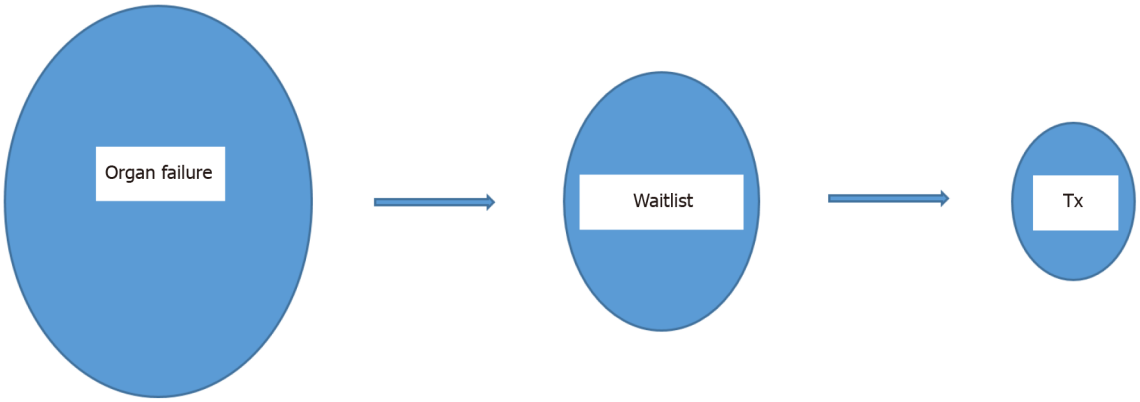

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Figure 1 Schematic illustration of global estimates of patients with terminal organ failure, waitlist patients, and patients undergoing transplantation. This is only an approximation and not actual numbers. More patients are waiting for kidneys than any other organ.

organ shortage. These new options will bring along with them new challenges in related fields such as pathology and diagnostic fields.

The role of transplant pathology in the diagnosis and management of graft rejection, particularly in the allotransplant setting, cannot be overemphasized. Although it is easy to conceptualize and classify rejection in theory, its diagnosis and classification are not always easy or straightforward in practice. The Banff process was initiated more than 30 years back to standardize the criteria for diagnosing and classifying the rejection process in human allotransplants. Considerable refinements and improvements in the classification system have been made over the last three decades and there are still many unmet needs to be fulfilled[21-25]. However, the Banff group is not oblivious to the developments or progress in the related fields of regenerative medicine/tissue engineering and XenoTx. In fact, the Banff researchers have proposed to create a new Banff classification, tentatively named TEP, to address issues related to the success or dysfunction of engineered tissues/organs[25]. It is also hoped that the Banff group will also address the issues related to standardization of the diagnostic criteria and classification of XenoTx pathology.

Herein, we review the pathobiology of the rejection process in the XenoTx setting and the current status of histopathology in clinical xenoTx, and focus on current results in the pig-to-primate model, as this is thought as the most relevant to human xenoTx. We will briefly review the histological findings in the three recently performed pig-to-human kidney transplants. We will also explore the future challenges and prospects of XenoTx pathology in light of advancements in human transplant pathology. We will not discuss further the topic of TEP, as it is beyond the scope of the present review.

PATHOGENETIC BASIS OF REJECTION IN XENOTX

The major barriers to successful solid organ XenoTx are natural antibodies to carbohydrate antigens, present in pigs but absent in humans and non-human primates, mainly galactose-α-1,3-galactose (Gal), which is produced by the enzyme α-1,3-galactosyltransferase (GT). Bi-allelic GT knockout (GTKO) pigs were used in early protocols of solid organ XenoTx[26-29]. The lifespan of grafts improved, and immediate and accelerated injury to xenografts was overcome. GTKO pigs with further genetic modifications in the form of knockout of two other xenospecific antigens, expressed in pigs but not in humans, termed triple knockout (TKO) pigs, were also used in these experiments. Further multiple transgenic modifications including the addition of human complement regulatory proteins, such as CD46 and CD55, and regulatory molecules of human coagulation cascade have further lengthened the lifespans of xenografts. Suggestions to introduce other transgenes to provide multi-dimensional lines of safety for the xenograft have been put forward, with the aim of countering rejection, coagulopathy, or additional mechanisms of immediate or early xenograft injury[30,31].

Three recent cases of pig-to-human kidney xenoTx utilizing 10 gene modifications in genetically engineered (GE) pigs, termed 10-GE pigs, demonstrate the feasibility of the procedure with no HAR. These were performed in brain-dead human recipients and were terminated at 2 to 3 d post-transplant [32,33]. These have attracted considerable public interest and re-kindled the interest of the transplant scientific community. The pigs used as organ donors in both procedures were produced and supplied by Revivicor, Inc., United States. Revivicor (https://www.revivicor.com/), a subsidiary of United Therapeutics Corporation, uses precise gene editing tools to delete or insert genes in the pig genome. Gene editing is carried out *in vitro* in pig cells cultured in Petri dishes. The cells are screened and analyzed to make sure that the gene editing is accurate. Somatic cell nuclear transfer (SCNT) is then

used to produce pigs from the gene-edited cells. SCNT involves the transfer of a nucleus from a gene-edited pig cell into an enucleated pig egg from which the nucleus has been extruded. The eggs are then transferred to surrogate sows where they develop and grow until natural birth (Figure 2). Revivicor raises the organ donor pigs in a designated pathogen-free facility to eliminate infectious agents that could transmit disease to human transplant recipients. Revivicor received approval from the Food and Drug Administration in 2020 for use of the GalSafe™ pig as a source of food for human consumption, and as a source of human therapeutics (https://www.revivicor.com/).

PATHOLOGIC EVALUATION OF XENOGRAFT AND CURRENT STATUS OF HISTOPATHOLOGY

Histopathology is presently considered the gold standard in the diagnosis of solid organ graft rejection. However, this status of histopathology is subject to certain conditions which must be fulfilled, such as adequacy of sampling and the experience of pathologists. Banff schema of transplant pathology represents a significant scientific effort in the recent past in the field of transplantation diagnostics. Substantial progress has been made in improving the diagnostic criteria and rationalizing the classification of rejection processes in human allografts. This was made possible with continued and concerted efforts by the Banff team and researchers in the transplant field worldwide over the past three decades. However, there are still many unmet needs and challenges in the field, and the Banff process is poised to tackle these in near future[21-24].

The status of histopathology in XenoTx is less developed as compared to its status in allotransplantation (alloTx), principally because there is a lack of extensive literature on this topic. In contrast to alloTx, during the rejection process of a xenograft, the host is likely to use almost the entire armamentarium of its immune mechanisms, encompassing all elements of innate immunity, such as naturally occurring xenoreactive antibodies. In addition, xenograft damage may be caused by mechanisms such as TMA initiated by molecular incongruities in the processes of homeostasis at the surface of the endothelium of blood vessels. Thus, the pathology of xenoTx rejection represents a more complex process and presents a wide variety of histologic features than allograft rejection[32-39]. With multiple transgenic modifications and combinations leading to potentially heterogeneous data in the XenoTx field, systematic study of the xenograft at gross and microscopic levels is crucial. At present, the Banff classification for renal allograft rejection is used by some researchers in some experimental studies [39]. Although the utility of the Banff classification in alloTx is now well-established throughout the world, the pathogenic processes involved in XenoTx and hence the pathologic patterns may be dissimilar. Presently, xenograft pathology classification relates to the diagnostic aspects of rejection, and also reflects, to some extent, the pathomechanisms of rejection. On the other hand, the pathologic evaluation of alloTx rejection provides information not only limited to diagnosis but also on the prognosis and the reversibility of the rejection process with treatment. However, it should be noted that similar to alloTx, histopathology can not be practiced in isolation, but represents a supportive component in the multidisciplinary evaluation of a xenograft[22].

The main focus in earlier Banff classifications of human allograft pathology was on the cellular part of rejection, with the role of alloantibodies relegated to the now obsolete category of HAR[21]. In contrast, in XenoTx, humoral rejection is considered the most important. Accordingly, the classifications have differed in construct and weightage to different categories. More recently, the focus of human allograft pathology has also shifted to humoral rejection beyond immediate and early posttransplant periods[22].

HISTOPATHOLOGIC CLASSIFICATION IN XENOTX

There are very limited studies that report specific morphological features of xenoTx rejection. Since most work on XenoTx has been done with pig-to-non-human primate models, the study of pathologic features has been reported in this setting[34-39]. Most researchers working with these XenoTx models have implemented a simple and mechanistic classification of rejection processes. The current xenograft pathology classification originated at Imutran, Cambridge, UK, in 2002 and has subsequently been used by other researchers as well[40]. Basically, three main diagnostic categories are distinguished: (1) Hyperacute rejection; (2) acute humoral xenograft rejection (AHXR); and (3) acute cellular xenograft rejection (ACXR), as shown in Table 1. As with Banff classification of human allograft pathology, this classification relies not only conventional morphology, but also needs immunofluorescence for immunoglobulin and complement proteins including C4d, and correlation with clinical information, including status of graft function for optimal evaluation and potential significance of pathological lesions[39,40].

