Report of the ISHLT Working Group on Primary Lung Graft Dysfunction Part I: Introduction and Methods

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Primary graft dysfunction is a form of acute lung injury that follows the sequence of events inherent in the lung transplantation process, beginning with the brain death of the donor, pulmonary ischemia, preservation of donor tissue, transplantation, and reperfusion of donor tissue in the recipient. Despite numerous recent advances in organ preservation, surgical technique and peri-operative care, post-transplant allograft dysfunction is sufficiently common to warrant the use of a wide range of synonyms.[1] These include ischemia–reperfusion injury, re-implantation response, re-implantation edema, reperfusion edema, non-cardiogenic pulmonary edema, early graft dysfunction, primary graft dysfunction (PGD), primary graft failure (PGF) and post-transplant acute respiratory distress syndrome (ARDS) or acute lung injury (ALI). The expressions used to describe this condition are not perfectly synonymous, with some representing the most severe end of the spectrum of lung allograft ischemia–reperfusion injury and others representing less severe clinical syndromes.[1,2] Despite variation in studies, it is clear that PGD is responsible for significant morbidity and mortality after lung transplantation.[3–6] Furthermore, with efforts in place to expand the donor pool, the expectation is that efforts to treat and/or prevent PGD will remain important to the field of lung transplantation.[7]

The International Society of Heart and Lung Transplantation (ISHLT) Working Group on Primary Lung Graft Dysfunction was formed at the suggestion of the ISHLT Pulmonary Council in 2003. The purpose of this group was to review the available literature to provide a state-of-the-art, comprehensive series of documents to serve as a resource for clinicians and researchers. In addition, a major goal was to standardize consensus-defining criteria to facilitate future studies of PGD.

HISTORY AND PROCESS FOR CONSENSUS GUIDELINE FORMATION

The ISHLT Pulmonary Council met in Vienna, Austria, on April 12, 2003, and Dirk Van Raemdonck and Jason Christie were appointed chairs of the new Working Group on Primary Graft Dysfunction. Minutes of the council meeting were forwarded to members on June 10, 2003. The Working Group chairs subsequently issued a call to all ISHLT members to initiate the consensus-forming process on August 7, 2003, with a deadline of August 31, 2003 for response. Ideas for individual sub-groups were solicited, topical sub-groups were identified by consensus of the entire working group, and a call for individual participation in sub-groups was issued on September 1, 2003, with sub-groups and chair assignments made by September 16, 2003 (see Table 1 for sub-group project names and leaders, and Appendix 1 for a list of all participants). During this entire process, participation in the Working Group was open to any and all interested ISHLT members.

Between September 2003 and January 2004, sub-group chairs instructed their sub-group members to identify key topics, form consensus over process, and divide work for the authorship. The sub-group reports were made available to all Working Group members on January 15, 2004, and were open for feedback during the following 6 weeks from the entire Working Group. The Working Group steering committee (composed of the sub-group chairs listed in Table 1) met in Philadelphia on March 5–6, 2004. During this meeting, the contents of the sub-group reports were refined, and the defining criteria for PGD were discussed in detail. Results of this meeting were reported back to the Working Group members by the sub-group heads.

The PGD Working Group sub-group reports were presented publicly to the entire ISHLT membership during a Satellite Symposium at the ISHLT Conference in San Francisco on April 21, 2004. An active solicitation

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Table 1. Sub-groups of the ISHLT PGD Working Group

Sub-group	Topic	Leader
1	Definition and grading	Jason Christie
2A	Donor risk factors and markers	Marc de Perrot
2B	Recipient factors and markers	Mark Barr
3	Outcomes	Selim Arcasoy
4	Treatment	Shaf Keshavjee

Chair pulmonary council: Jonathan Orens; project leaders: Dirk Van Raemdonck and Jason Christie.

of feedback was made, and time was allotted for discussion of the work. Subsequently, a special open-forum 2-hour session was held on April 23, 2004 at the ISHLT Conference. Included in this forum were all Working Group participants, as well as several experts who did not participate in the Working Group who were formally invited to attend this session as "external experts" (these external experts who attended and participated in discussions are listed in the Appendix 2). The defining criteria and sub-group reports were reviewed and solicitation of feedback was made. During this session, the criteria for definition were reviewed in detail and a consensus was formed. Final reports were reviewed by all sub-group chairs and manuscripts were submitted for peer review in August 2004.

