Postoperative Complications and Management

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Key Points

- Primary graft dysfunction is an early complication, defined by diffuse alveolar infiltrates and impairment of oxygenation, the most severe form might require extracorporeal membrane oxygenation support
- During the early phase after lung transplant (LTx) there is a high probability of bacterial and fungal infections with an associated high risk of morbidity
- Surveillance for multiple drug resistant bacteria should be done to avoid inappropriate empiric antibiotic treatment
- Antiviral prophylaxis should be given to all cytomegalovirus (CMV) seropositive recipients and CMV seronegative recipients who receive an organ from a seropositive donor (D+/R−)
- Acute rejection is an important risk factor for the development of chronic lung allograft dysfunction and particularly bronchiolitis obliterans syndrome.

Introduction

Lung transplant (LTx) recipients are at risk of developing post-operative complications including primary graft dysfunction (PGD), acute rejection, opportunistic infection and chronic lung allograft dysfunction (CLAD), which probably represents chronic rejection. The management of the post-LTx process is complex and significant progress has been made in the identification, prevention and treatment of the major complications related to the lung allograft during the post-transplant phase. Immunosuppression is mandatory to prevent acute and chronic rejection of the transplanted lung. However, the compromised immune system can increase the risk of infection, especially by opportunistic agents. This chapter will describe the main postoperative complications following LTx, the mechanisms behind them and the therapeutic options.

Primary Graft Dysfunction

PGD is a form of acute lung injury that may affect lung allografts early after transplantation. This condition was defined in 2005 by the International Society for Heart and Lung Transplantation (ISHLT) [1] and was recently modified in a consensus conference in 2016 [2]. In summary, PGD is defined by the presence...
of diffuse alveolar infiltrates on chest X-ray, together with oxygenation impairment (Fig. 1). According to the working group, PGD should be graded every 24 hours from lung reperfusion, over the first 72 hours [2].

**Epidemiology**

Despite attempts to refine the definition of PGD, the reported incidence depends on the PGD grading system used and on the timing of the assessment [3, 4]. Before the introduction of the ISHLT definition, Christie et al. reported a PGD incidence of 10.2% in a cohort of 5,262 lung recipients [5]. Later, using the ISHLT criteria, Kreisler et al. reported a PGD incidence of 22.1% [6] worldwide. More recently, Diamond et al. reported, that 16.8% of lung recipients developed grade 3 PGD at 48 or 72 h after reperfusion in a prospective multicenter cohort of 1,255 LTx [3, 7]. The 2016 ISHLT report summarised the available literature and reported an incidence of about 30% of PGD and about 15–20% of grade 3 PGD after LTx [4].

**Outcomes**

The development of PGD after LTx has been associated with poorer short- and long-term clinical outcomes (Table 1). In particular, PGD has been shown to be associated with bronchial complications, reduced pulmonary function tests performance, prolonged mechanical ventilation, in-hospital and ICU length of stay and increased mortality and the development of bronchiolitis obliterans syndrome (BOS) [4].

![ISHLT PGD definition 2016](image_url)
### Table 1  Impact of PGD on outcomes

| Reference                  | PGD grade | Timing from reperfusion | Sample | Outcome | Findings                                                                                                                                 |
|----------------------------|-----------|-------------------------|--------|---------|-------------------------------------------------------------------------------------------------------------------------------------------|
| Olland et al. (2017)       | All grades| 0–72 h                  | 259    | Bronchial complications | PGD within 72 is a major risk factor for bronchial complications (OR = 2.55; p = 0.08)                                                     |
| Armstrong et al. (2016)    | Grade 3   | 72 h                    | 243    | CPET    | No differences in CPET or 6MWD                                                                                                         |
|                            |           |                         |        | 6MWD    | Worse HLOS and PFT                                                                                                                       |
| Mizota et al. (2016a)      | Grade 3   | 0 h                     | 42     | VFDs    | Association of PGD grade 3 at T0 with decreased VFDs in lobar grafts                                                                      |
| DerHovanessian et al. (2016)| All grades| 0–72 h                  | 279    | BOS     | Increased rates of BOS incrementally increased with PGD severity                                                                       |
| Ius et al. (2014)          | Grade 2–3 | 48 h                    | 546    | DSA     | Association (OR 2.6, 95% CI 1.5–4.6, p = 0.001) with early DSA development, which were independently associated with an increased risk for mortality |
| Diamond et al. (2013b)     | Grade 3   | 48 or 72 h              | 1255   | Mortality | Significant association with 90-day and 1-year mortality                                                                                 |
| Samano et al. (2012)       | Grade 3   | 48 and 72 h             | 118    | MV time and mortality                                                                                                                   | Higher MV time and operative and 90-day mortality in grade 3 PGD                                                                 |
| Kreisel et al. (2011b)     | All grades|                         | 1000   | BOS and survival | Higher rates of BOS and impaired short- and long-term survival                                                                         |
| Christie et al. (2010)     | All grades| 24–72 h                 | 450    | Survival | Grade 3 had the highest 30-day and overall mortality PGD grade at 48 and 72 hours discriminated mortality better than PGD grade at 24 hours |
| Huang et al. (2008)        | All grades| 24–72 h                 | 334    | BOS     | Significant risk factor for both BOS development and progression Direct relationship between the severity of PGD and the risk of BOS development grade 3 was associated with the highest risk of BOS development and progression at all time points |
| Daud et al. (2007)         | All grades| ICU arrival             | 334    | BOS stage 1 | PGD is a significant risk factor for BOS independent of other recognized risk factors Direct relationship between the severity of PGD and the risk of BOS |
| Whitson et al. (2007)      | Grade 3   | 0–48 h                  | 374    | BOS and survival | Worst score T (0–48) Grade 3 PGD negatively affects long-term survival, BOS-free survival and pulmonary function of B LTx |
| Prekker et al. (2007)      | Grade 3   | 0 h                     | 96     | Mortality | P/F improvement in <20% in the first 12 h leads to a poor outcome                                                                          |
**Table 1 Continued**

| Reference                | PGD grade | Timing from reperfusion | Sample | Outcome               | Findings                                                                                                                                                                                                 |
|--------------------------|-----------|-------------------------|--------|-----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Burton et al. (2007)     | All grades| 0–72 h                  | 180    | Mortality and various | Worse 90-day postoperative mortality and 3-year survival Higher incidence of DAD and BOOP                                                                                                                  |
| Prekker et al. (2006)    | All grades| 0–48 h                  | 402    | Mortality and survival| Worst score T (0–48) Grade 3 PGD had significantly decreased long-term survival, longer ICU and hospital stay; worst score T (0–48) and T0 Grade 3 PGD was a significant RF for short- and long-term mortality |
| Christie et al. (2005c)  | Grade 3   | 0–48 h                  | 5262   | Mortality and survival| PGD is a major contributing factor to early mortality Survivors have an increased risk of death extending beyond the first post-transplant year                                                                    |
| Thabut et al. (2002)     | Grade 2–3 | 0–72 h                  | 251    | Mortality             | Association with increased duration of mechanical ventilation and ICU mortality                                                                                                                        |

*Lobar transplantation

List of abbreviations. LTx lung transplantation; B bilateral; M monolateral; L lobar; CPET cardiopulmonary exercise testing; 6MWD 6-minute walk test; HLOS hospital length of stay; PFT pulmonary function tests; VFDs ventilator free days; BOS bronchiolitis obliterans syndrome; DSA donor-specific anti-HLA antibodies; P/F PaO₂/FiO₂ ratio; ICU intensive care unit; DAD diffuse alveolar damage; BOOP bronchiolitis obliterans organizing pneumonia; MV mechanical ventilation
Pathophysiology and Risk Factors

The 2016 ISHLT consensus statement reaffirmed the notion that PGD has no recognised aetiology, but is the result of multiple donor and recipient related factors, many of which remain unknown [2]. Ischaemia-reperfusion induced injury (IRI) of the transplanted lung is considered the major determinant of PGD and it is triggered by the activation of the inflammatory cascade [8, 9]. Vascular endothelial and alveolar epithelial homeostasis impairment and tissue macrophage, neutrophil and lymphocyte activation are considered the key actors in PGD pathophysiology [8].