Although the xenograft rejection pathology classification primarily relates to pathogenetic rejection mechanisms, each type of rejection incorporates a wide range of cellular and humoral elements of the specific immune system and innate inflammatory mechanisms. It is likely that different histopathologic

Table 1 Classification and diagnostic criteria used in pig-to-primate solid organ transplantation pathology

Hyperacute rejection	Acute humoral xenograft rejection	Acute cellular xenograft rejection
Time period		
Immediately after reperfusion of the graft (typically within 24 h)	Later after reperfusion (after 24 h)	After 3 d
Immediate graft function		
No (no urine since reperfusion)	Yes, urine formation initially	Yes, urine formation initially
Histopathologic features		
Massive hemorrhage; Immunoglobulin and fibrin deposition; Complement (C5b-9) deposition; Presence of neutrophils; Thrombosis, ±	Hemorrhage present; Immunoglobulin and fibrin deposition; Complement (C5b-9) deposition; Presence of neutrophils; Lymphocytes may be present; Necrosis and transmural infiltration by neutrophils in blood vessels can be present; Apoptosis may be present; Thrombosis present	No hemorrhage; Immunoglobulin and fibrin deposition, rare; Complement, ±; Presence of mononuclear (lymphoid) cells associated with tissue destruction (*e.g.*, tubulitis); No thrombosis

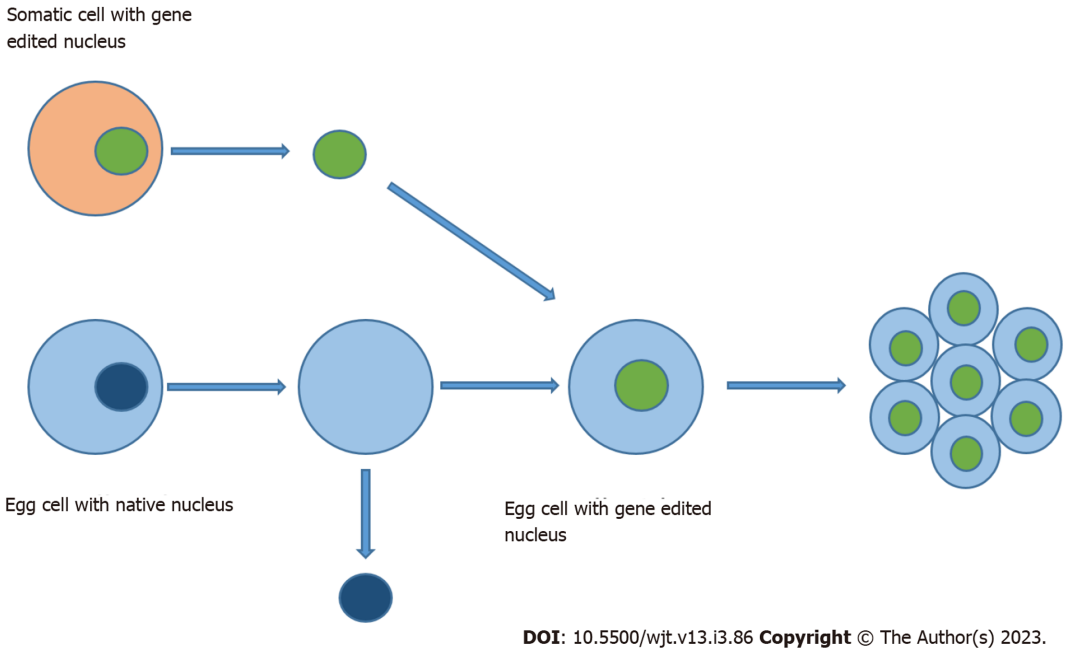

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Figure 2 Schematic diagram showing steps involved in somatic cell nuclear transfer. The process involves both *in vitro* and *in vivo* procedures under strict quality control mechanisms.

entities will emerge and the classification will evolve when additional genetically altered animal organs and novel immunosuppressive agents that subdue the immune system are made available. In expectation of this, the proponents of the above classification have kept the nomenclature of the classification schema relatively simple at this stage, leaving room for expansion or modification of the classification in the future, as more data accumulates on this subject[33].

HYPERACUTE REJECTION

HAR entails immediate destruction of the microvasculature and subsequently, the graft parenchyma following reperfusion, resulting in intravascular thrombosis and diffuse interstitial hemorrhage. HAR has, fortunately, become exceedingly rare in human alloTx. In the pig-to-primate model, HAR is mainly caused by the binding of naturally occurring xenospecific antibodies to Gal epitopes exposed on cell-surface glycoproteins and glycolipids of pig organs, followed by activation of the complement cascade. It can be prevented by the removal of naturally occurring anti-Gal antibodies or by chemical inhibition of complement activation. The removal of naturally occurring antibodies can be accomplished by extracorporeal immunoadsorption or these can be neutralized by the intravenous administration of soluble glycoconjugates. Many such conjugates have been tried with variable success rates. Similarly, many agents have been developed and tried that inhibit complement activation. Alternative options include the use of knockout or transgenic animal organs to circumvent this problem. Multi-transgenic

pigs by inserting multiple complement regulatory proteins have been developed in an attempt to augment complement inhibition. More recently, 10-GE pig kidneys have been used in clinical-grade xenotransplants in brain-dead human recipients with promising results[32,33]. However, there were some caveats in these trials, which need to be addressed in the future. Nevertheless, the reports have attracted public attention towards xenotransplantation which, if properly harnessed, should be of significant benefit to future progress. Although the above strategies have successfully overcome the barrier of HAR, a similar but less fulminant type of rejection still develops later and is called AHXR.

AHXR

AHXR, also known as ''acute vascular rejection'' or ''delayed xenograft rejection'', is an important form of antibody (Ab)-mediated rejection in xenoTx setting. The use of the AHXR term was adopted as it more closely represents the potential mechanism of Ab-induced rejection, mediated by the activation of complement pathway and/or infiltration by polymorphonuclear leucocytes. The other two terms either reflect the morphological aspect of rejection or the clinical aspect (delayed rejection) and hence, are better avoided.

The antibodies that cause AHXR can be both naturally occurring xenospecific antibodies, *e.g.*, anti-Gal antibodies in the pig-to-primate and pig-to-human situations, or they may be formed *de novo*. In the former case, AHXR is best considered a delayed form of HAR. In the latter situation, AHXR is due to induced antibodies after sensitization by the graft. The *de novo* antibodies may be directed against Gal or non-Gal antigens.

AHXR is the only type of humoral rejection to occur after Tx of organs between the concordant species, in which setting, HAR characteristically does not develop. The hamster-to-rat solid organ Tx model is the most commonly used such animal model, particularly in studies on immunosuppression or induction of immune tolerance in the presence of the development of sensitization. Among discordant species combinations, discrimination between the roles of pre-formed and *de novo* antibodies in the rejection process is vital for the development of plans to preclude or control the rejection. A few researchers have tried to address this topic but none has been completely successful in discriminating between the roles and significance of natural *vs de novo* antibodies in AHXR.

ACXR

ACXR has been studied to a much less extent than AHXR and hence, detailed accounts of this rejection type are scarcely reported[41]. This is mainly due to the fact these xenografts are usually lost as a result of HAR, which occurs before cellular rejection. In general, ACXR is more or less similar to that observed in human alloTx rejection. Cell-mediated rejection, in isolation, is a comparatively rare occurrence in pig-to-primate solid organ grafts. More commonly, it occurs in combination with AHXR but usually is of lesser intensity than AHXR. Morphologically, the entire range of mononuclear cells, including T lymphocytes (both CD4+ and CD8+ cells), B lymphocytes, and natural killer cells and macrophages, may be present in the interstitium and inside the tubules (tubulitis). Endothelialitis, and in severe forms, transmural vasculitis can be present in cellular rejection.

CHRONIC REJECTION

Chronic rejection is defined on theoretical grounds as the progressive and unremitting destruction of a transplant over months to many years. As one of the major causes of delayed graft failure from human donors, chronic rejection is currently considered as the major obstacle to the long-term success of alloTx. Chronic rejection has not been widely observed in xenoTx because of the generally short survival of xenotransplants and thus remains understudied. With recent developments resulting in prolonged graft survival in xenoTx, the challenge of chronic rejection is more likely to become prominent in the future as the initial barriers are surmounted and graft survival is extended. Currently, the literature on chronic vasculopathies and other chronic xenograft changes is scarce. In a GTKO porcine to baboon discordant xenoTx of hearts, morphological changes of chronic xenograft rejection were reported 78-179 d post-transplantation[42]. As is well described in the literature, in cardiac transplants, chronic rejection is mainly expressed by vascular changes. Hisashi *et al*[42] described four types of chronic xenograft vasculopathy in GTKO pig hearts transplanted into baboons, as shown in Table 2. Among these, fully developed and chronic antibody-mediated rejection-associated vasculopathy types were predominant in graftectomy specimens removed from the gradually weakened group between 78 and 179 d after transplantation. They hypothesized that fully developed vasculopathy was the end-result of combined chronic humoral and cell-mediated rejection-associated mechanisms, as the intimal fibrosis usually followed the infiltration of cells and deposition of fibrinoid material in the arterial intima. On the other

Table 2 Types of chronic xenograft vasculopathy

Type of vasculopathy	Histopathological features
Chronic humoral rejection-associated vasculopathy	Arterial intimal thickening; Presence of TUNEL+ cells; Deposits of fibrin, immunoglobulins (IgG and IgM), and complement components (C3, C4d, and C5b-9)
Chronic cellular rejection-associated vasculopathy	Mononuclear cell infiltration in the neointima; Active endothelialitis; TUNEL+ cells
Combined chronic humoral and cellular rejection-associated vasculopathy	Fibrinoid material deposition and cellular infiltration in the arterial neointima with immunoglobulin and complement deposition and infiltration of T cells, macrophages, and polymorphonuclear leukocytes
Fully developed vasculopathy	Narrowing of arteries with a fibrotic neointima, but without fibrinoid material, or cellular infiltration

TUNEL: Terminal deoxynucleotidyl transferase dUTP nick end labeling.

hand, evidence of chronic cell-mediated rejection-associated vasculopathy or a combination of both chronic humoral and cell-mediated rejection-associated vasculopathy was less frequent. Nevertheless, the precise mechanism by which chronic rejection and vasculopathy are mediated is still incompletely understood.

The relative roles of cellular and humoral immune components along with the roles of soluble serum inflammatory cytokines, such as tumor necrosis factor-alpha, interleukin-6, and interleukin-17, and their antagonists are yet to be fully explored in human recipients of xenografts[43-49]. Contemporary studies have focused on prolonging the graft survival and preventing the causes of early graft loss but future studies are likely to focus on detailed pathologic assessment of prolonged surviving grafts and protocol biopsies for elucidating the pathomechanisms of chronic rejection.

