# Report of the ISHLT Working Group on Primary Lung Graft Dysfunction Part II: Definition. A Consensus Statement of the International Society for Heart and Lung Transplantation

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Despite many advances in organ preservation, surgical technique, and peri-operative care, primary graft dysfunction (PGD) is responsible for significant morbidity and mortality after lung transplantation.[1–4] Variously referred to as severe ischemia-reperfusion injury, early graft dysfunction or the re-implantation response, PGD after lung transplantation has many features in common with other forms of acute lung injury (ALI), including severe hypoxemia in the first 72 hours after surgery, lung edema, and radiographic evidence of diffuse pulmonary infiltration without other identifiable cause.[5,6] PGD has a reported incidence at specific, individual centers of between 11% and 25%.[1–3,7] However, these incidence estimates are greatly affected by the lack of standard defining criteria across centers. It is clear that if a better understanding of PGD is to be achieved, more precise, uniform, defining criteria need to be developed.[6,8]

There are different ways to grade and define post-surgical lung injury, evident by the widely different incidence rates, risk factors and outcomes for PGD reported in the literature (as reviewed in the accompanying article investigating outcomes after PGD). Given that the operational criteria for PGD have such profound impact on further studies of risk factors, outcomes and novel treatments, the development of reliable, valid, defining criteria is essential in the study of this devastating syndrome.

## GOALS

The goals of this consensus group center on standardizing taxonomy as well as specifying schema that capture the spectrum of the syndrome and are appropriate for many clinical research uses, including clinical trials and translational mechanistic studies (Table 1). The process for achieving these goals has been outlined in the accompanying study, "Report of the ISHLT Working Group on Primary Lung Graft Dysfunction Part I: Introduction and Methods."

## BACKGROUND

### Clinical Epidemiology Principles for Definition of Clinical Syndromes

To be consistently useful, a definition needs to be valid and reliable. The *validity* (or accuracy) of an operational syndrome definition is the ability of a definition to distinguish between those people who have the syndrome and those who do not.[9,10] Validity essentially asks the question: "Is the operational definition capturing the true clinical syndrome?" There are many components that contribute to the concept of a valid definition.[11] When defining a syndrome such as PGD, measures of validity include *face*, *content*, *construct*, *criterion* and *discriminant* (*predictive*) validity. In the initial stages of defining PGD, face validity refers to whether the definition makes sense to different experts, and *content* validity may be established if the criteria have been reviewed by a group of experts who form a consensus on the contents of the definition. These two initial stages are a focus of this consensus study.

The validity of a diagnostic test or syndrome definition is usually measured against a "gold standard" (*criterion validity*). In the setting of PGD, this gold standard is not readily apparent. Although a gold standard could be represented by biopsy specimen characteristics, the presence of pathologic characteristics of diffuse alveolar damage (DAD) on a biopsy may not capture the full spectrum of the syndrome, and may be prone to sampling error or informative censoring (the sickest subjects cannot tolerate the biopsy). *Predictive* validity implies that different levels of a definition are

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**Table 1.** Goals of the Consensus Definition of Primary Graft Dysfunction (PGD)

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| 1. Standardize the language and taxonomy. |
| 2. Utilize defining criteria to capture the spectrum of PGD severity and time course. |
| 3. Utilize defining criteria to suit the needs of different lines of scientific inquiry. |
| 4. Identify and consider limitations in applying diagnostic criteria; such as inconsistency of chest radiographs, indices of oxygenation and limitations of sampling pathology. |
| 5. Identify future studies that can refine the definition and address specific limitations, such as studies on inter-rater reliability and construct, predictive and criterion validity. |

associated with different clinical outcomes. This form of validity may be helpful in future studies investigating outcomes of different PGD grades.

The *reliability* of an operational syndrome definition refers to the ability of a test to provide consistent results with repeat testing. Components of reliability include consistency with repeat testing by a single observer ("test-retest reliability"), and consistency between different observers assigning the definition ("inter-rater reliability"). Statistically, these differences in the presence or absence of a syndrome are evaluated with percent agreement, and the kappa statistic. Reliability of X-ray interpretation in PGD is an important concern, given the experience with X-ray inconsistency in acute respiratory distress syndrome (ARDS).[12,13]

Neither the reliability nor the validity of the definition of PGD has been the topic of clinical investigation to date. However, this consensus statement aims to provide the face and content validity of standardized defining criteria to provide a basis for refining and testing reliability and validity.