Several risk factors might contribute to PGD development although the literature remains somewhat controversial. These can be broadly divided into donor or recipient related risk factors. The 2016 ISHLT report indicates that the recipient’s primary lung disease, pulmonary arterial hypertension, obesity and preoperative inflammation have been associated with PGD development, as well as donor traumatic brain injury, advanced age, smoking and alcohol use. Perioperative factors such as single versus bilateral LTx, the use of cardio-pulmonary bypass, ischaemic time and the amount of blood transfusions may also influence the early graft outcome [4]. A list of studies focusing on PGD risk factors, including those about the impact of organs retrieved from donation after circulatory death (DCD) donors and of the use of ex vivo lung perfusion (EVLP) for marginal donors on PGD development, is presented in Table 2.

Treatment

The treatment strategy for PGD is to provide support therapy in order to gain time for the PGD-associated lung injury to recover and to prevent secondary organ damage. The treatment is similar to that for acute respiratory distress syndrome (ARDS): limiting fluid administration and positive fluid balance, a lung protective ventilator strategy, low haematocrit (25–30%) and optimisation of coagulation parameters [10].

Inhaled nitric oxide (iNO) can improve ventilation-perfusion mismatch and decrease the pulmonary vascular resistance (PVR) without affecting the systemic blood pressure. Some studies have shown that the use of iNO reduced the duration of mechanical ventilation (MV) [11, 12].

In severe PGD, patients who do not respond to conventional therapy and iNO might benefit from extracorporeal membrane oxygenation (ECMO) support as a bridge to recovery [12]. Veno-venous (VV) ECMO provides respiratory support and permits the use of protective lung ventilation, thus avoiding the potential harmful effects of aggressive MV [13, 14]. ECMO should ideally be used within 24 h from the diagnosis of PGD [12]. VV ECMO is generally well tolerated and is associated with fewer complications than veno-arterial (VA) ECMO providing that the patient does not require simultaneous mechanical circulatory support [15].

a. Protective lung ventilation strategy

Lung-protective ventilator strategies including use of a low tidal volume ($V_T$) improve survival in patients with ARDS [16–18]. As it has been shown that the type of damage on the lung in PGD and ARDS is similar, it follows that a similar approach could prevent or improve recovery from PGD in the LTx recipient.

Undersized allografts can lead to hyperinflation by a high $V_T$ setting, increasing the risk of ventilator-associated lung injury.

In such patients, the vascular bed is also undersized giving risk to an increased PVR and therefore higher pulmonary artery pressure, which can result in right ventricle strain. This contributes significantly to PGD after LTx.

Therefore, the ventilator parameters should be set on estimates of the allograft size, i.e., predicted donor weight, rather than recipient weight [19].

b. Pulmonary Vasodilators

The development of PGD correlates with a reduction in the endogenous nitric oxide and cyclic guanosine monophosphate (cGMP) levels. Nitric oxide (NO) is a vasodilator that acts
| Reference | Year | Topic | Study design | Sample | Findings and OR (if available) |
|-----------|------|-------|--------------|--------|-------------------------------|
| Lansink-Hartgring et al. (2018) | 2018 | Donor | Retrospective SC | 474 | Donor hypernatremia was not associated with grade 3 PGD at 0–72 h, MV duration, or long-term survival |
| Hamilton et al. (2018) | 2018 | Plasma PAI-1 | Prospective SC | 25 | Recipients who developed grade 2–3 PGD had higher donor plasma levels of PAI-1 |
| Hin et al. (2018) | 2018 | CCSP G38A polymorphism | Retrospective MC | 104 | Donor CCSP G38A polymorphism is associated with a decreased risk of grade 3 PGD (OR 0.22, 95%IC 0.041–0.88, p = 0.045) |
| Park et al. (2018a) | 2018 | Anti-HLA Ab | Retrospective SC | 76 | Grade 2–3 PGD within 72 h was more frequent in patients with anti-HLA antibodies with moderate-to-high MFI values |
| Belhaj et al. (2017) | 2017 | SP-A/SP-B gene expression | Prospective SC (pilot) | 13 | SP-A and SP-B gene expression in the donors’ lungs was reduced in grade 1/3 PGD patients |
| Abbas et al. (2017) | 2017 | TTV in BAL | Prospective SC with matched control | 46 | Changes in TTV levels during the perioperative period were significantly associated with grade 3 PGD within 72 h |
| Holley et al. (2017) | 2017 | Donor age | Retrospective SC | 396 | No interaction was seen between donor age and risk of grade 3 PGD at 72 h |
| Mizota et al. (2016b) | 2016 | Lobar LTx | Retrospective SC | 75 | Grade 3 PGD at 48–72 h was not different between living lobar and cadaveric LTx donors |
| Grimm et al. (2015) | 2015 | Prolonged (>6 h) graft ischemic time | Retrospective MC | 10225 | >6 h ischemic time was not an independent predictor of PGF (odds ratio, 1.11; 95% CI, 0.88–1.39, P = 0.37) |
| Eberlein et al. (2015) | 2015 | Lung size matching | Prospective MC | 812 | Oversized allografts are associated with a decreased risk of grade 3 PGD within 72 h |
| Somers et al. (2015) | 2015 | Extended donor criteria (EDC) | Retrospective SC | 431 | Grade 3 PGD at 12, 24 and 48 h was significantly higher in EDC recipients |
| Cantu et al. (2015) | 2015 | Oxidant stress regulatory genetic variation | Prospective MC | 1038 | Donor NADPH Oxidase 3 (p = 0.01) and recipient glutathione peroxidase and NRF-2 (p = 0.01) were significantly associated with grade 3 PGD within 72 h |
| Zych et al. (2014) | 2014 | Extended donor criteria (EDC) | Retrospective SC | 248 | After adjustment, grade 3 PGD at 72 h was more frequent in the EDC group (p = 0.046) |
| Baldwin et al. (2013) | 2013 | Donor age | Retrospective MC | 8860 | Marginally increased risk of grade 3 PGD at 72 h with donors age 55–64 years compared to 30–54 years (RR 1.27, 95% CI 0.99–1.63) |
| Moreno et al. (2013) | 2013 | Timing retrieval after trauma | Retrospective SC | 132 | PGD did not differ among donor lungs retrieved within 24 h from donor lungs retrieved after 24 h of brain death |

continued
Table 2 Continued

| Reference               | Year | Topic                     | Study design | Sample | Findings and OR (if available)                                                                 |
|-------------------------|------|---------------------------|--------------|--------|-----------------------------------------------------------------------------------------------|
| Alvarez et al. (2013)   | 2013 | Gender mismatch           | Retrospective SC | 256    | Donor–recipient gender mismatch does not have a negative impact on high grade PGD at 72 h      |
| Diamond et al. (2013c)  | 2013 | Clinical RF               | Prospective MC | 1255   | Independent RF for grade 3 PGD at 48 or 72 h were history of donor smoking (OR 1.8, 95% CI 1.2–2.6; P = 0.002); FiO₂ during reperfusion (OR, 1.1 per 10% increase in FiO₂; 95% CI, 1.0–1.2; P = 0.01); single LTx (OR, 2; 95% CI, 1.2–3.3; P = 0.008); use of CPB (OR, 3.4; 95% CI, 2.2–5.3; P < 0.001); overweight (OR, 1.8; 95% CI, 1.2–2.7; P = 0.01) and obese (OR, 2.3; 95% CI, 1.3–3.9; P = 0.004); recipient BMI; preoperative sarcoidosis (OR, 2.5; 95% CI, 1.1–5.6; P = 0.03) or PAH (OR, 3.5; 95% CI, 1.6–7.7; P = 0.002); and PAPm (OR, 1.3 per 10 mm Hg increase; 95% CI, 1.1–1.5; P < 0.001) |
| Samano et al. (2012)    | 2012 | Clinical RF               | Retrospective SC | 188    | Donor smoking history was an independent RF for grade 3 PGD at 48 h (OR 4.83; 95% CI 1.23–18.89; P = 0.022) and older donors for PGD at 72 hours (OR 1.04; 95% CI 0.997–1.098; P = 0.022) |
| Oto et al. (2008)       | 2008 | Heart and kidney PGD same donor | Retrospective SC | 231    | In multivariate analysis, same donor heart PGD (OR 3.37, 95% CI 1.19–9.50, p = 0.02) was an independent RF for grade 3 PGD at 6 h |
| Cottini et al. (2018)   | 2018 | Recipient PAH and others  | Retrospective SC | 96     | Low HDL-C (OR 0.10, 95% CI 0.02–0.65, p = 0.016) but not PAH is associated with grade 3 PGD within 72 h (multivariable logistic regression) |
| Park et al. (2018b)     | 2018 | CTD-ILD diagnosis         | Retrospective SC | 62     | Incidence of PGD (all grades) within 72 h did not differ between CTD-ILD and IPF patients |
| Todd et al. (2017)      | 2017 | ECMO (bridge)             | Retrospective SC | 93     | Grade 3 PGD within 72 h was similar between patients with ECMO bridge to LTxs and standard recipients |
| Cantu et al. (2016)     | 2016 | TOLLIP gene               | Prospective MC  | 728    | TOLLIP gene was significantly associated with grade 3 PGD within 72 h (p = 0.006). The increased risk of PGD for carrying at least one copy of this variant was 11.7% [95% CI: 4.9%, 18.5%] |
| Cottini et al. (2016)   | 2016 | Pre-Ltx dyslipidemia      | Retrospective SC | 264    | Dyslipidemia is an intermediate risk factor for grade 3 PGD within 72 h (OR = 1.93, p = 0.049) |
| Porteous et al. (2016)  | 2016 | Diastolic dysfunction     | Retrospective SC | 117    | Higher E/e’ were associated with an increased risk of grade 3 PGD at 48 h/72 h (E/e’ OR = 1.93; p = 0.04; E/e’ > 8 OR = 5.29; p = 0.01) |
| Soresi et al. (2016)    | 2016 | Recipient pleural abnor-malities | Retrospective SC | 163    | Pleural disease was associated with a significantly higher incidence of grade 3 PGD at 0 and 48 h (p = 0.037 and p = 0.032, respectively) |