FUTURE PROSPECTS

Although extensive pig genome editing and recent pig-to-human kidney transplants in brain-dead recipients have opened the doors of clinical xenoTx in humans, much remains to be done before this becomes a routine activity. The potential advantages of kidney XenoTx are enormous if the immunological barriers are surmounted. Immunological tolerance to the graft may be easier to induce in models of xenoTx than in alloTx. It is hoped that eventually, XenoTx will compete favorably with alloTx. The recent cases of pig-to-human kidney transplants, albeit in brain-dead recipients, have also provided an opportunity to educate healthcare professionals and the public about xenoTx's potential, as well as its public health risks and logistic and economic implications. Increased public awareness and full transparency during clinical trial planning and execution will be required to generate support for xenoTx trials. Kidney xenoTx pathology will also evolve as the activity in clinical xenoTx increases and the xenograft survival is prolonged. There is abundant opportunity to learn from the evolution of the Banff process of human kidney allograft pathology.

CONCLUSION

Overall, XenoTx pathology is a comparatively new and evolving field of transplant diagnostics. The currently used classification is simple, mechanistic-cum-time based, and flexible. In general, humoral components of the specific immune system and innate immunity play important roles in the immediate and early post-transplant period. These are relatively well reported in the literature and now well controlled, resulting in improved xenograft survival. The transplant obstacles related to the regulation of complement and coagulation cascades due chiefly to species incompatibility and chronic rejection are yet to be investigated and understood. Obviously, with the prolongation of graft survival to years, there is more need of understanding the mechanisms of chronic rejection and to enrich the diagnostic armamentarium for pathologic evaluation. There is a need to increase awareness and train transplant pathologists in this emerging field of transplant diagnostics.

FOOTNOTES

Author contributions: Mubarak M is the sole author of the manuscript, and he conceived and designed the study, performed the research, participated in primary and final drafting, and has read and approved the final manuscript.

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REFERENCES

1 **Huang B**, Zeng Z, Zhang CC, Schreiber ME, Li Z. Approaches to kidney replacement therapies-opportunities and challenges. *Front Cell Dev Biol* 2022; **10**: 953408 [PMID: 35982852 DOI: 10.3389/fcell.2022.953408]
2 **Bonventre JV**, Hurst FP, West M, Wu I, Roy-Chaudhury P, Sheldon M. A Technology Roadmap for Innovative Approaches to Kidney Replacement Therapies: A Catalyst for Change. *Clin J Am Soc Nephrol* 2019; **14**: 1539-1547 [PMID: 31562182 DOI: 10.2215/CJN.02570319]
3 **Thurlow JS**, Joshi M, Yan G, Norris KC, Agodoa LY, Yuan CM, Nee R. Global Epidemiology of End-Stage Kidney Disease and Disparities in Kidney Replacement Therapy. *Am J Nephrol* 2021; **52**: 98-107 [PMID: 33752206 DOI: 10.1159/000514550]
4 **Lai X**, Zheng X, Mathew JM, Gallon L, Leventhal JR, Zhang ZJ. Tackling Chronic Kidney Transplant Rejection: Challenges and Promises. *Front Immunol* 2021; **12**: 661643 [PMID: 34093552 DOI: 10.3389/fimmu.2021.661643]
5 **Chapman JR**. What are the key challenges we face in kidney transplantation today? *Transplant Res* 2013; **2**: S1 [PMID: 24565161 DOI: 10.1186/2047-1440-2-S1-S1]
6 **Ekser B**, Ezzelarab M, Hara H, van der Windt DJ, Wijkstrom M, Bottino R, Trucco M, Cooper DK. Clinical xenotransplantation: the next medical revolution? *Lancet* 2012; **379**: 672-683 [PMID: 22019026 DOI: 10.1016/S0140-6736(11)61091-X]
7 **Cascalho M**, Ogle BM, Platt JL. Xenotransplantation and the future of renal replacement. *J Am Soc Nephrol* 2004; **15**: 1106-1112 [PMID: 15100350 DOI: 10.1097/01.asn.0000113298.28480.7e]
8 **Cooper DK**, Bottino R. Recent advances in understanding xenotransplantation: implications for the clinic. *Expert Rev Clin Immunol* 2015; **11**: 1379-1390 [PMID: 26548357 DOI: 10.1586/1744666X.2015.1083861]
9 **Meier RPH**, Longchamp A, Mohiuddin M, Manuel O, Vrakas G, Maluf DG, Buhler LH, Muller YD, Pascual M. Recent progress and remaining hurdles toward clinical xenotransplantation. *Xenotransplantation* 2021; **28**: e12681 [PMID: 33759229 DOI: 10.1111/xen.12681]
10 **Cooper DK**, Gollackner B, Sachs DH. Will the pig solve the transplantation backlog? *Annu Rev Med* 2002; **53**: 133-147 [PMID: 11818467 DOI: 10.1146/annurev.med.53.082901.103900]
11 **Iwase H**, Klein EC, Cooper DK. Physiologic Aspects of Pig Kidney Transplantation in Nonhuman Primates. *Comp Med* 2018; **68**: 332-340 [PMID: 30208986 DOI: 10.30802/AALAS-CM-17-000117]
12 **Cowan PJ**, Cooper DK, d'Apice AJ. Kidney xenotransplantation. *Kidney Int* 2014; **85**: 265-275 [PMID: 24088952 DOI: 10.1038/ki.2013.381]
13 **Cooper DKC**, Hara H, Iwase H, Yamamoto T, Wang ZY, Jagdale A, Bikhet MH, Nguyen HQ, Foote JB, Paris WD, Ayares D, Kumar V, Anderson DJ, Locke JE, Eckhoff DE. Pig kidney xenotransplantation: Progress toward clinical trials. *Clin Transplant* 2021; **35**: e14139 [PMID: 33131148 DOI: 10.1111/ctr.14139]
14 **Cooper DK**, Ayares D. The immense potential of xenotransplantation in surgery. *Int J Surg* 2011; **9**: 122-129 [PMID: 21059418 DOI: 10.1016/j.ijsu.2010.11.002]
15 **Logan JS**. Prospects for xenotransplantation. *Curr Opin Immunol* 2000; **12**: 563-568 [PMID: 11007360 DOI: 10.1016/s0952-7915(00)00139-4]
16 **Lechler RI**, Sykes M, Thomson AW, Turka LA. Organ transplantation--how much of the promise has been realized? *Nat Med* 2005; **11**: 605-613 [PMID: 15937473 DOI: 10.1038/nm1251]
17 **Zhou Q**, Li T, Wang K, Zhang Q, Geng Z, Deng S, Cheng C, Wang Y. Current status of xenotransplantation research and the strategies for preventing xenograft rejection. *Front Immunol* 2022; **13**: 928173 [PMID: 35967435 DOI: 10.3389/fimmu.2022.928173]
18 **Igaz P**. Recent strategies to overcome the hyperacute rejection in pig to human xenotransplantation. *Yale J Biol Med* 2001; **74**: 329-340 [PMID: 11769339 DOI: 10.1016/s0041-1345(96)00634-3]
19 **Cooper DKC**, Ekser B, Tector AJ. Immunobiological barriers to xenotransplantation. *Int J Surg* 2015; **23**: 211-216 [PMID: 26159291 DOI: 10.1016/j.ijsu.2015.06.068]
20 **Lin CC**, Cooper DK, Dorling A. Coagulation dysregulation as a barrier to xenotransplantation in the primate. *Transpl Immunol* 2009; **21**: 75-80 [PMID: 19000927 DOI: 10.1016/j.trim.2008.10.008]
21 **Solez K**, Axelsen RA, Benediktsson H, Burdick JF, Cohen AH, Colvin RB, Croker BP, Droz D, Dunnill MS, Halloran PF. International standardization of criteria for the histologic diagnosis of renal allograft rejection: the Banff working classification of kidney transplant pathology. *Kidney Int* 1993; **44**: 411-422 [PMID: 8377384 DOI: 10.1038/ki.1993.259]

22 **Loupy A**, Mengel M, Haas M. Thirty years of the International Banff Classification for Allograft Pathology: the past, present, and future of kidney transplant diagnostics. *Kidney Int* 2022; **101**: 678-691 [PMID: 34922989 DOI: 10.1016/j.kint.2021.11.028]

23 **Farris AB**, Moghe I, Wu S, Hogan J, Cornell LD, Alexander MP, Kers J, Demetris AJ, Levenson RM, Tomaszewski J, Barisoni L, Yagi Y, Solez K. Banff Digital Pathology Working Group: Going digital in transplant pathology. *Am J Transplant* 2020; **20**: 2392-2399 [PMID: 32185875 DOI: 10.1111/ajt.15850]

24 **Wood-Trageser MA**, Lesniak AJ, Demetris AJ. Enhancing the Value of Histopathological Assessment of Allograft Biopsy Monitoring. *Transplantation* 2019; **103**: 1306-1322 [PMID: 30768568 DOI: 10.1097/TP.0000000000002656]

25 **Solez K**, Fung KC, Saliba KA, Sheldon VLC, Petrosyan A, Perin L, Burdick JF, Fissell WH, Demetris AJ, Cornell LD. The bridge between transplantation and regenerative medicine: Beginning a new Banff classification of tissue engineering pathology. *Am J Transplant* 2018; **18**: 321-327 [PMID: 29194964 DOI: 10.1111/ajt.14610]

26 **Cooper DK**, Ezzelarab MB, Hara H, Iwase H, Lee W, Wijkstrom M, Bottino R. The pathobiology of pig-to-primate xenotransplantation: a historical review. *Xenotransplantation* 2016; **23**: 83-105 [PMID: 26813438 DOI: 10.1111/xen.12219]

27 **Tai HC**, Ezzelarab M, Hara H, Ayares D, Cooper DK. Progress in xenotransplantation following the introduction of gene-knockout technology. *Transpl Int* 2007; **20**: 107-117 [PMID: 17239018 DOI: 10.1111/j.1432-2277.2006.00398.x]

28 **Cooper DKC**, Iwase H, Wang L, Yamamoto T, Li Q, Li J, Zhou H, Hara H. Bringing Home The Bacon: Update on The State of Kidney Xenotransplantation. *Blood Purif* 2018; **45**: 254-259 [PMID: 29478054 DOI: 10.1159/000485163]

29 **Iwase H**, Kobayashi T. Current status of pig kidney xenotransplantation. *Int J Surg* 2015; **23**: 229-233 [PMID: 26305729 DOI: 10.1016/j.ijsu.2015.07.721]