### Non-Transplant ALI and ARDS

Since the initial identification of the clinical syndrome causing diffuse radiographic pulmonary opacities and hypoxemia, efforts have been made to more precisely define ARDS.[14-16] Early studies of risk factors for ARDS conflicted and employed different definitions. They were also composed of basic clinical characteristics, including severe hypoxemia of acute onset with evidence of diffuse alveolar infiltration radiographically and the exclusion of cardiogenic causes. In 1994, the American European Consensus Conference (AECC) standardized the definitions of ALI and ARDS as: acute onset; bilateral pulmonary infiltrates on chest X-ray consistent with pulmonary edema; absence of evidence of left atrial hypertension; and poor systemic oxygenation.[17] The last criterion is measured as the ratio of arterial oxygen ($Pa_{O_2}$) to the fraction of inspired oxygen ($Fi_{O_2}$). The syndrome is called ALI when the ratio is $\leq$300 and ARDS when $\leq$200.[17]

Although the etiology of ARDS remains elusive, standardization in defining the syndrome appropriately and uniformly has likely led to better understanding of its pathogenesis and epidemiology.[18] Studies investigating the validity and reliability of the ALI/ARDS defining criteria, such as the chest X-ray, are ongoing, and further serve to refine the definition.[12,13]

### Potentially Different Needs for Definitions of PGD

The need for different defining criteria may vary across different study designs (Table 2). For example, mechanistic studies aimed at exploring gene expression, genomics or biomarkers may have artificial null associations if the outcome definition is poorly defined.[8] This is an illustration of "outcome misclassification," where study subjects with lung injury may be classified as not having lung injury, or those without lung injury are classified as having it. Given that a small amount of outcome misclassification can dramatically increase the number of subjects needed to study an association, accurate definitions of PGD are necessary for mechanistic studies. In contrast, randomized trials aimed at inclusion of subjects with PGD may be more interested in earlier or broader definitions of lung injury, aiming at a subject population that may be associated with worse outcomes and, thus, would benefit from therapy.

There was some disagreement among the working group about how stringent the definition should be, particularly with reference to exclusion of "secondary" causes. Some favored a narrow clinical definition for observational studies, rigorously excluding "secondary" causes of PGD. Others believed that, because so little is known about the timing and natural history of PGD, a broader set of inclusive criteria would be more appropriate at this early stage. In what follows, we attempt to address and balance these concerns.

## DEFINITIONS-A REVIEW OF THE LUNG TRANSPLANT LITERATURE

Although there have been many terms used to describe PGD in the literature (Table 3), most studies have employed variations of the ARDS classification schemes to define PGD in their own patient populations (Table 4). Specifically, classification schemes have used oxygenation characteristics, defined as a ratio of the partial pressure of arterial oxygen ($Pa_{O_2}$) to the fraction of inspired oxygen

**Table 2.** Potential Applications of the Consensus Primary Graft Dysfunction (PGD) Definition

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| As an outcome in observational studies and/or translational mechanistic studies |
| As an outcome in clinical trials (preventing PGD) |
| To define populations for early clinical trials inclusion (treating PGD) |
| Standardized registry recording for large-scale epidemiologic studies |

**Table 3.** Different Terms Used for Primary Graft Dysfunction (PGD)

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|---|
| Re-implantation edema |
| Re-implantation response |
| Reperfusion injury |
| Reperfusion edema |
| Primary graft failure |
| Early graft dysfunction |

($Fio_2$). Generally, when this ratio (the P/F ratio) is <200, investigators have concluded that a patient meets the oxygenation criteria for PGD. Other studies employing more liberal definitions of the P/F ratio (<300) have found the largest incidences and fewer differences in outcomes.[19] The presence or absence of positive end-expiratory pressure (PEEP) is usually commented upon in the lung transplant literature but is not currently used as an inclusion or exclusion criteria according to the AECC definitions of ARDS and ALI.[17] Most studies have also used radiographic parameters, such as the presence of diffuse, alveolar infiltrates during a specified time in the early post-operative period. Several studies have used grading schemes of X-ray infiltrates, although these have varied among studies.[7,20,21] Furthermore, in most observational investigations, other causes of early allograft dysfunction, such as infection, acute rejection, native lung hyperinflation in single-lung transplants for emphysema, and venous anastomosis complications, were excluded in patients evaluated in previous lung transplant studies. The methodology for exclusion varied among the different studies.