continued
| Reference                  | Year | Topic                                | Study design          | Sample | Findings and OR (if available)                                                                                                                                                                                                 |
|---------------------------|------|--------------------------------------|-----------------------|--------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Geube et al. (2016)       | 2016 | Intraoperative fluid volume          | Retrospective SC      | 494    | Each intraoperative liter of fluid increased the OR grade 3 PGD within 72 h by 22% (OR = 1.22; p < 0.001). The volume of transfused red blood cell concentrate was associated with grade 3 PGD (OR = 1.7; p = 0.002) |
| Kelm et al. (2016)        | 2016 | Low muscle mass                      | Retrospective SC      | 36     | No evidence of a difference in any PGD in the first 72 h by muscle index adjusted by age and sex (OR = 2.219; p = 0.32)                                                                                                          |
| Pérez-Terán et al. (2016) | 2016 | Right ventricular function           | Prospective MC        | 72     | Better right ventricular function is a risk factor for the development of grade 3 PGD within 72 h                                                                                                                       |
| Cantu et al. (2015)       | 2015 | Oxidant stress regulatory genetic variation | Prospective MC      | 1038   | Donor NADPH Oxidase 3 (p = 0.01) and recipient glutathione peroxidase and NRF-2 (p = 0.01) were significantly associated with grade 3 PGD within 72 h                                                                 |
| Liu et al. (2014)         | 2014 | Various                              | Systematic review and metanalysis | 10042 | Female gender (OR 1.38, 95% CI 1.09–1.75), African American (OR 1.82, 95% CI 1.36–2.45), IPF (OR 1.78, 95% CI 1.49–2.13), sarcoidosis (OR 4.25, 95% CI 1.09–16.52), PPH (OR 3.73, 95% CI 2.16–6.46), elevated BMI (OR 1.83, 95% CI 1.26–2.64), and use of CPB (OR 2.29, 95% CI 1.43–3.65) were significantly associated with increased risk of PGD |
| Shah et al. (2014)        | 2014 | Club (clara) cell secretory protein levels | Prospective MC      | 714    | After adjustment, pre-operative CC-16 levels remained associated with grade 3 PGD at 48 or 72 h (OR: 3.03, p = 0.013) in non-IPF subjects                                                                                           |
| Diamond et al. (2012)     | 2012 | Plasma angiopoietin-2 levels         | Prospective MC        | 119    | Angiopoietin-2 levels were significantly associated with the development of grade 3 PGD within 72 h after lung transplantation, in particular in IPF patients                                                               |
| Fang et al. (2011)        | 2011 | PAPm                                 | Prospective MC        | 126    | Each 10-mm Hg increase in PAPm was associated with increase in odds of grade 3 PGD at 72 h (OR = 1.64; p = 0.003—unadjusted)                                                                                             |
| Lederer et al. (2011)     | 2011 | Obesity                              | Prospective MC        | 512    | Obesity was associated with a twofold increased risk of primary graft dysfunction (adjusted RR 2.1, p < 0.001). The risk of grade 3 PGD within 72 h increased by 40% for each 5 kg/m² increase in BMI after adjustment. Higher plasma leptin levels were associated with a greater risk of PGD (sex-adjusted P = 0.02) |
| Warnecke et al. (2018)    | 2018 | EVLP OCS device VS standard cold storage | Prospective non-inferiority RCT (phase 3) | 320    | Reduced incidence of grade 3 PGD within 72 h in the OCS group                                                                                                                                                    |
| Hashimoto et al. (2017)   | 2017 | sVCAM in EVLP donor perfusate        | Retrospective SC      | 100    | sVCAM-1 at 1 h and at 4 h were significantly associated with grade 3 PGD within 72 h                                                                                                                                  |
| Wallinder et al. (2016)   | 2016 | EVLP                                 | Prospective SC        | 27 (EVLP) 145 | Grade 2–3 PGD at 72 h did not show any significant difference between EVLP and standard lungs                                                                                                                  |
| Reference                  | Year  | Topic                        | Study design | Sample  | Findings and OR (if available)                                                                 |
|----------------------------|-------|------------------------------|--------------|---------|-----------------------------------------------------------------------------------------------|
| Terragni et al. (2016)     | 2016  | VILI and stress index        | Prospective SC | 14      | PGD of any grade did not differ among lungs ventilated with a protective or non-protective ventilatory setting |
| Boffini et al. (2014)       | 2014  | EVLP                         | Prospective SC | 36      | PGD incidence and severity at 0 and 72 h did not show any difference between EVLP and standard lungs |
| Cypel et al. (2012)         | 2012  | EVLP                         | Retrospective SC | 317     | Grade 3 PGD at 72 h did not show any significant difference between EVLP and standard lungs     |
| Inci et al. (2018)          | 2018  | DCD                          | Prospective SC | 21 (DCD) 130 (DBD) | PGD grade comparable between DBD and DCD                                                      |
| Villavicencio et al. (2018) | 2018  | DCD Maastricht III           | Retrospective SC | 15 (DCD) 113 (DBD) | Greater incidence of grade 2–3 PGD at time 0 for the DCD group (p=0.001)                      |
| Ruttens et al. (2017)       | 2017  | DCD Maastricht III-IV-V      | Retrospective SC | 59 (DCD) 331 (DBD) | Grade 3 PGD within 72 h was similar in the DCD compared with the DBD group                     |
| Sabashnikov et al. (2016)   | 2016  | DCD Maastricht III-IV        | Prospective SC | 60 (DCD) 242 (DBD) | Recipients from the DCD group had as higher incidence of grade 3 PGD at ICU arrival (P=0.014) |
| Levvey et al. (2015)        | 2015  | DCD in PAH recipients        | Retrospective SC | 11 (DCD) 20 (DBD) | Grade 3 PGD did not differ between groups                                                      |
| Zych et al. (2012)          | 2012  | DCD Maastricht III           | Retrospective SC | 26 (DCD) 129 (DBD) | PGD grade within 72 h comparable between DBD and DCD                                          |
| De Vleeschauwer et al. (2011)| 2011  | DCD Maastricht III           | Retrospective SC | 21 (DCD) 154 (DBD) | The incidence of PGD within 48 h was not different between the groups                          |
| De Oliveira et al. (2010)   | 2010  | DCD Maastricht III           | Retrospective SC | 18 (DCD) 406 (DBD) | The incidence of PGD was not different between the groups                                      |

List of abbreviations. LTx lung transplant; OR odds ratio; EVLP ex vivo lung perfusion; DCD donation after circulatory death; DBD donation after brain death; SC single-center; MC multi-center; RCT randomized-controlled trial; MV mechanical ventilation; PR3 proteinase 3; NE neutrophil elastase; AAT α1-anti-trypsin; CCSP Club Cell Secretory Protein; IRI ischemia-reperfusion injury; sVCAM soluble VCAM-1; TTV Torque teno viruses; VILI ventilator-induced lung injury; PAH pulmonary arterial hypertension; CPB cardio-pulmonary bypass; BMI body mass index; PAPm mean pulmonary artery pressure; Ab antibodies; MFI mean fluorescence intensity; HDL-C high density lipoprotein-cholesterol; CTD-ILD connective tissue disease-related interstitial lung disease; IPF idiopathic pulmonary fibrosis; RBC red blood cells
upon the vascular endothelium. Under normal conditions, NO is predominantly produced by endothelial nitric oxide synthase (eNOS) [20, 21]. Therefore, the administration of inhaled nitric oxide (iNO) during lung transplantation might be a possible method to prevent or attenuate PGD.