30 **Fischer K**, Kind A, Schnieke A. Assembling multiple xenoprotective transgenes in pigs. *Xenotransplantation* 2018; **25**: e12431 [PMID: 30055014 DOI: 10.1111/xen.12431]

31 **Nottle MB**, Beebe LF, Harrison SJ, McIlfatrick SM, Ashman RJ, O'Connell PJ, Salvaris EJ, Fisicaro N, Pommey S, Cowan PJ, d'Apice AJ. Production of homozygous alpha-1,3-galactosyltransferase knockout pigs by breeding and somatic cell nuclear transfer. *Xenotransplantation* 2007; **14**: 339-344 [PMID: 17669176 DOI: 10.1111/j.1399-3089.2007.00417.x]

32 **Porrett PM**, Orandi BJ, Kumar V, Houp J, Anderson D, Cozette Killian A, Hauptfeld-Dolejsek V, Martin DE, Macedon S, Budd N, Stegner KL, Dandro A, Kokkinaki M, Kuravi KV, Reed RD, Fatima H, Killian JT Jr, Baker G, Perry J, Wright ED, Cheung MD, Erman EN, Kraebber K, Gamblin T, Guy L, George JF, Ayares D, Locke JE. First clinical-grade porcine kidney xenotransplant using a human decedent model. *Am J Transplant* 2022; **22**: 1037-1053 [PMID: 35049121 DOI: 10.1111/ajt.16930]

33 **Montgomery RA**, Stern JM, Lonze BE, Tatapudi VS, Mangiola M, Wu M, Weldon E, Lawson N, Deterville C, Dieter RA, Sullivan B, Boulton G, Parent B, Piper G, Sommer P, Cawthon S, Duggan E, Ayares D, Dandro A, Fazio-Kroll A, Kokkinaki M, Burdorf L, Lorber M, Boeke JD, Pass H, Keating B, Griesemer A, Ali NM, Mehta SA, Stewart ZA. Results of Two Cases of Pig-to-Human Kidney Xenotransplantation. *N Engl J Med* 2022; **386**: 1889-1898 [PMID: 35584156 DOI: 10.1056/NEJMoa2120238]

34 **Rosales IA**, Colvin RB. The pathology of solid organ xenotransplantation. *Curr Opin Organ Transplant* 2019; **24**: 535-542 [PMID: 31348015 DOI: 10.1097/MOT.0000000000000681]

35 **Shimizu A**, Yamada K. Pathology of renal xenograft rejection in pig to non-human primate transplantation. *Clin Transplant* 2006; **20** Suppl 15: 46-52 [PMID: 16848876 DOI: 10.1111/j.1399-0012.2006.00550.x]

36 **Shimizu A**, Yamada K. Histopathology of xenografts in pig to non-human primate discordant xenotransplantation. *Clin Transplant* 2010; **24** Suppl 22: 11-15 [PMID: 20590687 DOI: 10.1111/j.1399-0012.2010.01270.x]

37 **Schuurman HJ**, Cheng J, Lam T. Pathology of xenograft rejection: a commentary. *Xenotransplantation* 2003; **10**: 293-299 [PMID: 12795678 DOI: 10.1034/j.1399-3089.2003.02092.x]

38 **Foote JB**, Jagdale A, Yamamoto T, Hara H, Bikhet MH, Schuurman HJ, Nguyen HQ, Ezzelarab M, Ayares D, Anderson DJ, Fatima H, Eckhoff DE, Cooper DKC, Iwase H. Histopathology of pig kidney grafts with/without expression of the carbohydrate Neu5Gc in immunosuppressed baboons. *Xenotransplantation* 2021; **28**: e12715 [PMID: 34644438 DOI: 10.1111/xen.12715]

39 **Shimizu A**, Yamada K, Robson SC, Sachs DH, Colvin RB. Pathologic characteristics of transplanted kidney xenografts. *J Am Soc Nephrol* 2012; **23**: 225-235 [PMID: 22114174 DOI: 10.1681/ASN.2011040429]

40 **Schuurman HJ**, Pino-Chavez G, Phillips MJ, Thomas L, White DJ, Cozzi E. Incidence of hyperacute rejection in pig-to-primate transplantation using organs from hDAF-transgenic donors. *Transplantation* 2002; **73**: 1146-1151 [PMID: 11965048 DOI: 10.1097/00007890-200204150-00024]

41 **Miettinen ME**, Niinistö S, Honkanen J, Erlund I, Knip M, Virtanen SM. The role of vitamin D in the aetiology of type 1 diabetes. Reply to Korsgren O [letter]. *Diabetologia* 2020; **63**: 1281-1282 [PMID: 32236733 DOI: 10.1007/s00125-020-05135-2]

42 **Hisashi Y**, Yamada K, Kuwaki K, Tseng YL, Dor FJ, Houser SL, Robson SC, Schuurman HJ, Cooper DK, Sachs DH, Colvin RB, Shimizu A. Rejection of cardiac xenografts transplanted from alpha1,3-galactosyltransferase gene-knockout (GalT-KO) pigs to baboons. *Am J Transplant* 2008; **8**: 2516-2526 [PMID: 19032222 DOI: 10.1111/j.1600-6143.2008.02444.x]

43 **Allison SJ**. A model of pig-to-human kidney transplantation. *Nat Rev Nephrol* 2022; **18**: 199 [PMID: 35132215 DOI: 10.1038/s41581-022-00550-7]

44 **Riella LV**, Markmann JF, Madsen JC, Rosales IA, Colvin RB, Kawai T, Pierson RN 3rd. Kidney xenotransplantation in a brain-dead donor: Glass half-full or half-empty? *Am J Transplant* 2022; **22**: 1935-1936 [PMID: 35213783 DOI: 10.1111/ajt.17011]

45 **Ganchiku Y**, Riella LV. Pig-to-human kidney transplantation using brain-dead donors as recipients: One giant leap, or only one small step for transplantkind? *Xenotransplantation* 2022; **29**: e12748 [PMID: 35616243 DOI: 10.1111/xen.12748]

46 **Carrier AN**, Verma A, Mohiuddin M, Pascual M, Muller YD, Longchamp A, Bhati C, Buhler LH, Maluf DG, Meier RPH. Xenotransplantation: A New Era. *Front Immunol* 2022; **13**: 900594 [PMID: 35757701 DOI: 10.3389/fimmu.2022.900594]

47 **Cooper DKC**, Hara H, Iwase H, Yamamoto T, Jagdale A, Kumar V, Mannon RB, Hanaway MJ, Anderson DJ, Eckhoff

DE. Clinical Pig Kidney Xenotransplantation: How Close Are We? *J Am Soc Nephrol* 2020; **31**: 12-21 [PMID: 31792154 DOI: 10.1681/ASN.2019070651]

48 **Yamada K**, Yazawa K, Shimizu A, Iwanaga T, Hisashi Y, Nuhn M, O'Malley P, Nobori S, Vagefi PA, Patience C, Fishman J, Cooper DK, Hawley RJ, Greenstein J, Schuurman HJ, Awwad M, Sykes M, Sachs DH. Marked prolongation of porcine renal xenograft survival in baboons through the use of alpha1,3-galactosyltransferase gene-knockout donors and the cotransplantation of vascularized thymic tissue. *Nat Med* 2005; **11**: 32-34 [PMID: 15619627 DOI: 10.1038/nm1172]

49 **Dangi A**, Yu S, Luo X. Emerging approaches and technologies in transplantation: the potential game changers. *Cell Mol Immunol* 2019; **16**: 334-342 [PMID: 30760918 DOI: 10.1038/s41423-019-0207-3]

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ORIGINAL ARTICLE

Retrospective Study

Long-term outcomes of pediatric liver transplantation in acute liver failure *vs* end-stage chronic liver disease: A retrospective observational study

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Abstract

BACKGROUND

Children with acute liver failure (ALF) who meet the criteria are eligible for super-urgent transplantation, whereas children with end-stage chronic liver disease (ESCLD) are usually transplanted electively. Pediatric liver transplantation (PLT) in ALF and ESCLD settings has been well described in the literature, but there are no studies comparing the outcomes in these two groups.

AIM

To determine if there is a difference in post-operative complications and survival outcomes between ALF and ESCLD in PLT.

METHODS

This was a retrospective observational study of all primary PLTs performed at a single center between 2000 and 2019. ALF and ESCLD groups were compared for pretransplant recipient, donor and operative parameters, and post-operative outcomes including graft and patient survival.

RESULTS

Over a 20-year study period, 232 primary PLTs were performed at our center; 195

were transplanted for ESCLD and 37 were transplanted for ALF. The ALF recipients were significantly older (median 8 years *vs* 5.4 years; $P = 0.031$) and heavier (31 kg *vs* 21 kg; $P = 0.011$). Living donor grafts were used more in the ESCLD group (34 *vs* 0; $P = 0.006$). There was no difference between the two groups concerning vascular complications and rejection, but there were more bile leaks in the ESCLD group. Post-transplant patient survival was significantly higher in the ESCLD group: 1-, 5-, and 10-year survival rates were 97.9%, 93.9%, and 89.4%, respectively, compared to 78.3%, 78.3%, and 78.3% in the ALF group ($P = 0.007$). However, there was no difference in 1-, 5-, and 10-year graft survival between the ESCLD and ALF groups (90.7%, 82.9%, 77.3% *vs* 75.6%, 72.4%, and 66.9%; $P = 0.119$).

CONCLUSION

Patient survival is inferior in ALF compared to ESCLD recipients; the main reason is death in the 1st year post-PLT in ALF group. Once the ALF children overcome the 1st year after transplant, their survival stabilizes, and they have good long-term outcomes.

Key Words: Pediatric liver transplantation; Acute liver failure; End-stage chronic liver disease; Graft failure; Patient survival; Complications

Core Tip: To the best of our knowledge, this is the first study to compare the complications and survival outcomes in acute liver failure (ALF) and end-stage chronic liver disease (ESCLD) children post-pediatric liver transplantation (PLT). This study not only showed that survival in the ALF group was significantly inferior post-PLT but also showed a different pattern of survival where ALF survival was mostly affected in the 1st year post-transplant and then stabilized, whereas ESCLD survival declined steadily over time.