In 1998, Christie and colleagues at the University of Pennsylvania determined the incidence of PGD by performing a retrospective cohort study on 100 transplant recipients.[1] PGD occurred in 15% of the recipients and was associated with increased mortality and length of hospitalization as well as a trend toward impaired intermediate-term exercise tolerance and pulmonary function. They defined PGD as: presence of diffuse radiographic infiltrates in the allograft during the first 72 hours after surgery; P/F ratio <200 beyond the initial 48 hours; ventilator dependence beyond the first 5 days directly attributable to allograft dysfunction; absence of other identifiable causes for poor allograft function; and, in the event of death in the first 6 days post-operatively, histologic evidence of DAD after meeting all other criteria for PGD. They also found that pathologic specimens on subjects defined in this way all had findings of DAD consistent with the time interval since transplantation. In 2003, the same investigative team updated the cohort study to include 250 subjects.[2] Using the same defining criteria for PGD, the investigators identified several risk factors for PGD, as discussed in the accompanying studies concerning donor and recipient risk factors.

Khan and colleagues reported on the Cleveland Clinic experience with pulmonary re-implantation response (PRR).[7] Overall, 56 of the 99 recipients (57%) transplanted from 1990 to 1995 met the criteria for PRR, which was defined as: (1) allograft infiltrates on chest radiographs that were graded according to severity; (2) hypoxemia as defined by $Fio_2$ of ≥0.3 to maintain a $Pao_2$ of ≥65 mm Hg; (3) pulmonary artery occlusion pressure of ≤12 mm Hg; and (4) absence of infection or rejection. Of note, patients who developed chest radiographic infiltrates after 24 hours post-transplant were not considered to have PRR. The investigators were unable to correlate the development of PRR with type of transplant operation, ischemic time, pre-operative pulmonary hypertension, underlying lung disease and age or gender of the recipient. Use of cardiopulmonary bypass during the operation did increase the likelihood of developing PRR. Patients who did experience PRR had longer courses of mechanical ventilation and longer ICU stays but similar 1- and 3-year survival compared with those who did not develop PRR.

Investigators at the University of Virginia reviewed their first 100 lung transplant recipients to determine the incidence of reperfusion injury (RI).[3] They defined

**Table 4.** Different Defining Criteria Employed in Prior Studies

| | First author | | | | | |
|---|---|---|---|---|---|---|
| | Christie | Khan | King | Thabut | Chatilla | Fisher |
| Year | 2003 | 1999 | 2000 | 2002 | 2003 | 2002 |
| *N* | 252 | 99 | 100 | 259 | 115 | 291 |
| Time course | 48–72 hr | <24 h | 48 h | <72 h | >48 h | 7 days |
| $Pao_2/Fio_2$ ratio | <200 | $Fio_2 \geq 0.3$ to maintain $Pao_2 \geq 65$ | <200 | <300 | Mechanical ventilation | — |
| Radiograph | Diffuse infiltrate | Severity grading | Severity grading | Diffuse infiltrate | Diffuse infiltrate | — |
| Heart failure | PAOP ≤18 or negative fluid balance | PAOP ≤12 | — | Clinical evidence | — | — |
| Other | No rejection or infection | No rejection or infection | No rejection or infection | — | — | Evidence of DAD on biopsy |

moderate-to-severe RI as those having a chest X-ray severity score of ≥6 and a P/F ratio of <200 mm Hg during the first 48 hours post-transplant. Twenty-two patients met the criteria for RI and 78 did not. Patients diagnosed with RI had greater in-hospital mortality and morbidity (prolonged ventilation and ICU stay and greater hospital cost). In this study, the incidence of RI was correlated with pre-operative pulmonary hypertension but not donor organ ischemic time.

In a French study from two transplant centers, 259 patients undergoing lung transplantation were analyzed over a 12-year period.[19] One hundred thirty-one patients (51%) met PGD criteria: radiographic infiltrates within the first 3 post-operative days associated with P/F ratios <300 mm Hg and not associated with evidence of infection, rejection or atelectasis. The investigators found that PGD was common. Furthermore, they used four parameters (graft ischemic time, degree of oxygenation impairment, recipient age, presence of severe early hemodynamic dysfunction) that could be used in a scoring system to predict ICU outcomes. The scoring system was termed the ischemia-reperfusion injury severity score (IRISS). The importance of the P/F ratio to the mortality prediction in this study highlights the importance of different P/F thresholds on outcomes.

In 2003, Chatila et al evaluated the respiratory dysfunction that occurred in 45 (55%) of their lung transplant recipients.[22] Respiratory dysfunction was defined simply as any patient who required mechanical ventilation at >48 hours post-operatively or the need for re-intubation during the initial transplant hospitalization. Of the 45 patients with respiratory dysfunction, 24 (55%) had what the investigators termed ischemic reperfusion lung injury (IRLI), presumably used synonymously with PGD. Of the patients with IRLI, 4 (19%) died. The major risk factor for IRLI was right ventricular dysfunction, which necessitated cardiopulmonary bypass. Other causes of respiratory dysfunction included surgical technical injury and cardiac dysfunction. IRLI was defined as the presence of radiographic infiltrates during the first 48 hours after surgery in the absence of rejection or infection and with no evidence of cardiogenic pulmonary edema (pulmonary arterial occlusion pressure <16 mm Hg). Of note, they relied more heavily on the radiographic appearance of their patients rather than on more traditional oxygenation parameters, which may have led to a more inclusive definition of IRLI. In an accompanying editorial to the report,[8] it was noted that the broad definition employed in the study may be difficult to interpret.