The administration of iNO during severe PGD might reduce pulmonary vasoconstriction, thus reducing right ventricular afterload [22] without altering systemic vascular resistance. It might also improve oxygenation by dilating the pulmonary vasculature of ventilated areas, reducing the shunt fraction and the degree of V/Q mismatch [21, 23].

However, data regarding the effectiveness of iNO in reducing time to extubation, length of intensive care and hospital stay and mortality [24] are unclear. For this reason, the routine use of prophylactic iNO in LTx cannot be recommended [21, 24, 25]. Since the effectiveness of iNO in preventing PGD is unproven, the ISHLT Working Group on PGD summarised that it may only have benefit in certain patient groups with established PGD.

Inhaled NO may be used in selected cases of severe hypoxemia and/or elevated pulmonary artery pressures. Extrapolating knowledge from the studies on ARDS, the beneficial effects of iNO may be real but transient. At the same time, the efficacy of inhaled prostacyclin as a pulmonary vasodilator in PGD has not been studied, but it is used in refractory hypoxia after LTx, especially when there is concomitant severe pulmonary hypertension and right heart failure [25]. A small recent study reported on the effectiveness of intraoperative inhaled iloprost in preventing PGD and preserving allograft function [26].

The administration of iNO with pentoxifylline (PTX), a methyl xanthine derivative that decreases neutrophil sequestration, might prevent PGD in lung recipients [27, 28]. It is accompanied by significant improvements in oxygenation and reductions in reperfusion-induced edema, duration of mechanical ventilation and mortality [29].

In summary, despite some positive effects from experimental and small observational studies, the use of iNO after LTx has no significant effect on oxygenation or on PGD prevention in randomised clinical trials [30–32].

c. Extracorporeal membrane oxygenation

ECMO can be used to provide cardiorespiratory support in patients with refractory hypoxemia or right ventricular failure caused by severe PGD and it might help in applying lung protective ventilation strategies [33]. It is reported that ECMO is used in 2–9% of patients undergoing lung transplantation [34–37, 38].

Mortality rates vary between 30 and 60%, depending on the patient’s characteristics, time of ECMO duration, coexisting infection or rejection, and the type of ECMO support (VV vs. VA) [34, 35, 39–42].

In adult lung transplantation, only a few studies reported on the effectiveness of ECMO for treatment of PGD and data on long-term survival are still lacking [43].

The success of ECMO support after LTx is primarily influenced by the reversibility of allograft dysfunction rather than by the type of support used. VA ECMO may improve both oxygenation and haemodynamic and potentially limit the ischaemic-reperfusion response from decreasing the pulmonary artery pressure, but requires higher anticoagulation levels which increase the risk of hemorrhagic and neurologic complications. VV ECMO is associated with less vascular complications and often lower anticoagulation requirements [14] and is hence the preferred mode of support for PGD unless there is severe, concomitant ventricular dysfunction or hemodynamic impairment.

Moreover, since the bronchial arteries are not routinely revascularized at LTx, the use of VA ECMO could worsen parenchymal ischaemia by limiting pulmonary arterial blood flow, while VV ECMO offers the controlled flow of oxygenated blood through the lung parenchyma, minimizing the hypoxic pulmonary vasoconstrictive response and the risk of distal pulmonary vascular thrombosis.
Allograft recovery from PGD usually occurs within 7–10 days of ECMO support and successful weaning after a period longer than 14 days is uncommon. Therefore, the futility of support longer than 14 days must be considered in patients with PGD unless re-transplantation is considered.

The main causes of early mortality in these patients are infections and permanent graft failure.

In conclusion, the use of ECMO for PGD after LTx is associated with acceptable survival and complication rates [33].

**Cannulation Strategies**

Cannulation for VV-ECMO usually involves the direct cannulation of two central veins: drainage of deoxygenated blood from the inferior vena cava (IVC) via the femoral vein and reinfusion of oxygenated blood into the superior vena cava (SVC) and right atrium via the internal jugular vein or femoral vein [44]. This approach might be performed at the bedside without the need for imaging guidance. However, femoral cannulation compared to jugular one tends to limit the patient’s ability to ambulate [45]. The possibility of placing a bicaval, dual-lumen cannula via a single internal jugular allowing for both drainage and reinfusion has certain attractions [46]. The use of fluoroscopy or transoesophageal echocardiography is recommended during cannulation to ensure safe and correct cannula placement and orientation [47]. VV ECMO can usually be instituted in awake patients and indeed there are benefits of remaining free from sedation and mechanical ventilation if this is possible. For patients requiring ECMO support for the management of PGD, especially if the duration of ECMO support is estimated to be short-term, a two-site VV configuration is more practical.

For transplant candidates with concomitant cardiac impairment, VA ECMO support may be necessary [48]. This scenario is most commonly encountered in patients with pulmonary arterial hypertension and right ventricular dysfunction, with or without diffuse parenchymal lung disease [49–51]. Traditionally, VA ECMO involves femoral venous drainage and femoral arterial reinfusion, which poses a significant limitation to mobilisation. Importantly this configuration may be inadequate for upper-body oxygenation if there is impaired native gas exchange and sufficient residual native left ventricular output such that the ascending aorta and aortic arch are supplied with relatively deoxygenated blood (Harlequin syndrome) [48, 52]. Patients at risk of Harlequin syndrome should be monitored carefully and upper body saturation monitoring used (e.g. right arm pulse oximetry, cerebral oximetry).

The addition of a reinfusion cannula into the internal jugular vein via a Y-connection off the arterial reinfusion limb, creating a veno-arterial venous circuit, may provide better upper-body oxygenation [52].

**Retransplantation**

Re-transplantation raises many of the same considerations as the initial transplantation, with higher incidence of complications such as PGD, rejection, and infection [53]. The most common reasons for re-transplantation are BOS (63%), PGD (15%), and acute rejection (4%) [17].

**Airway Complications**

Airway complications occur in up to a third of patients after LTx and result in significant morbidities and mortality (2–4%) [54]. Airway complications may become apparent acutely in the early postoperative period or develop days or weeks later. The development of airway complications after LTx can add significant limitations to the patient’s quality of life because of respiratory symptoms and functional impairment, the need for regular follow up, bronchoscopic surveillance, additional medications and interventions [54–56].

Airway complications may occur around the bronchial anastomoses or distal airways and include stenosis, infection, bronchopleural
fistula, formation of excess endobronchial granulation tissue, ischaemia, necrosis, dehiscence and bronchomalacia. The main cause of airway complications is ischaemia of the donor bronchi. After the normal anatomical bronchial arterial blood supply has been severed at the time of donor lung procurement, the newly transplanted lung becomes dependent on retrograde blood flow from the pulmonary arteries until revascularization occurs some weeks later. Airway complications are more likely in recipients with chronic infections such as cystic fibrosis, hence the need to aggressively treat suspected postoperative infections in these patients. Surgical technique is an important factor in the development of airway complications and bronchial anastomotic techniques have been refined to preserve bronchial blood supply [54, 55, 57].

Bronchial stenosis is the commonest airway complication affecting around 15% of LTx recipients, occurring either at the anastomosis or distal to it. This usually becomes apparent after 2–3 months and can result in significant morbidity and mortality. The main causes include ischaemia, infection and rejection. Diagnosis is made from bronchoscopy, spirometry and CT scan [55].

Dehiscence of the bronchial anastomosis is a serious complication with a high mortality. It is suspected in patients with persistent air leak, pneumothorax or sepsis, or simply observed on routine bronchoscopy. Ischaemia is the most likely cause but the use of drugs that inhibit the mammalian target of Rapamycin (mTOR inhibitors) such as sirolimus may contribute to this [55].