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INTRODUCTION

Liver disease is a leading cause of morbidity and mortality in children. The spectrum of liver pathologies in this age group includes infectious, genetic, metabolic, and drug-induced disorders that may eventually progress to either acute liver failure (ALF) or end-stage chronic liver disease (ESCLD). Pediatric liver transplantation (PLT) is the only treatment option for children with ALF or ESCLD[1].

The diagnosis of ALF in children can be challenging, as hepatic encephalopathy in this age group is usually difficult to define, particularly in its early stages and sometimes it may not be clinically evident until the ALF becomes advanced[2-4]. Also in some cases, accurate diagnosis of the etiology of ALF may not be possible, primarily in candidates who present with unrecognized metabolic diseases shortly after birth or those who clinically deteriorate over a short period not allowing enough room for full biochemical and radiological testing[3].

Managing children suffering from ALF is a dynamic process, with the decision to list for PLT made in an emergent manner, when the probability of spontaneous recovery is low but also before any irreversible neurological or respiratory sequalae take place[2]. At times, the window from presentation to PLT may span from only few hours up to a small number of days, posing significant challenges for the clinical team[5]. Optimum clinical and logistical management is essential as successful PLT in this special group has a dramatic effect on their survival[4-6]. Hence at the national level, the graft allocation system gives ALF children the highest priority being labeled as "super-urgent."

In comparison, the clinical and logistic dynamics are completely different in the case of children with ESCLD because PLT is usually performed on an elective basis, as candidates are usually in less critical clinical condition and the transplant team has enough time for evaluation and planning, aiming for optimum timing and potentially improved outcomes.

Both groups were discussed among other categories in publications describing the experience of PLT centers, but to the best of our knowledge, no previous studies have directly compared the outcomes of PLT in ALF and ESCLD settings. This study was conducted to determine if there is a difference in post-

PLT complications between the ALF and ESCLD groups, and to describe any variance in survival between the two cohorts. The importance of this comparison is to provide insights for transplant centers and organ allocation systems dealing with these two divergent groups to make the best use of limited resources including a limited graft pool and to anticipate differences in behavior between candidates in each group to tailor their clinical care accordingly. This comparison also opens the door for future research to overcome obstacles and improve PLT outcomes, especially in the ALF group where the underlying cause of the liver failure remains unknown in a considerable number of children.

MATERIALS AND METHODS

This was a retrospective cross-sectional observational study of the long-term outcomes of PLT performed at Leeds Teaching Hospitals NHS Trust between 2000 and 2019. Hospital documents and electronic records were used to retrieve donor and recipient data. Ethical approval was not required for this retrospective analysis of already collected data, and the study was registered as a service improvement project within the hospital clinical governance department, with no patient identifiable information stored while collecting and analyzing the data for this project.

Eligibility

The inclusion criteria were all PLT recipients of the first liver transplant in our center ≤ 18 years with either ALF or ESCLD as the recorded indication for PLT. Exclusion criteria were retransplants, primary PLTs for liver tumors, or metabolic disorders without underlying liver disease. Retransplants were excluded as they represent a heterogenous group with well-reported inferior outcomes compared to primary transplants. Children with liver tumors are unique with a well-defined transplant indication, and their disease may be complicated by the burden of chemotherapy before undergoing a liver transplant, although they tend to be systemically well with no effects of acute or chronic liver disease. So, we think they should be ideally studied separately. PLT for metabolic diseases usually has excellent patient and graft survival than PLT for other indications. In addition to this, genotypic and phenotypic diversity in metabolic disorders complicate the possibility of forecasting long-term outcomes in this group of children; hence, they were excluded from the study.

Definitions

For the objective of this article, ALF was specified to match the Pediatric Acute Liver Failure Study Group[6] definition, as biochemical proof of liver injury, excluding records of recognized chronic liver illness, international normalized ratio > 1.5 if the patient had encephalopathy or > 2.0 if the patient did not have encephalopathy, and coagulopathy not rectified by vitamin K use.

ESCLD was specified as enduring hepatic inflammation identified by biochemical investigations and clinical examination, spanning more than 6 mo causing cirrhosis or permanent liver injury[7].

Data collected and outcomes studied

Data were collected through a retrospective case note review. We recorded 24 peritransplant parameters for this study, which were grouped into four classes: Pretransplant recipient as well as donor parameters, operative parameters, and post-transplant recipient observations. Pretransplant recipient variables were sex, age, weight, liver failure category (ALF and ESCLD), fundamental liver illness etiology, time on the transplant waiting list, and patient location when graft became available (an indirect marker of recipient sickness instantly pretransplant). Donor parameters were sex, age, weight, type of graft (living and deceased), and type of graft (whole or variant graft such as split or reduced). The intraoperative parameters studied were warm ischemia time and cold ischemia time. The post-operative outcomes studied were the incidence of vascular and biliary complications, post-transplant pediatric intensive care unit (PICU) and overall hospital stay, the incidence of biopsy-proven acute/chronic rejection, retransplantation, causes of graft and patient loss, and 1-, 5-, and 10-year graft as well as patient survival.

The primary outcome of this article was to determine if there is a difference in patient and graft survival in PLT recipients transplanted for ALF or ESCLD. The secondary outcome was to compare the incidence of vascular, biliary complications, and biopsy-proven rejection in PLT for both groups.

Statistical analyses of the data

Data were evaluated using IBM SPSS software version 20.0. (IBM Corp., Armonk, NY, United States). Kolmogorov-Smirnov was employed to validate the normality of variable allocation. Assessments for categorical variables were conducted using the χ^2 test (Fisher's exact adjustment). Student's *t*-test was applied to assess two normally distributed quantitative variables between two cohorts, whereas the Mann-Whitney test was applied to assess non-normally distributed quantitative data. Missing data were taken into account through statistical evaluation. The Kaplan-Meier survival curve was employed to examine the graft and patient survival. The significance of the recorded outcomes was determined at the 5% level.

RESULTS

Between November 2000 and August 2019, 322 PLTs were performed in our center. We excluded retransplants, transplants for children with liver tumors, or metabolic disorders without underlying liver disease (90 PLTs) from the final analysis. The remaining 232 PLTs were classified into 195 PLTs due to ESCLD and 37 PLTs as emergency management of ALF (Figure 1). The median follow-up for the ALF group was 8.3 years (1–19.3 years), while the median follow-up for the ESCLD group was 8.1 years (1–19.6 years).

During the study period, 232 children presented to our institute with ALF. Unfortunately, 58 (25.0%) of them did not survive to undergo transplantation, 37 (15.9%) underwent transplantation, and 137 (59.1%) recovered without transplantation.

Pretransplant recipient parameters

Both groups were homogenous in terms of recipients' sex (P = 0.312), whereas recipients' age and weight were significantly higher in the ALF group. Further analysis of the ALF group showed that 6 patients were transplanted at below 1 year of age, 10 patients were transplanted at 1 year to 4 years of age, 3 patients were transplanted at above 4 years to 10 years of age, and 18 patients were older than 10 years of age at the time of transplant. Biliary atresia and progressive familial intrahepatic cholestasis were the most common causes of liver failure in the ESCLD group, whereas seronegative hepatitis and autoimmune hepatitis were the most common causes in the ALF group (Table 1). There was a significant difference in waiting time on the transplant list between both groups; the median waiting time for the ALF group was 3 d (1–41 d), whereas the median waiting time for ESCLD patients was 60.5 d (1-560 d; P < 0.001). The location of the recipient when the liver graft became available also showed a significant difference as the home locality was greater in the ESCLD group, whereas in the ALF group, hospital, as well as PICU locality (with or without invasive ventilation), were significantly higher (Table 1).

Donor parameters

There was no statistically significant difference in terms of donor sex or weight; however, donors in the ALF group were significantly older than those in the ESCLD group (Table 1). Concerning the graft resource, living donors were used more commonly in the ESCLD cohort (34 donors) than in the ALF cohort, which did not receive any graft from living donors (P = 0.006).

Operative parameters

Technical variant (reduced and split) grafts were used significantly more in the ESCLD group (Table 1). There was no difference in cold ischemia time between the two groups, but warm ischemia time was significantly longer in the ALF group (median 55 min, 32–81 min) than in the ESCLD group (median 45.5 min, 29–81 min; P = 0.004).

Post-transplant recipient variables

Vascular complications occurrence: There was no distinction among the groups regarding vascular complications. Five patients in the ALF group and forty-one patients in the ESCLD group had at least one post-transplant vascular event (Table 2). Some patients in the ESCLD group had more than one vascular complication; two recipients had both hepatic artery thrombosis and portal vein thrombosis (PVT), two recipients developed both hepatic artery stenosis and portal vein stenosis (PVS), and one patient had PVS then PVT (Table 2).

Incidence of biliary complications: Bile leak was significantly higher in the ESCLD group, whereas biliary stricture and common hepatic duct sludge showed no significant difference between the two groups. It was also of note that three of the ESCLD recipients developed both bile leakage and biliary stricture (Table 2).

Incidence of rejection: There was no difference in biopsy-proven acute or chronic rejection between the two groups. Seventeen (45.9%) ALF patients had one or more episodes of rejection and sixty-two patients (31.8%) in the ESCLD group experienced rejection (P = 0.096).

Post-transplant stay

PICU stay post-PLT was longer in the ALF group by a median of half a day (2.5 *vs* 2 d), but this difference was not statistically significant (P = 0.112). In keeping with their sick status before the transplant, the ALF patients had a longer median hospital stay (29 *vs* 21 d) compared to ESCLD patients (P = 0.013).

Retransplantation rate

There was no difference among the studied groups in terms of the need for retransplantation; 5 (13.5%) in the ALF group and 27 (13.8%) in the ESCLD group (P = 0.957).