In a study investigating the relationship of non-immune graft injury and future development of bronchiolitis obliterans syndrome, Fisher and colleagues employed a definition based on the presence of DAD on biopsy, performed on Day 7 after surgery.[23] In their population of 291 subjects, 19% had DAD on biopsy. Those with DAD had significantly longer lasting mechanical ventilation, with a mean of 60.8 hours for those with DAD vs 32.7 hours without ($p = 0.03$). The P/F ratio at 24 hours was significantly worse in the DAD group (240 vs 315 without DAD [$p = 0.006$]). In addition, the 30-day survival rate was 62.5% in the DAD group vs 87.5% without DAD ($p = 0.001$). Although this definition may be important and useful for testing a specific association with chronic rejection, it has not been widely employed.

## POTENTIAL DIFFICULTIES WITH THE DEFINING CRITERIA FOR PGD

The criteria used to define PGD may be problematic to employ. The inter-observer reliability of chest radiographs for ARDS is inconsistent, even when simply assessing for presence or absence of diffuse bilateral infiltrates. However, inconsistency may be improved by training sessions.[12] Variations between observers in ARDS raise concerns over use of X-ray grading systems and point scores in PGD. In addition, gas-exchange impairment has been assessed by using the P/F ratio. Although this is a widely accepted parameter, it can be problematic at the extremes of the range of $Fio_2$, or with application of partial end-expiratory pressure (PEEP). For example, an individual with an $Fio_2$ of 0.24 and a $Pao_2$ of 65 has a $Pao_2/Fio_2$ score of 271 and would meet criteria for PGD in some studies. Some have suggested use of the oxygenation index (which includes mean airway pressure in the calculation); however, this has not been employed routinely due to the need for measurements on mechanical ventilation.

Similarly, "exclusion" criteria for PGD may be very difficult to define clearly. The presence of bacterial infection may be difficult to ascertain on bronchoscopy. Furthermore, although bacterial infection may present a clinical picture similar to PGD, it may also be present in addition to PGD. Most studies of PGD have excluded overt volume overload or heart failure as a cause of hypoxia and pulmonary infiltrates. However, the pulmonary artery occlusion pressure can be fraught with difficulties of interpretation in critical illness.[24] Conversely, severe PGD may exist in the setting of elevated right-sided heart pressures, or clinical volume overload. Although acute cellular rejection may not be a problem until the later post-surgical stages, hyperacute (humoral) rejection may represent a clinical scenario similar to PGD. Most researchers conducting studies aimed at investigating mechanisms of PGD would have preferred to separate this cause of post-operative graft dysfunction from the case definition; however, most have relied on criteria based on retrospective cross-matching, which may not capture all patients at risk for hyperacute rejection. Technical issues, including venous anastomosis blockage, may be missed on echocardiography.

**Table 5.** Recommendations for Grading of Primary Graft Dysfunction (PGD) Severity

| Grade | $Pao_2/Fio_2$ | Radiographic infiltrates consistent with pulmonary edema |
|---|---|---|
| 0 | >300 | Absent |
| 1 | >300 | Present |
| 2 | 200–300 | Present |
| 3 | <200 | Present |

For some studies, inclusion of other "exclusion factors," such as infection, may be important to the research question. These issues, as well as issues with validity of operational definitions of exclusion factors, were prominent in working group discussions on criteria for "secondary causes" of early graft dysfunction, and are addressed in what follows.

## RECOMMENDATIONS OF THE WORKING GROUP ON PRIMARY GRAFT DYSFUNCTION

The following recommendations represent the results of months of process, as described in the introductory report in this series. They contain changes recommended at the 2004 ISHLT Conference following the Satellite Symposium and the meetings that followed.

### Nomenclature

The expression "primary graft dysfunction" was the consensus selection for the name of the syndrome. This choice for the set of symptoms, variously referred to as primary graft failure, early graft dysfunction or the re-implantation response, was heavily influenced by the desire to capture the spectrum of lung injury from milder dysfunction to more severe lung injury.