Bronchomalacia leads to dynamic airway collapse and obstruction. It is usually seen within four months after LTx and patients typically present with dyspnœa, cough, an obstructive defect on spirometry and recurrent infections. Bronchoscopy remains the gold standard for diagnosis [54, 55].

Suspected or proven airway complication necessitates frequent bronchoscopic surveillance. Potential interventions include bronchial toilet and clearance of secretions, dilatation, stent insertion, ablation e.g. cryotherapy and surgery including reconstructing the anastomosis or re-transplant [55, 57].

Infections are commonly associated with airway complications and may increase morbidity and mortality. Prophylactic antibacterial and antifungal agents are hence commonly used [54].

Pleural Complications

Chest drains are routinely placed at the time of LTx and typically removed within seven days. Pleural effusion occurs commonly and in around a quarter of LTx recipients as the result of increased alveolar permeability, pleural inflammation, postoperative atelectasis and impairment of lymphatic drainage. Most of these are non-infective. The effusion fluid is usually exudative; an elevated LDH and neutrophil count in the fluid are markers of infection [58].

Neurological Complications

Neurological complications after LTx are observed in 50–70% of patients. The central (CNS), peripheral (PNS) or autonomic (ANS) nervous systems can all be affected. The most common complications affecting the CNS are cerebrovascular accidents (ischaemic or haemorrhagic stroke) and encephalopathy, with age being the most important risk factor. Encephalopathy or impairment of consciousness may be due to hypoxia, metabolic derangements, immunosuppressant drug toxicity and sepsis. Neurotoxicity is mainly due to calcineurin inhibitors and can manifest as confusion, tremor, paraesthesia, blindness, seizures and encephalopathy. Changing cyclosporine for tacrolimus often improves symptoms of neurotoxicity [59, 60].

Within the PNS, neuromuscular complications may affect single or multiple nerves, plexuses or muscles. Neuropathies includes phrenic nerve and recurrent laryngeal nerve injuries presumably arising from surgery or compression injuries (deep peroneal, brachial plexus).
Phrenic nerve injury and subsequent diaphragmatic palsy may present as a patient slow to wean from mechanical ventilation. This can be demonstrated on chest ultrasound. Treatment is conservative but diaphragmatic plication is an option in persistent cases [60].

The most common complication of the PNS is critical illness polyneuropathy/myopathy. It occurs in 30–40% of patients and it is characterized by profound limb weakness and difficulty in weaning from mechanical ventilation. These patients have a longer ICU and hospital stays and are therefore more susceptible to infections and other complications [60]. Gastroparesis is the most common ANS complication, as result of surgical damage to the vagus nerve at the time of surgery, although gastroparesis after lung transplant is often multifactorial in aetiology and not solely limited to vagal injury [61].

Gastrointestinal Complications

Gastroparesis leads to delayed gastric emptying, gastro-oesophageal reflux, aspiration and a delayed return to normal oral intake. Gastro-oesophageal reflux disease (GORD) and chronic aspiration is associated with allograft injury, functional decline, and acute and chronic rejections. Long-term gastrointestinal complications are commonly associated with higher doses of immunosuppression, manifesting as nausea, vomiting, GORD and abdominal pain [61, 62].

Anti-reflux surgery is safe in selected LTx recipients and can improve lung function and survival [63].

Cardiovascular Complications

Atrial Arrhythmias

Atrial arrhythmias occur in 30% of LTx patients and atrial fibrillation (AF) is the most common, occurring within the first two to seven days [64]. The aetiology is unclear but is perhaps linked to changes in the left atrium that occur during LTx surgery. The main risk factors for the development of AF after LTx include advanced age, idiopathic pulmonary fibrosis, coronary artery disease, diastolic dysfunction, left atrial enlargement and the use of vasopressors. Patients who develop arrhythmias have a longer postoperative stay and a higher mortality. Furthermore, postoperative pain, fluid shifts and use of vasopressor or inotropic agents can exacerbate or precipitate arrhythmias, so should be managed carefully in these patients [64, 65]. Rate control should be the priority and anticoagulation should be considered if the arrhythmia persists over 24 hours. The use of amiodarone should be limited owing to its implications in lung injury and amiodarone has been shown to significantly increase mortality in LTx recipients.

Right Ventricular Dysfunction

Patients with significant preexisting cardiovascular disease are generally excluded from LTx. However, right ventricular (RV) dysfunction is commonly associated with chronic lung diseases, especially those with pulmonary hypertension due to pulmonary vascular disease [66]. The thin-walled RV is prone to dysfunction due to its inability to tolerate abrupt increases in afterload (pressure) or preload (volume). RV failure is uncommon but may occur as the result of increased afterload, excessive volume or reduced contractility. Many of these factors can also affect left ventricular (LV) function although LV dysfunction is often the result of RV dysfunction, perhaps through ventricular interdependence when there is a leftwards shifting of the interventricular septum [67]. Single lung ventilation, which may be required to perform LTx, especially prior to implantation of the first donor lung, may worsen RV function by deleterious effects on pulmonary vascular resistance (hypoxia, hypercarbia, respiratory acidosis) and increases in intrathoracic pressure. Studies have shown that RV size, strain, function and pulmonary artery (PA) pressures usually improve after LTx, due to reduction of RV afterload and subsequent reverse remodelling. Thus, postoperative RV dysfunction and elevated PA pressures are predictors of mortality. A group of patients particularly at risk of acute heart failure after LTx are those with pulmonary arterial
hypertension (PAH), e.g. idiopathic or primary pulmonary hypertension [66]. These patients are challenging to manage and their survival is amongst the lowest of all LTx recipients. PAH is also one of the most significant recipient-related risk factors for developing PGD. Following LTx, there is a sudden normalisation of pulmonary vascular resistance and reduction in RV afterload, with an immediate increase in cardiac output and LV filling, which may unmask LV failure. Another mechanism of LV dysfunction is through ventricular interdependence in cases of acute RV failure post operatively, as such these patients need to be carefully managed in centres with expertise, using inotropic agents and often ECMO pre- and post-surgery to mitigate the sudden physiological changes on both ventricles.

Renal Complications

Acute kidney injury (AKI) occurs in 25–60% of LTx recipients when using either R-(risk), I-(injury) or F-(failure) criteria from the RIFLE definition. The aetiology may be related to lung ‘biotrauma’ affecting the kidneys, the inflammatory response, hypoperfusion and nephrotoxic drugs (excess diuretics, immunosuppressants and antibiotics). Renal dysfunction from calcineurin inhibitors is the most common long-term complication encountered in LTx recipients. Management involves adding angiotensin converting enzyme inhibitors, reducing doses of calcineurin inhibitors and avoiding nephrotoxic levels, or replacing them with alternatives such as the mTOR inhibitors such as sirolimus or everolimus and/or the anti-proliferative mycofenolate mofetil [68].

Identifiable risk factors for the development of kidney injury include poor preoperative renal function, a diagnosis of idiopathic pulmonary fibrosis or primary pulmonary hypertension, the need for ventilatory or ECMO support pre-operatively, and bilateral lung transplantation. ‘Prerenal’ hypoperfusion appears to be the most significant risk factor as seen in those patients with peri-operative haemodynamic instability and requirement for high doses of vasopressors [69, 70]. Around 5–15% of patients with AKI will require dialysis and those with severe AKI (RIFLE-F) have increased length of stay and mechanical ventilation and increased mortality. At one year after LTx, the incidence of severe renal dysfunction (creatinine > 2.5 mg/L) or requiring chronic dialysis is around 5%. This goes up to 25% at ten years. Management involves identifying at-risk patients, supportive care (judicious use of fluids and vasoactive drugs, management of heart failure and avoidance of further insults such as nephrotoxic drugs).

Infections

Infections are frequent complications in patients recovering from LTx, accounting for 20–25% of all post-transplant death during the first year. More than two thirds of infectious complications affect the respiratory tract [71–73].

The risk of infection in LTx is related to recipient factors and the type of transplant and severity and progression by the infecting microorganism and the state of immunosuppression.

In assessing a patient for a possible LTx, it is essential to investigate for former infectious diseases with a panel of serological tests including cytomegalovirus (CMV), Epstein-Barr virus (EBV), hepatitis B (HBV) and C viruses, herpes simplex virus (HSV), human immunodeficiency virus (HIV), Treponema pallidum and varicella-zoster virus (VZV). It is also important to perform bronchoalveolar lavage to document the bronchial flora. In case of methicillin-resistant Staphylococcus aureus (MRSA) carriers, some groups suggest an eradication protocol for the upper and lower respiratory tract [74].