Table 1 Donors and recipients demographics

Demographics	ALF (*n* = 37), %	ESCLD (*n* = 195), %	*P* value
Donor demographics			
Sex			
Male	45.7	46.9	0.902
Female	54.3	53.1	
Weight, kg	66.2 (8–90)	65.8 (10–98)	0.912
Age, yr	35.2 (0.9–65)	29 (1–66)	0.039
Type of liver graft			
Whole liver	14 (37.8)	38 (19.7)	0.016
Variant graft including split, reduced, living donor	23 (62.2)	155 (80.3)	
Recipient demographics			
Sex			
Male	16 (43.2)	102 (52.3)	0.312
Female	21 (56.8)	93 (47.7)	
Age at transplant, yr	8 (0.1–16.7)	5.4 (0.3–17.2)	0.031
Weight, kg	31 (2.7–66.5)	21 (4.7–89)	0.011
Etiology of liver disease			
Alagille's syndrome	0 (0)	12 (6.2)	0.222
Alpha-1-AT deficiency	0 (0)	15 (7.7)	0.138
Autoimmune	4 (10.8)	13 (6.7)	0.487
Biliary atresia	0 (0)	92 (47.2)	< 0.001
Biliary cirrhosis	0 (0)	2 (1.0)	1.000
CF liver disease	0 (0)	13 (6.7)	0.232
Drug induced	2 (5.4)	0 (0)	0.025
Hepatitis A	2 (5.4)	0 (0)	0.025
HSV	2 (5.4)	0 (0)	0.025
Seronegative hepatitis	17 (45.9)	0 (0)	< 0.001
PFIC	0 (0)	29 (14.9)	0.006
Post-liver resection	2 (5.4)	0 (0)	0.025
PSC	0 (0)	8 (4.1)	0.361
Others	8 (21.6)	11 (5.6)	0.004
Location of the recipient when the graft is available			
Home	0 (0)	137 (71.4)	< 0.001
Hospital	15 (40.5)	47 (24.5)	0.044
PICU not ventilated	7 (18.9)	5 (2.6)	0.001
PICU ventilated	15 (40.5)	3 (1.6)	< 0.001

ALF: Acute liver failure; CF: Cystic fibrosis; ESCLD: End-stage chronic liver disease; HSV: Herpes simplex virus; PFIC: Progressive familial intrahepatic cholestasis; PICU: Pediatric intensive care unit; PSC: Primary sclerosing cholangitis.

Patient survival

During the follow-up period, 17 (8.7%) of the ESCLD recipients died while in the ALF group, and 9 (24.3%) recipients died (P = 0.011) (Figure 2A and Table 3). Sepsis and liver failure were the two most common causes of death in PLT recipients, but there was no statistically significant difference between the two groups (Table 2). Analysis of ALF group survival in conjunction with the age of transplant (less

Table 2 Post-transplant outcomes

Outcome	ALF among *n* = 37, *n* (%)	ESCLD among *n* = 195, *n* (%)	*P* value
Vascular complications			
AV malformation post-liver biopsy	0 (0)	1 (0.5)	1.000
Retroperitoneal hematoma, femoral vein bypass cannula	0 (0)	1 (0.5)	1.000
HAS	2 (5.4)	13 (6.7)	1.000
PVS	0 (0)	14 (7.2)	0.134
HAT	1 (2.7)	10 (5.1)	1.000
PVT	1 (2.7)	7 (3.6)	1.000
HVS	1 (2.7)	0 (0)	0.159
Biliary complications			
CHD sludge	0 (0)	2 (1)	1.000
Biliary stricture	3 (8.1)	21 (10.8)	0.775
Bile leak	0 (0)	23 (11.8)	0.031
Cause of graft loss	*n* = 5	*n* = 27	
HAT	0 (0)	9 (33.3)	0.288
PNF	2 (40)	5 (18.5)	0.296
Chronic rejection	3 (60)	6 (22.2)	0.121
Biliary tract complications	0 (0)	7 (25.9)	0.560
Cause of death	*n* = 9	*n* = 17	
Unknown	0 (0)	5 (29.4)	0.129
Cardiopulmonary	3 (33.3)	1 (5.9)	0.104
Cerebral oedema	1 (11.1)	0 (0)	0.346
Fungal infection	1 (11.1)	0 (0)	0.346
Gastrointestinal	0 (0)	1 (5.9)	1.000
Intracranial hemorrhage	1 (11.1)	0 (0)	0.346
Liver failure	1 (11.1)	4 (23.5)	0.628
Recurrence of disease	0 (0)	1 (5.9)	1.000
Sepsis	2 (22.2)	5 (29.4)	1.000

ALF: Acute liver failure; AV: Arteriovenous; CHD: Common hepatic duct; ESCLD: End-stage chronic liver disease; HAS: Hepatic artery stenosis; HAT: Hepatic artery thrombosis; HVS: Hepatic vein stenosis; PNF: Primary non-function; PVS: Portal vein stenosis; PVT: Portal vein thrombosis.

than 1 year, 1-4 years, 4-10 years, more than 10 years) showed 5-year patient survival of 50%, 90%, 100%, and 77.8%, respectively.

Graft survival

Median graft survival was longer in the ESCLD group (2412 d) compared to the ALF group (2292 d), but this difference was not statistically significant (P = 0.587) (Figure 2B and Table 3). Despite some causes of graft failure being more frequent in one group than the other, there was no statistically significant difference (Table 2).

DISCUSSION

In the United Kingdom, children with ALF or ESCLD who are candidates for PLT are referred to one of the three centers in the country for evaluation, including our center. When the indication for PLT is established, patients are offered transplantation if there is more than 50% survival likelihood at 5 years

Table 3 Survival among category groups- 1-, 5-, 10-yr and end of study for patients and grafts

Survival outcome	Mean	%1 yr	%5 yr	%10 yr	%End of study	Log rank	
						χ^2	*P* value
Patient survival							
ALF	14.86	78.3	78.3	78.3	69.6	7.370	0.007
ESCLD	17.71	97.9	93.9	89.4	85.0		
Graft survival							
ALF	12.46	75.6	72.4	66.9	47.8	2.426	0.119
ESCLD	14.46	90.7	82.9	77.3	56.8		

ALF: Acute liver failure; ESCLD: End-stage chronic liver disease.

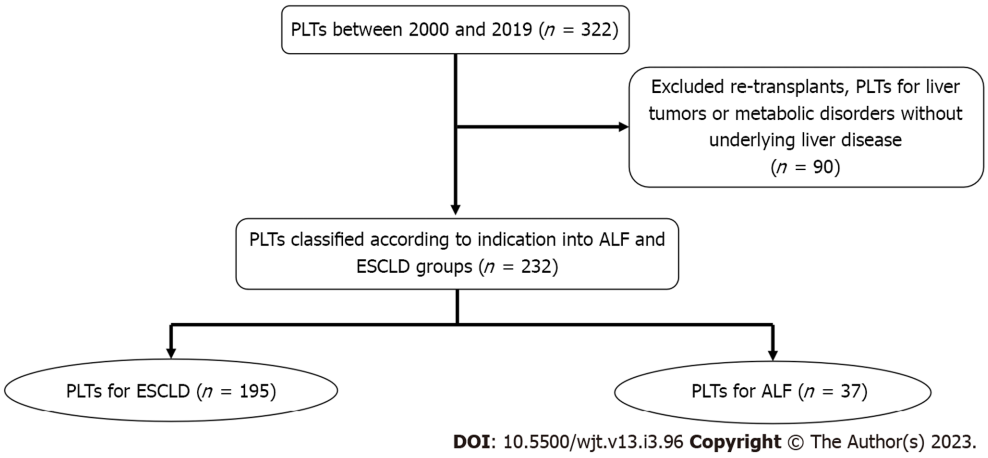

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Figure 1 Flow diagram of study participants. ALF: Acute liver failure; ESCLD: End-stage chronic liver disease; PLT: Pediatric liver transplantation.

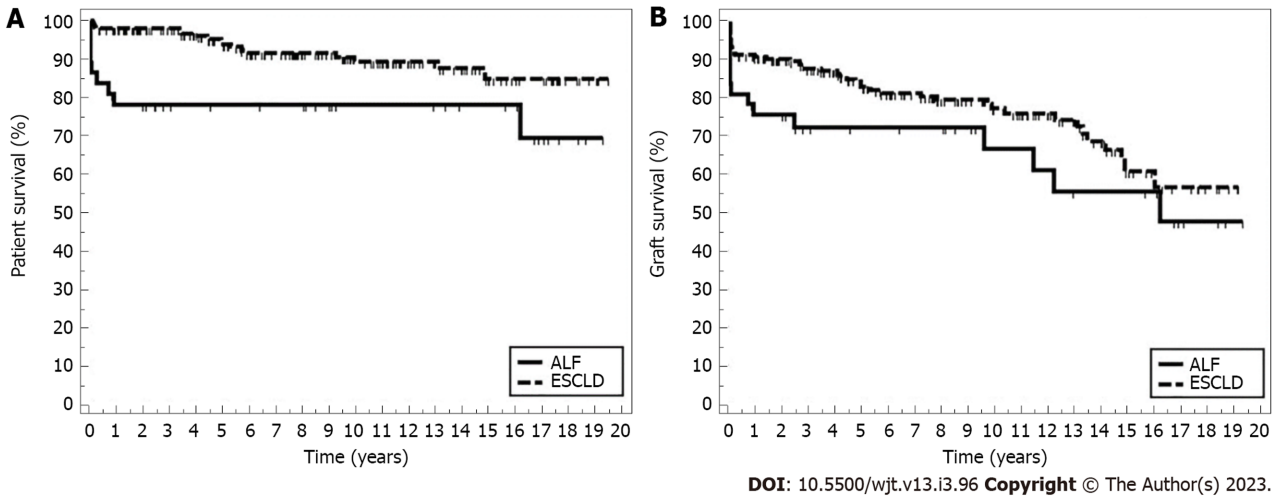

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Figure 2 Kaplan-Meier survival curve for patient survival, and graft survival. A: Patient survival; B: Graft survival. ALF: Acute liver failure; ESCLD: End-stage chronic liver disease.

after PLT with an acceptable quality of life. But the dynamics of PLT are completely divergent between ALF and ESCLD settings, leading to separate selection criteria for candidates needing emergency transplantation compared to elective procedure.