### Classification

The classification scheme contains both (1) a grading for severity of PGD and (2) an indicator of different time-points for classification. The rationale for separation of these two elements is that studies with different goals may require different time points for severity grading. For example, researchers trying to predict outcome based on immediate post-operative variables may choose to evaluate the relationship of early or "time-zero" values, whereas those performing an observational study may focus on dysfunction beyond 48 hours as an outcome.

The proposed scheme takes into consideration only two clinical parameters: the chest X-ray and the P/F ratio (Table 5). The timing of the lung dysfunction is also included in the scheme as follows:

*T-zero (T0):* Defined as within 6 hours of final lung reperfusion. The first blood gas assessment in the ICU is ideal for this; ideally, measurement on $Fio_2$ 1.0 and PEEP = 5 while still on MV.

*T24, T48 and T72:* Later times are to be measured at potentially multiple time-points after 24 hours, up to 72 hours. Times will be measured after T0 ±6 hours. This is indicated as a "T score." Recognizing that after 72 hours other factors may confound the definition, the working group does not recommend grading beyond 72 hours.

There are several caveats to the grading scheme. Although this scheme can be used for all transplants, the type of transplant may influence $PaO_2/FiO_2$. Future studies may consider grading single and bilateral transplants separately. Absence of infiltrates on chest radiograph is sufficient for Grade 0, even if $PaO_2/FiO_2$ ratio is less than 300. If the subject is on nasal canula for oxygen or $FiO_2 < 0.3$, the subject is graded as 0 or 1, based on chest radiograph. Any patient on extracorporeal oxygenation is automatically Grade 3. Any subject mechanically ventilated with $FiO_2$ greater than 0.5 on nitric oxide beyond 48 hours from the time of transplant should be considered Grade 3. If multiple blood gas values are available, the worst P/F ratio will be used for the purposes of this grading scheme.

### Other Contributing or "Exclusion" Factors

Studies with different hypotheses may choose to investigate different variants of PGD. It is recommended by the working group that observational and mechanistic studies of lung injury after surgery focus on grading beyond 48 hours and take into account certain contributing etiologies, to be assessed by exclusion or by sub-group analyses; these include:

Hyperacute rejection.
Venous anastomotic obstruction.
Cardiogenic pulmonary edema.
Pneumonia (both viral and bacterial pneumonias should be considered).

## SUMMARY AND CONCLUSIONS

The working group recognizes that the syndrome of PGD represents a spectrum of disease and that the proposed PGD definitions should be a starting point for further discussion. The group has attempted to incorporate the best features of previous single-center studies, recognizing that different studies have been associated with different definition schemes. Given that our understanding of the clinical course of PGD is evolving, the group concludes that there should be a separation of the time course from the grading system, noting that, in our experience, the clinical appearance of PGD may vary by time (presenting immediately post-operatively and 48 to 72 hours later). We believe that research leading to the description of different forms of PGD using these schemes, and evaluating other contributing and "exclusion" factors, will be important next steps. Thus, we created a scheme that can provide flexibility for different study types, standardize and cap-

ture the spectrum of injury, and is ideally suited to provide a platform for the next wave of scientific inquiry. Some within the working group expressed a desire to create a more detailed categoric (or "yes/no") definition of PGD for use in observational studies; however, most members of the working group acknowledged that our understanding of PGD is in an early stage and insisted that the first step should be standardization of defining criteria. We encourage utilization of the specifics of the taxonomy in individual studies—for example, "T72 Grade 3 PGD" as an outcome in observational studies. We view this first consensus grading scheme as an initial step toward more refined definitions over time.

## FUTURE DIRECTIONS AND SUGGESTIONS FOR RESEARCH

The working group particularly encourages several types of research in future studies refining the definitions of PGD. If conducted carefully, these types of studies may lead to future refinements of the definition, which will be the cornerstone to more complete study of PGD. Specific recommendations for future research on the risk factors, outcomes, and therapy of PGD are covered in subsequent manuscripts from the ISHLT PGD working group. Specific recommendations regarding future research on definition of PGD include:

1. Studies investigating the reliability of the defining criteria, including inter-observer reliability of radiographs.
2. Studies investigating the validity of the defining criteria, including comparisons with pathologic specimens (criterion validity), or the impact of different time-points and grades on clinical outcomes (predictive or discriminant validity).
3. Studies investigating the reliability and validity of the contribution of potential exclusion criteria, including studies describing the impact of different definitions of exclusion criteria; studies describing the clinical characteristics of different varieties of PGD as defined by different "exclusion" factors such as pneumonia or heart failure; and studies performing sensitivity analyses based on inclusion of subjects with contributing factors such as pneumonia or heart failure.

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