At the time of listing, history of possible tuberculosis (TB) should be carefully investigated. In case of active TB, proper therapy should be completed. Tuberculin skin testing and/or QuantiFERON Gold TB test is recommended in all patients [75].

Transplant centres should follow the national vaccination program prior to lung transplantation. HBV, pneumococcal and meningococcal vaccinations should be implemented,
Postoperative Complications and Management

Advanced age, on mechanical ventilation, or with impaired nutritional status (both with obesity or malnutrition) have a higher incidence of infection after LTx [77]. Underlying chronic diseases, such as diabetes mellitus, may also be relevant to the type and severity of infections. Currently, most programs accept MV as a bridge to LTx for patients previously included on the waiting-list [78]. However, pre-transplant MV is a risk factor for nosocomial infection and prolonged postoperative ventilatory support.

Various treatments administered to candidates before LTx, especially corticosteroids or antimicrobials are associated with a higher incidence of bacterial and fungal infection in the immediate post-transplantation period.

Some risk factors are related to the transplant surgery and the type of technique used. The duration of ischaemia after donor lung extraction, the reimplantation without re-establishment of the graft’s lymphatic drainage and

**Recipient Derived Infections**

The recipient’s pre-transplantation clinical status is essential; patients with renal failure, with advanced age, on mechanical ventilation, or with impaired nutritional status (both with obesity or malnutrition) have a higher incidence of infection after LTx [77].

Underlying chronic diseases, such as diabetes mellitus, may also be relevant to the type and severity of infections. Currently, most programs accept MV as a bridge to LTx for patients previously included on the waiting-list [78]. However, pre-transplant MV is a risk factor for nosocomial infection and prolonged postoperative ventilatory support.

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**Fig. 2** Risk of infection during the different phases in the post-transplant period

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innervation may all affect the graft’s defense mechanisms, as these may paralyse the mucociliary clearance of the airway. The graft denervation and the airway anastomosis compromise the cough reflex, hindering the control of secretions. A small inoculum of microorganisms from the graft can cause severe pneumonia in the already immunosuppressed recipient, as does constant contact with ubiquitous airborne virus and bacteria.

Patients with BOS are usually heavily immuno suppressed and have mucociliary dysfunction and are more prone to serious infections, which is the leading cause of death in this population.

Donor Derived Infection

Almost all potential lung donors harbor pathogenic microorganisms at the time of procurement, with important considerations on donor selection and on the choice of prophylactic antibiotics for the recipients [79].

A bronchial microbiological sampling, aspiration or washing, to carry out Gram and Ziehl-Neelsen staining and specific cultures for bacteria, fungi and mycobacteria, should be routinely performed in the lung donor so as to choose the appropriate recipient antibiotic prophylaxis. To avoid a long delay in results new technologies may play a role; such as rapid diagnostic tools, PCR assays for serum, swabs, bronchoalveolar lavage and other fluids.

Although the presence of a positive Gram stain or scanty purulent secretions should not be a contraindication for accepting a donor lung, some groups consider the presence of pneumonia, abundant and persistent purulent secretions or the growth of filamentous fungi an important risk factor for the development of subsequent infections and, in selected cases, a contraindication to lung acceptance. The role of prophylactic or even pre-emptive antimicrobial therapy is not clearly demonstrated and advice from infectious diseases specialists experienced in lung transplant may be required [80].

Antimicrobial Prophylaxis

The general trend for antibacterial prophylaxis in solid organ transplantation is one of a short duration of treatment primarily aimed at the skin flora, to prevent surgical site infections [81, 82].

Few well-design, prospective, comparative studies of antimicrobial prophylaxis have been conducted with patients undergoing solid organ transplantation, and no formal recommendations are available from expert consensus panels or professional organisations [83–85].

No formal studies have shown the optimal prophylaxis for patients undergoing LTx and reports are generally retrospective, single-centre studies using a variety of agents and treatment durations. Most centres maintain antimicrobial prophylaxis up to 7 days after transplantation or at least until drainage removal [86].

Multi-drug Resistant (MDR) Organisms

Multidrug-resistant (MDR) and especially carbapenem-resistant gram negative (GN) bacteria are spreading at an alarming rate. These organisms are increasingly recognised as cause of severe infections in transplant recipients [87].

In a recent Italian study on 887 transplant recipients, the incidence of carbapenem-resistant gram-negative (CR-GN) isolates was found to be 2.39 per 1000 recipient-days. In those with positive cultures for gram negative bacteria within three months after transplantation, 26.5% were CR-GNs. Carbapenems resistance was particularly frequent among Klebsiella spp. isolates (49.1%). The isolation of GN bacteria was most frequent among recipients with a longer hospital stay, lung recipients and those admitted to hospital for more than 48 h before transplantation. Recipients with CR-GM isolates had a 10.23-fold increase in mortality rate [88].

Another study reported that the length of ICU stay and previous exposure to broad-spectrum antibiotics were associated with an increased risk of emergence of MDR bacteria [85].
Donor colonisation does not represent a contraindication to transplantation, although actively infected lung grafts should be avoided. It is, however, associated with an increased risk of infection. Recipient colonisation is not a contraindication to transplantation although these patients are at increased risk of infection post-transplant. Patients colonised with CR-GN bacteria do not require different surgical prophylaxis regimens. Timely detection of carriers and contact isolation, as well as antibiotic control policies are fundamental preventive measures [89].

Colonised recipients should receive empirical treatment, better called pre-emptive, since the antimicrobial therapy may be adjusted on susceptibility study results as well as based on the severity of infection. In selected cases of colonisation, and specifically in case of *P. aeruginosa*, lung transplant recipients may benefit from prophylactic inhaled antibiotics [89].

Recipient colonisation with *ESBL-producing Enterobacteriaceae* is associated with worse outcome, but it is not a contraindication for transplantation. In case of infection, empirical treatment should avoid the use of carbapenems. Currently, there is no evidence that decolonisation of lung recipients confers benefits [87, 89].

Respiratory tract colonisation by MDR *P. aeruginosa* is especially common in patients with cystic fibrosis, with a prevalence of >50% that may increase to 75% after transplantation. *P. aeruginosa* is also the leading cause of hospital-acquired pneumonia after lung transplantation, accounting for up to 25% of cases [90]. *Acinetobacter baumannii* infections are commonly associated with epidemic outbreaks, causing more commonly hospital or ventilator-acquired pneumonia, but also urinary tract infections, catheter-related bloodstream infections and surgical site infections. All the infectious complications caused by *A. baumannii* involve a high mortality rate [90, 91]. Moreover, *Burkholderia* spp. has been related to various complications after LTx, such as chronic lung infections, mediastinal abscesses, mediastinitis, pleural effusion or chest wall infection [92]. *Clostridium difficile* causes over 70% of antibiotic-associated colitis, and over 90% of antibiotic-associated pseudomembranous colitis, with an estimated incidence of 7–31% [93, 94]. Risk factors for *C. difficile* are prolonged ICU and hospital stays, intense immunosuppression and exposure to broad-spectrum antimicrobial agents. Presentation after LTx may be atypical, with little diarrhoea. Abdomen CT scan may be useful to rule out pseudomembranous colitis, burdened by a high risk of bowel perforation. Treatment options specific for organ transplant recipient have recently been issued and include oral metronidazole in the absence of severe complications or a combination of intravenous metronidazole and oral vancomycin in complicated cases [95].

**Fungal Infection**

Lung transplant recipients have a high risk of fungal infections, especially from *Aspergillus spp.* Other fungi that can cause severe infections in this population are *Cryptococcus, Fusarium, Scedosporium, Mucor* and endemic agents (*Blastomyces, Coccidioides* and *Histoplasma*). *Pneumocystis jirovecii* is a unicellular fungus that may cause severe disease in immunocompromised hosts, including LTx patients. Lifelong prophylaxis with trimethoprim-sulfamethoxazole is highly recommended.

Invasive aspergillosis (IA) is one of the most hazardous infectious complications after LTx that usually occurs within one year after transplantation. Bronchial anastomotic infections with aspergillus commonly occur within the first three months after LTx and may evolve towards an ulcerative tracheobronchitis [96].

There is significant controversy regarding fungal infections in LTx and wide variation in practice regarding prophylaxis and treatment among centres. In general, the risk of invasive candidiasis is low amongst transplant recipients but IA remains a significant problem with a high mortality [96, 97].