The studied cohorts have diverse etiology with distinct differences in short-term prognosis. Similarly, graft allocation procedures are unique for elective and emergency transplantation, showing that those cohorts have a distinct probability of mortality without PLT. In our study, the percentage of PLTs

performed as emergency management for ALF was 11.5%, consistent with studies from other centers[8-10], whereas some other authors have reported higher rates of PLT in ALF patients that may reach up to 35%[11,12]; this difference reflects the absence of a reliable prognostic model for ALF patients that can accurately predict ALF candidates who would not survive without PLT.

Identifying ALF patients who would be saved by successful PLT and differentiating them from those who may recover spontaneously or those who will eventually die with or without PLT cannot be guided by currently available data[13-16]. Using isolated biomarkers such as ammonia, actin-free Gc-globulin, and lactate is not reliable and cannot be applied to all ALF patients without being sufficiently studied in the pediatric population[17-19]. Prognostic scoring models applying clinical and laboratory variables such as King's college criteria and liver injury unit score cannot be confidently used to anticipate ALF patient death[19-21].

In terms of the etiology of liver failure, biliary atresia was the most common indication for PLT in ESCLD patients in our study (47.2%), consistent with the literature[1,8,11,22,23]. On the other hand, the etiology of the underlying liver disease could not be identified in 45.9% of our ALF recipients. Most of the literature concerned with PLT in ALF patients has shown the same observation[3,12,24,25]. Failure to identify the etiology of ALF is probably multifactorial. First, most of the data concerned with ALF in children and infants are retrieved from case reports, exploration of adult data, individual practice, and retrospective studies of single centers[2]. Second, the rapid progression of liver failure to transplant or death does not give enough room for the extensive work-up required[4]. The inability to identify the cause of ALF is always stressful for the treating physicians as it may affect the outcome of this group of patients because of its effects on prognosis, therapy, and prevention.

Until 2008, we were using molecular adsorbent recirculating system as bridging therapy for ALF patients, but we did not find it helpful in terms of changing outcomes for patients. We use plasmapheresis in selected patients, as we used it in a paracetamol overdose patient in the last 3 years. Such bridging therapies are not commonly used in our program for ALF children, due to the lack of evidence for survival benefits. Time on the transplant waiting list was significantly shorter in the ALF group; this is the outcome of labeling such patients as "super-urgent," which puts them on top of the national waiting list. Receiving a timely PLT in this group is vital as prolonged waiting can lead to the development or progression of respiratory and neurological complications, which can eventually result in the de-listing of the child who becomes "too sick" for transplantation and eventually patient mortality.

The location of the recipient when the graft became available showed a significant difference between the two groups. ALF patients are mostly located in the hospital ward or PICU while ESCLD patients are usually admitted to our center from home. This is explained by the fact that ALF patients are usually sicker in the immediate pretransplant period; thus, they are usually hospitalized or even admitted to the PICU if multiple organ support is needed, while ESCLD patients are mostly less critical and thus usually followed up in outpatient clinics and admitted to the transplant center only when the graft becomes available. This was also reflected in the post-transplant hospital stay that was significantly longer in ALF patients who are expected to require a longer time to recover before discharge.

In contrast to the ESCLD group, ALF candidates in our study did not receive a living donor graft; this is possibly linked to a brief window that does not provide sufficient time for meticulous assessment of possible living donors. Living donation intended for ALF candidates has consistently been a matter of discussion[26]. Various studies have expressed concerns about the ultra-short period utilized for radiological and clinical assessment of the living donor along with the emotional element in PLT that might affect the outcomes[27]. Other reports claim that PLT using living donor grafts has a possibly better outcome due to a briefer waiting period as the sick child does not have to wait for the liver graft allocation system to receive a suitable graft in addition to the presumed better-quality graft due to limited cold ischemia time as shown by the inferior primary non-function incidence in grafts from living donors[28].

Technical variant grafts were used significantly higher in the ESCLD group; this is explained by the significantly lower age at transplant of this group compared to the ALF group, so smaller grafts were needed to match recipient size. This can also explain higher rates of bile leakage in the ESCLD group from the cut surface of reduced or split grafts.

ALF recipients in our study have a significantly lower survival rate than ESCLD recipients, which has been reported in multiple studies[11,22], while only one study to the best of our knowledge has reported similar patient survival in both groups[25]. This can be explained by multiple factors. First, the more critical condition of ALF patients in the pretransplant period that was reflected in our study by significantly higher PICU location of these patients when the graft becomes available and was linked in some reports to low post-transplant survival[11]. Second is the scarcity of suitable grafts for the pediatric population[29], which prolongs the waiting time of ALF patients and may put pressure on the transplant centers to accept marginal grafts, as survival of this critical group is largely dependent on receiving a PLT within a short window of opportunity[28]. The third is the fact that the etiology is unknown in most cases of ALF, and this will surely affect post-transplant disease management and progression.

Interestingly, we noticed that the recipient's survival in the ALF group is most affected in the 1st-year post-transplant and remained almost stable after that, while survival in the ESCLD group continued to decline gradually over the years. This observation is probably related to how unwell the ALF recipients were at the time of transplant (a considerable proportion was in intensive care), but after the 1st year, survival stabilizes. Whereas in ESCLD, the 1st-year outcomes are better, probably because most of these patients were stable and admitted for transplant from home. However, after that, there seems to be a steady decrease in their survival, possibly because of the effects of disease chronicity where ESCLD itself or its underlying etiology like cystic fibrosis or alpha-1-antitrypsin deficiency would have affected other systems such as the lungs and kidneys and this effect would reflect on patient survival over the years.

There were some limitations in this study. The larger study cohort, longer follow-up duration, single-center population with uniform pretransplant and post-transplant protocol, and careful retrieval of data allowed us to overcome the limitation of the retrospective nature of the study. More importantly, no such studies are comparing ALF with ESCLD in the paediatric transplant literature.

CONCLUSION

This was a retrospective study that compared the long-term outcomes of PLT in ALF and ESCLD settings. Survival of PLT recipients was significantly higher in the ESCLD group due to multiple factors such as the critical general condition of ALF patients in the peritransplant time, scarcity of suitable grafts for pediatric recipients, and obscure etiology of ALF in most of the cases. The rate of complications did not show a significant difference apart from higher rates of bile leak in the ESCLD group.

ARTICLE HIGHLIGHTS

Research background

Settings of pediatric liver transplantation (PLT) in end-stage chronic liver disease (ESCLD) and acute liver failure (ALF) are divergent. ALF recipients are transplanted within a narrow window of opportunity, whereas ESCLD recipients are usually transplanted electively.

Research motivation

Outcomes of PLT in ALF and ESCLD were previously described by different centers but to the best of our knowledge, they were not compared to establish if there is a difference in post-PLT survival and complication rates between these two groups.

Research objectives

To determine if there is a difference in post-operative complications and survival outcomes between the ALF and ESCLD in PLT.

Research methods

This was a retrospective observational study of all primary PLTs performed at a single center between 2000 and 2019. ALF and ESCLD groups were compared for the pretransplant recipient, donor and operative parameters, and post-operative outcomes including graft and patient survival.

Research results

During the 20-year study period, 232 primary PLTs were performed at our center; 195 were transplanted for ESCLD and 37 were transplanted for ALF. The ALF recipients were significantly older (median 8 years *vs* 5.4 years; $P = 0.031$) and heavier (31 *vs* 21 kg; $P = 0.011$). Living donor grafts were used more in the ESCLD group (34 *vs* 0; $P = 0.006$). There was no difference between the two groups concerning vascular complications and rejection, but there were more bile leaks in the ESCLD group. Post-transplant patient survival was considerably superior in the ESCLD group: 1-, 5-, and 10-year survival rates were 97.9%, 93.9%, and 89.4% correspondingly compared to 78.3%, 78.3%, and 78.3% in the ALF group ($P = 0.007$). However, there was no difference in 1-, 5-, and 10-year graft survival rates between the ESCLD and ALF groups - 90.7%, 82.9%, and 77.3% *vs* 75.6%, 72.4%, and 66.9% ($P = 0.119$).

Research conclusions

Post-PLT survival in ALF patients is inferior to ESCLD patients. This may be due to several factors including uncertainty of the underlying pathology in most ALF patients and the more critical clinical status of ALF candidates in the immediate pre-transplant period. Survival post-PLT in the ALF group was adversely affected in the 1st year and then stabilized, while post-PLT survival in the ESCLD group showed a gradual decline over the study period.

Research perspectives

Future research should address the dilemma of identifying the underlying pathology in a considerable portion of ALF candidates and should also try to overcome liver graft shortage by identifying methods to widen the graft pool.

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FOOTNOTES

Author contributions: Alnagar AM and Hakeem AR contributed equally to this study; Alnagar AM and Attia MS conceived the study concept and design; Alnagar AM and Daradka K collected the data; Alnagar AM, Kyrana E, Methga M, and Palaniswamy K analyzed the data; Rajwal S, Mulla J, Upasani V, and Vijayanand D drafted the manuscript; Hakeem AR, Prasad R, O'meara M, and Attia MS critically revised the manuscript.

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Informed consent statement: Informed consent is not required.

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Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at abdul.hakeem1@nhs.net. Participants' consent was not obtained but the presented data are anonymized, and risk of identification is low.

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REFERENCES

1 **Uribe M**, Buckel E, Ferrario M, Godoy J, González G, Hunter B, Ceresa S, Cavallieri S, Berwart F, Herzog C, Santander MT, Calabrán L. Pediatric liver transplantation: ten years of experience in a multicentric program in Chile. *Transplant Proc* 2005; **37**: 3375-3377 [PMID: 16298599 DOI: 10.1016/j.transproceed.2005.09.096]

2 **Rivera-Penera T**, Moreno J, Skaff C, McDiarmid S, Vargas J, Ament ME. Delayed encephalopathy in fulminant hepatic failure in the pediatric population and the role of liver transplantation. *J Pediatr Gastroenterol Nutr* 1997; **24**: 128-134 [PMID: 9106097 DOI: 10.1097/00005176-199702000-00004]

3 **Squires RH Jr**, Shneider BL, Bucuvalas J, Alonso E, Sokol RJ, Narkewicz MR, Dhawan A, Rosenthal P, Rodriguez-Baez N, Murray KF, Horslen S, Martin MG, Lopez MJ, Soriano H, McGuire BM, Jonas MM, Yazigi N, Shepherd RW, Schwarz K, Lobritto S, Thomas DW, Lavine JE, Karpen S, Ng V, Kelly D, Simonds N, Hynan LS. Acute liver failure in children: the first 348 patients in the pediatric acute liver failure study group. *J Pediatr* 2006; **148**: 652-658 [PMID: 16737880 DOI: 10.1016/j.jpeds.2005.12.051]

4 **Sundaram SS**, Alonso EM, Narkewicz MR, Zhang S, Squires RH; Pediatric Acute Liver Failure Study Group. Characterization and outcomes of young infants with acute liver failure. *J Pediatr* 2011; **159**: 813-818.e1 [PMID: 21621221 DOI: 10.1016/j.jpeds.2011.04.016]

5 **Bhatia V**, Lodha R. Intensive care management of children with acute liver failure. *Indian J Pediatr* 2010; **77**: 1288-1295 [PMID: 20799075 DOI: 10.1007/s12098-010-0167-1]

6 **Ng VL**, Li R, Loomes KM, Leonis MA, Rudnick DA, Belle SH, Squires RH; Pediatric Acute Liver Failure Study Group (PALFSG). Outcomes of Children With and Without Hepatic Encephalopathy From the Pediatric Acute Liver Failure Study Group. *J Pediatr Gastroenterol Nutr* 2016; **63**: 357-364 [PMID: 27367788 DOI: 10.1097/MPG.0000000000001178]

7 **Mews C**, Sinatra F. Chronic liver disease in children. *Pediatr Rev* 1993; **14**: 436-444 [PMID: 8284282]

8 **Broering DC**, Kim JS, Mueller T, Fischer L, Ganschow R, Bicak T, Mueller L, Hillert C, Wilms C, Hinrichs B, Helmke K, Pothmann W, Burdelski M, Rogiers X. One hundred thirty-two consecutive pediatric liver transplants without hospital mortality: lessons learned and outlook for the future. *Ann Surg* 2004; **240**: 1002-12; discussion 1012 [PMID: 15570206 DOI: 10.1097/01.sla.0000146148.01586.72]

9 **Venick RS**, Farmer DG, Soto JR, Vargas J, Yersiz H, Kaldas FM, Agopian VG, Hiatt JR, McDiarmid SV, Busuttil RW. One Thousand Pediatric Liver Transplants During Thirty Years: Lessons Learned. *J Am Coll Surg* 2018; **226**: 355-366 [PMID: 29410290 DOI: 10.1016/j.jamcollsurg.2017.12.042]

10 **Kim WR**, Lake JR, Smith JM, Skeans MA, Schladt DP, Edwards EB, Harper AM, Wainright JL, Snyder JJ, Israni AK, Kasiske BL. OPTN/SRTR 2013 Annual Data Report: liver. *Am J Transplant* 2015; **15** Suppl 2: 1-28 [PMID: 25626341 DOI: 10.1111/ajt.13197]

11 **Guariso G**, Visonà Dalla Pozza L, Manea S, Salmaso L, Lodde V, Facchin P; SIGENP Group of Liver Transplantation. Italian experience of pediatric liver transplantation. *Pediatr Transplant* 2007; **11**: 755-763 [PMID: 17910653 DOI: 10.1111/j.1399-3046.2007.00739.x]

12 **Farmer DG**, Venick RS, McDiarmid SV, Duffy JP, Kattan O, Hong JC, Vargas J, Yersiz H, Busuttil RW. Fulminant hepatic failure in children: superior and durable outcomes with liver transplantation over 25 years at a single center. *Ann Surg* 2009; **250**: 484-493 [PMID: 19730179 DOI: 10.1097/SLA.0b013e3181b480ad]

13 **Squires JE**, Rudnick DA, Hardison RM, Horslen S, Ng VL, Alonso EM, Belle SH, Squires RH. Liver Transplant Listing in Pediatric Acute Liver Failure: Practices and Participant Characteristics. *Hepatology* 2018; **68**: 2338-2347 [PMID: 30070372 DOI: 10.1002/hep.30116]

14 **Bhaduri BR**, Mieli-Vergani G. Fulminant hepatic failure: pediatric aspects. *Semin Liver Dis* 1996; **16**: 349-355 [PMID: 9027948 DOI: 10.1055/s-2007-1007248]

15 **Schiodt FV**, Atillasoy E, Shakil AO, Schiff ER, Caldwell C, Kowdley KV, Stribling R, Crippin JS, Flamm S, Somberg KA, Rosen H, McCashland TM, Hay JE, Lee WM. Etiology and outcome for 295 patients with acute liver failure in the United States. *Liver Transpl Surg* 1999; **5**: 29-34 [PMID: 9873089 DOI: 10.1002/Lt.500050102]

16 **Ostapowicz G**, Fontana RJ, Schiødt FV, Larson A, Davern TJ, Han SH, McCashland TM, Shakil AO, Hay JE, Hynan L, Crippin JS, Blei AT, Samuel G, Reisch J, Lee WM; U. S. Acute Liver Failure Study Group. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med* 2002; **137**: 947-954 [PMID: 12484709 DOI: 10.7326/0003-4819-137-12-200212170-00007]

17 **Bagchi A**, Kumar S, Ray PC, Das BC, Gumma PK, Kar P. Predictive value of serum actin-free Gc-globulin for complications and outcome in acute liver failure. *J Viral Hepat* 2015; **22**: 192-200 [PMID: 24774007 DOI: 10.1111/jvh.12259]

18 **Schiødt FV**, Bangert K, Shakil AO, McCashland T, Murray N, Hay JE, Lee WM; Acute Liver Failure Study Group. Predictive value of actin-free Gc-globulin in acute liver failure. *Liver Transpl* 2007; **13**: 1324-1329 [PMID: 17763387 DOI: 10.1002/Lt.21236]

19 **Cholongitas EB**, Betrossian A, Leandro G, Shaw S, Patch D, Burroughs AK. King's criteria, APACHE II, and SOFA scores in acute liver failure. *Hepatology* 2006; **43**: 881; author reply 882 [PMID: 16557559 DOI: 10.1002/hep.21121]

20 **Cholongitas E**, Theocharidou E, Vasianopoulou P, Betrosian A, Shaw S, Patch D, O'Beirne J, Agarwal B, Burroughs AK. Comparison of the sequential organ failure assessment score with the King's College Hospital criteria and the model for end-stage liver disease score for the prognosis of acetaminophen-induced acute liver failure. *Liver Transpl* 2012; **18**: 405-412 [PMID: 22213443 DOI: 10.1002/lt.23370]

21 **Lu BR**, Zhang S, Narkewicz MR, Belle SH, Squires RH, Sokol RJ; Pediatric Acute Liver Failure Study Group. Evaluation of the liver injury unit scoring system to predict survival in a multinational study of pediatric acute liver failure. *J Pediatr* 2013; **162**: 1010-6.e1 [PMID: 23260095 DOI: 10.1016/j.jpeds.2012.11.021]

22 **Martin SR**, Atkison P, Anand R, Lindblad AS; SPLIT Research Group. Studies of Pediatric Liver Transplantation 2002: patient and graft survival and rejection in pediatric recipients of a first liver transplant in the United States and Canada. *Pediatr Transplant* 2004; **8**: 273-283 [PMID: 15176966 DOI: 10.1111/j.1399-3046.2004.00152.x]

23 **Feng S**, Si M, Taranto SE, McBride MA, Mudge C, Stritzel S, Roberts JP, Rosenthal P. Trends over a decade of pediatric liver transplantation in the United States. *Liver Transpl* 2006; **12**: 578-584 [PMID: 16555314 DOI: 10.1002/Lt.20650]

24 **Baliga P**, Alvarez S, Lindblad A, Zeng L; Studies of Pediatric Liver Transplantation Research Group. Posttransplant survival in pediatric fulminant hepatic failure: the SPLIT experience. *Liver Transpl* 2004; **10**: 1364-1371 [PMID: 15497159 DOI: 10.1002/Lt.20252]

25 **Heffron TG**, Pillen T, Smallwood G, Rodriguez J, Sekar S, Henry S, Vos M, Casper K, Gupta NA, Fasola CG, Romero R. Pediatric liver transplantation for acute liver failure at a single center: a 10-yr experience. *Pediatr Transplant* 2010; **14**: 228-232 [PMID: 19519799 DOI: 10.1111/j.1399-3046.2009.01202.x]

26 **Éboli L**, Tannuri AC, Gibelli N, Silva T, Braga P, Tannuri U. Comparison of the Results of Living Donor Liver Transplantation Due to Acute Liver Failure and Biliary Atresia in a Quaternary Center. *Transplant Proc* 2017; **49**: 832-835 [PMID: 28457406 DOI: 10.1016/j.transproceed.2017.03.001]

27 **Cariús LP**, Pacheco-Moreira LF, Balbi E, Leal CR, Gonzalez AC, Agoglia LV, Araújo C, Enne M, Martinho JM. Living donor liver transplantation for acute liver failure: a single center experience. *Transplant Proc* 2009; **41**: 895-897 [PMID: 19376382 DOI: 10.1016/j.transproceed.2009.02.007]

28 **Szymczak M**, Kaliciński P, Kowalewski G, Broniszczak D, Markiewicz-Kijewska M, Ismail H, Stefanowicz M, Kowalski A, Teisseyre J, Jankowska I, Patkowski W. Acute liver failure in children-Is living donor liver transplantation justified? *PLoS One* 2018; **13**: e0193327 [PMID: 29474400 DOI: 10.1371/journal.pone.0193327]

29 **Wu YM**, Ho MC, Hu RH, Ko WJ, Yang PM, Lai MY, Lee PH. Liver transplantation for acute hepatic failure. *Transplant Proc* 2004; **36**: 2226-2227 [PMID: 15561199 DOI: 10.1016/j.transproceed.2004.08.062]

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