With the introduction of inhaled Amphotericin B (Amph-B), there has been a dramatic reduction in the incidence of invasive candida infections since the 1980s. Moreover,
the survival rate of those patients who developed and those who did not develop invasive candida infections is similar [98].

A recent world-wide survey showed that thirty-four centres of fifty-eight involved in the study (58.6%) administered universal antifungal prophylaxis within the first six months after transplantation[99]. This was primarily directed against *Aspergillus species* in nearly all centres. The most common antifungal prophylaxis was voriconazole for up to three months after lung transplant as monotherapy, followed by itraconazole and inhaled Amph-B. Others centres preferred a combination therapy for prophylaxis within the first six months after transplant and the majority chose the combination of voriconazole and inhaled Amph-B. Half of the centres discontinued antifungal prophylaxis after six months.

A recent systematic review and meta-analysis of 22 reports showed that there was no significant reduction in invasive aspergillosis (IA) between patients that received universal anti-fungal prophylaxis and those ones that did not received prophylaxis [100, 101]. However, inhaled lipid preparation of Amph-B appeared to be significantly superior to no prophylaxis. While many studies addressed the clinical effectiveness of inhaled Amph-B in preventing IA in LTx recipients, with different formulations and dose of administration, only one study evaluated the intrapulmonary disposition of Amph-B after aerosolised delivery of the lipid preparation: daily administration of 1 mg/kg of inhaled Amph-B lipid complex for 4 consecutive days, followed by a weekly administration achieved Amph-B concentration in epithelial lining fluid above minimum inhibitory concentration (MIC) for *Aspergillus* [102–104]. If systemic antifungal prophylaxis or treatment with azoles is needed, therapeutic drug monitoring should be integrated in the post LTx follow up to reduce the risk of sub-therapeutic azole plasma trough levels in patients with cystic, and toxicity in patients older than 65 years [105, 106].

In conclusion, antifungal prophylaxis should be considered to reduce the risk of IA. A lipid formulation of Amph-B is preferred with aerosolised administration, to minimise the side effects. Routine prophylaxis with intravenous fluconazole for *Candida* should be discouraged, to avoid the risk of resistance or the selection of *non-albicans* species. Mucomycosis accounts for approximately 2% of all invasive fungal infections in transplant recipients. Diabetes, renal impairment and recent rejection represent risk factors. Mucomycosis is characterised by invasion of the vasculature by fungal hyphae that cause infarction and necrosis of host tissues. Pulmonary disease manifestations, such as consolidation, nodules and cavities, are the most frequent presentation in LTx recipients, even if cutaneous, sino-orbital, and disseminated disease have been reported. Histopathology and culture are both necessary for the diagnosis. Mucomycosis has an overall mortality ranging from 49 to 90%. Immunosuppression reduction and intravenous lipid Amph-B are the cornerstone of therapy, together with surgical debridement and a subsequent change to oral posaconazole if stabilisation is achieved [100].

**Viral Infections**

Cytomegalovirus (CMV) is the most common viral infection in solid organ transplantation and represents the major cause of morbidity and mortality during the first six months after LTx. The incidence of symptomatic CMV disease ranges from 30 to 50% with the highest incidence and severity among LTx recipients. The greatest risk of CMV infection is in seronegative recipients who receive an organ from a seropositive donor (D+/R−) and in seropositive recipients, independently from the donor (D+/R+ or D−/R+). Beyond pneumonitis, CMV has been associated with numerous indirect effects including an increased risk of opportunistic infections via immune suppression by CMV itself and increased risk of acute and chronic rejections [107–111]. When pre-transplant serology of the recipient is negative, re-testing at the time of transplant is mandatory. If the pre-transplant serology is equivocal in the donor, assume
it is positive. Prophylaxis should be administered in seronegative recipients who receive an organ from a seropositive donor (D+/R−) and in seropositive recipients, independently from the donor. Both antigen levels and viral load tests are acceptable options for diagnosis, decisions regarding pre-emptive therapy, and monitoring response to therapy. A large Cochrane systematic review on CMV prophylaxis has provided high quality evidence for antiviral prophylaxis when compared to placebo or no treatment for preventing CMV disease and for reducing mortality associated with CMV disease in solid organ transplants [107]. Ganciclovir, and more recently valganciclovir, have been recognised as the drugs of choice for both prevention and treatment of CMV in transplant recipients. Currently, several preventative strategies exist to reduce the incidence of CMV disease. Some practitioners endorse universal prophylaxis, whereas others promote pre-emptive therapy (viral monitoring with early treatment) [107, 110]. The optimal duration of antiviral prophylaxis is unknown. A multicentre randomised trial showed that extending prophylaxis with Valganciclovir from three months to 12 months significantly reduced CMV infection, CMV disease and disease severity without increased ganciclovir resistance or toxicity [112]. In addition, prophylaxis with CMV immunoglobulin combined with antiviral prophylaxis might offer an advantage [113–118].

Other Viruses

Community acquired respiratory viruses (CARV) include influenza, parainfluenza, rhinovirus, adenovirus, respiratory syncytial virus, and coronaviruses. All these infections are of concern in LTx recipients and potentially increase the risk of lung allograft dysfunction [119].

The incidence of CARV varies between 7.7 and 64% and is largely dependent on the diagnostic techniques used and seasonal variation [120–122]. For most viral infections, no specific therapy is available and management is supportive. For those viruses in which treatment options are available (e.g. oseltamivir and zanamivir for influenza, ribavirin for paramyxovirus family), timely initiation is essential to limit complications [123, 124].

Recent evidence indicates that approximately 10% of LTx recipients present with Epstein Barr virus (EBV) mismatch (D+/R−). Acute EBV infection causes a polyclonal expansion of B cells hosting the virus [125]. In immunosuppressed LTx recipients, the latently infected B cells could cause post-transplant lymphoproliferative disorders (PTLD). Routine monitoring of blood specimens from transplanted patients to track EBV viral load may provide early detection of possible PTLD [126].

The rate of PTLD in LTx recipients ranges between 5 and 15% [127].

Although not supported by evidence-based medicine, some transplant centres use prophylactic antiviral treatment consisting of acyclovir or ganciclovir in high-risk patients for primary EBV infection following surgery (EBV D+/R−).

In the case of Varicella Zoster Virus (VZV), pre-transplant evaluation of recipient VZV immune status is highly advisable, as well as vaccination of non-immune recipients. Reactivation of VZV in LTx recipients typically occurs later than CMV or HSV. Cutaneous lesions may be delayed or atypical with haemorrhage. In LTx recipients, there is an increased risk of severe VZV complications, such as cutaneous dissemination and visceral end organ involvement (pneumonia, hepatitis, encephalitis) [128].

Mycobacteria

Amongst the differential diagnoses in LTx recipients with infection, Mycobacterial infections must be considered, including both Mycobacterium tuberculosis (MTB) and non-tuberculous mycobacteria (NTM). All mycobacterial infections are difficult to diagnose due to their prolonged culture requirements, and the complexity of multi-pharmacological treatment regimens, especially in the context of antimicrobial resistance. All solid organ transplants are at an increased risk of
post-transplant TB with a highest risk in LTx recipients, with reported incidence ranging from 6.4 to 10%, [129, 130].

Over 90% of TB cases develop within the first year following transplantation, and roughly three quarters involve the lungs [131]. Clinical presentation of active TB involves systemic symptoms and signs in association with respiratory symptoms, as the lung is the most commonly involved site. Diagnosis is challenging because of traditional time-consuming microbiological culture, but the recent introduction of nucleic amplification tests may provide rapid results and differentiation between MTB and NTM species. Treatment for LTx recipients with active TB is the same as for immunocompetent patients. However, it must be considered that the number of drugs used, the length of treatment, the drug induced toxicity and the risk of drug interactions is more complex in LTx recipients [132].

**Acute Rejection**

Despite advances in immunosuppression, acute allograft rejection remains a common complication in the first year after LTx and its incidence is highest in the first six months. Rejection can be hyperacute (occurring within minutes after the vascular anastomosis), acute (days to weeks after transplantation), late-acute (occurring three months after transplantation), or chronic (months to years after transplantation). Rejection is classified according with the pathophysiologic process as acute cellular rejection (ACR) or antibody-mediated rejection (AMR) [133].

Acute rejection may affect the vasculature and the small airways of the lung allograft and manifest as ACR, involving small vessels, or lymphocytic bronchiolitis (LB) involving the small airways. According to the ISHLT registry report, almost 30% of LTx recipients have at least one episode of ACR in their first year after transplantation, which may be an underestimate. Acute rejection is an important risk factor for the development of CLAD and particularly BOS[133–135].

Induction therapy is an intense immunosuppressive therapy administered at the time of LTx with the aim of reducing early acute rejection. Patients with acute rejection present with non-specific respiratory symptoms including cough, dyspnoea, sputum production and low-grade pyrexia which may be difficult to differentiate from infection or other complications. Spirometry and imaging (CXR or CT) are not very sensitive or specific and transbronchial lung biopsy remains the gold standard for the diagnosis of acute rejection. Pulse-dose corticosteroids are the cornerstone of therapy for ACR. Mild rejection (which is usually not associated with clinical signs or symptoms of allograft dysfunction) is the threshold for most centers to start therapy with bolus methylprednisolone (10–15 mg/kg daily for three days). Augmented immunosuppression can improve graft function, lessen lung injury and protect from future acute rejection episodes [133, 135].

AMR is mediated by the presence of donor-specific antibodies (DSA). The antigen–antibody complex results in an amplified immune response leading to histopathological changes to the graft and subsequent dysfunction to a variable degree. AMR may occur in either a pre-sensitized patient during the early post-transplant period, or after the emergence of de novo DSAs in the late post-transplant period, typically after inadequate immunosuppression. Clinical AMR is associated with measurable allograft dysfunction, which can be asymptomatic. AMR may also be sub-clinical, with histological changes seen but normal allograft function. Hyperacute rejection is now extremely unlikely after LTx because screening for preformed antihuman leukocyte antigen (HLA) antibodies is very sensitive. A less severe form of AMR occurring weeks or months after transplantation has been reported [133].

Treatment includes depletion of circulating antibodies, suppressing B-cells to mitigate further antibody-mediated allograft injury and reducing inflammation in the allograft, without affecting the immune system in such a way to risk serious infections. Plasmapheresis and intravenous immunoglobulin are the main treatments
with other therapies such as Rituximab also used. AMR may stabilise, progress or indeed reverse but mortality is usually high. AMR is a major risk factor for the development of chronic rejection and CLAD [134, 135].

**Chronic Lung Allograft Dysfunction**

Beyond one year after LTx, the greatest threat to survival is the onset and progression of CLAD. This includes a range of pathologies leading to a late and persistent decline in lung function and has been defined as a drop of FEV1 and/or FVC to ≤80% of baseline for ≥3 weeks. Patients present with decline in lung function manifest by symptoms of dyspnea, cough, infections and worsening FEV1 on spirometry [136].

CLAD is predominantly a consequence of chronic rejection, and there are three phenotypes each with typical histopathological findings: obstructive (bronchiolitis obliterans syndrome, BOS), restrictive (restrictive allograft syndrome, RAS) and neutrophilic reversible allograft dysfunction (NRAD), also known as azithromycin-responsive allograft dysfunction (ARAD), a subset of patients whose FEV1 improve after treatment with azithromycin, which has immunomodulatory as well as antibiotic properties [134, 135].

BOS is the clinical correlate of the pathological process of obliterator bronchiolitis or chronic rejection and is defined as a persistent and progressive decline in FEV1 after LTx which is mostly irreversible. Once BOS is diagnosed, the median survival is restricted to approximately 2.5 years.

Patients with RAS demonstrate a restrictive pattern on spirometry and chronic decline in FEV1 of at least 20% and a drop in total lung capacity (TLC) of at least 10%. RAS account for around 30% of all patients with CLAD and have an even lower survival than those with BOS [135].

Risk factors for the development of CLAD include PGD, rejection (acute cellular, antibody-mediated and lymphocytic bronchiolitis), infections (viral/bacterial/fungal), GORD, autoimmunity and persistent bronchoalveolar lavage (BAL) neutrophilia. Chronic rejection is usually diagnosed by spirometry and imaging, although BAL may be used to differentiate between subtypes such as BOS and NRAD [124].

Efforts should be made to identify the reasons behind decline in lung function and causes of CLAD. Treatment options are limited and evidence favouring specific treatment is lacking. Prevention of CLAD is best accomplished by avoiding precipitants i.e. rejection, infection and GORD with adequate immunosuppression and infection prophylaxis. Established CLAD does not respond well to medical therapies and management options include modifying the immunosuppressive treatments, addition of methotrexate, cyclophosphamide, montelukast, total lymphoid irradiation, extracorporeal photopheresis (ECP) and re-transplant in highly-select patients [137].

**Malignancy**

LTx recipients have a 60-fold increase risk of malignancy compared with the general population with a five year incidence of almost 20%. The two commonest malignancies are skin cancer and PTLD. Post-transplant malignancy may arise from either de novo carcinogenesis, direct transmission of tumors that pre-existed in the donor or recurrence of a recipient’s pre-transplant malignancy. Long-term use of immunosuppressants predisposes patients to malignancies due to the direct oncogenic effects [126, 138].

**Other Complications, Immunosuppressant Drugs and Pharmacotherapy**

In addition to infections, malignancies and side effects affecting cardiovascular, renal, neurologic and gastrointestinal systems as mentioned above; haematological complications may occur primarily bone marrow suppression from azathioprine, mycophenolate mofetil, valganciclovir
or trimethoprim/sulfamethoxazole. Metabolic complications include osteoporosis and osteopaenia. LTx recipients are likely to require a multitude of drugs, and there should be vigilance for drug-interactions.

**Self-study**

1. Primary graft dysfunction is:
   a. An early complication, defined by diffuse alveolar infiltrates and oxygen impairment
   b. A late complication associated with viral infections
   c. A type of acute rejection
   d. A complication that occurs only in patients with Cystic Fibrosis

2. In severe primary graft dysfunction (PGD3):
   a. There is no indication to retransplantation
   b. ECMO support might be useful to support refractory hypoxemia and give time to the graft to recover
   c. ECMO is contraindicated
   d. VA ECMO is the only therapeutic option

3. Airway complications:
   a. Occurs always late after transplantation
   b. Are rare after lung transplantation
   c. Are caused exclusively by acute rejection
   d. Are common and the stenosis is the most frequent (15%): main causes are ischemia, infection and rejection

4. In the early phase after lung transplantation:
   a. There is high probability of bacterial and fungal infections
   b. There is high probability of viral and opportunistic infections
   c. Infections depends only on donor potential infections
   d. Infections occur only in colonized recipients

5. Chronic lung allograft dysfunction
   a. Is an early complication after lung transplantation
   b. Is different from bronchiolitis obliterans syndrome
   c. Represents a range of pathologies leading to a late and persistent decline in lung function
   d. Should be treated with different interventions, focused on depleting circulating antibodies, suppressing B-cells and mitigating further antibody mediated allograft and reducing inflammation, without affecting the immune system in such a way to risk serious infections

**Answers**

1. Primary graft dysfunction is:
   a. An early complication, defined by diffuse alveolar infiltrates and oxygen impairment CORRECT
   b. A late complication associated with viral infections
   c. A type of acute rejection
   d. A complication only in patients with Cystic Fibrosis

2. In severe primary graft dysfunction (PGD3):
   a. There is no indication to retransplantation
   b. ECMO support might be useful to support refractory hypoxemia and give time to the graft to recover CORRECT
   c. ECMO is contraindicated
   d. VA ECMO is the only therapeutic option

3. Airway complications:
   a. Occurs always late after transplantation
   b. Are rare after lung transplantation
   c. Are caused exclusively by acute rejection
   d. Are common and the stenosis is the most frequent (15%): main causes are ischemia, infection and rejection

4. In the early phase after lung transplantation:
   a. There is high probability of bacterial and fungal infections CORRECT
   b. There is high probability of viral and opportunistic infections
   c. Infections depends only on donor potential infections
   d. Infections occur only in colonized recipients

5. Chronic lung allograft dysfunction
   a. Is an early complication after lung’s transplant
   b. Is different from bronchiolitis obliterans syndrome
c. Represents a range of pathologies leading to a late and persistent decline in lung function CORRECT

d. Should be treated with different interventions, focused on depleting circulating antibodies, suppressing B-cells and mitigating further antibody mediated allograft and reducing inflammation, without affecting the immune system in such a way to risk serious infections.

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