OVERVIEW OF THE CONSENSUS STATEMENT ON PGD

Definition and Incidence

PGD typically occurs in the first hours up to 3 days after lung transplantation. Poor oxygenation is the *sine qua non* characteristic of the condition, although there is some disagreement as to how to depict differences in severity. PGD is also characterized by low pulmonary compliance, interstitial/alveolar edema, pulmonary infiltrates on chest radiographs, increased pulmonary vascular resistance, intrapulmonary shunt and acute alveolar injury, as revealed by diffuse alveolar damage (DAD) on pathology.

PGD has been defined in various ways, resulting in wide variations in reported incidences, risk factors and outcomes. In the absence of precise, standardized defining criteria and methods for collecting clinical data from lung transplant centers, the reported incidence of PGD has been inconsistent.[7] The purpose of Sub-group 1 (chaired by Dr. Christie) was to standardize defining criteria for PGD, to facilitate all aspects of future research.

Pathogenesis and Risk Factors

There are many cellular and molecular events underlying development of PGD, and both donor and recipient factors appear to play a role. Donor clinical factors, such as age, as well as various molecular markers have been associated with PGD. Donor risk factors, including methods of organ preservation, are presented in the report of Sub-group 2A, chaired by Dr. de Perrot. Likewise, recipient clinical factors, such as primary pulmonary hypertension, as well as operative techniques and therapies may be associated with PGD. These risk factors are presented in the report of Sub-group 2B, chaired by Dr. Barr.

Clinical Picture and Outcomes

PGD imposes a significant impact on lung transplant patients. Clinically, patients face prolonged ventilation, prolonged stays in the ICU and the hospital overall, increased medical costs, and increased risk of morbidity and mortality. The purpose of Sub-group 3 was to review the outcomes of PGD, as chaired by Dr. Arcasoy.

Treatment Options

There are various treatment options available for PGD that can be tailored to the patient based on the grade of severity. Options fall into the following categories: increased ventilatory support; negative fluid balance (diuretics); pulmonary vasodilation (prostaglandins and inhaled nitric oxide); surfactant replacement (nebulized synthetic); extracorporeal membrane oxygenation; and urgent re-transplantation. A detailed description of the treatment options of PGD are presented by Sub-group 4, chaired by Dr. Keshavjee.

In conclusion, it is our hope that this Consensus Statement of the Working Group will provide a state-of-the-art, comprehensive resource for both research studies and clinical care of PGD. We aimed to provide a broad overview of all available literature on definition, clinical and biologic risks, outcomes and treatment of PGD. Furthermore, our goal was to standardize the criteria for defining PGD to facilitate future research. Given the profound impact on cost and outcomes of lung transplantation, we believe that, as the lung transplant community pursues efforts to expand the donor pool and do more procedures, efforts at limiting PGD will be very important to the overall future of lung transplantation.

REFERENCES

1. de Perrot M, Liu M, Waddell TK, et al. Ischemia–reperfusion-induced lung injury. Am J Resp Crit Care Med 2003; 167:490–511.
2. Christie JD, Bavaria JE, Palevsky HI, et al. Primary graft failure following lung transplantation. Chest 1998;114: 51–60.
3. King RC, Binns OA, Rodriguez F, et al. Reperfusion injury significantly impacts clinical outcome after pulmonary transplantation. Ann Thorac Surg 2000;69:1681–5.
4. Christie JD, Kotloff RM, Pochettino A, et al. Clinical risk factors for primary graft failure following lung transplantation. Chest 2003;124:1232–41.

5. King RC, Binns OA, Rodriguez F, et al. Reperfusion injury significantly impacts clinical outcome after pulmonary transplantation. Ann Thorac Surg 2000;69:1681–5.
6. Christie JD, Sager JS, Kimmel SE, et al. Impact of primary graft failure on outcomes following lung transplantation. Chest 2005;127:161-5.
7. Zaas D, Palmer SM. Respiratory failure after lung transplantation: now that we know the extent of the problem, what are the solutions? Chest 2003;123:14–6.

APPENDIX 1

List of All Participants

Jackie Abrams, Houston, TX; Vivek Ahya, Philadelphia, PA; Selim Arcasoy, New York, NY; Abbas Ardehali, Los Angeles, CA; Remzi Bag, Houston, TX; Mark Barr, Los Angeles, CA; Robert Bonser, Birmingham, UK; Heidi Böttcher, Berlin, Germany; Martin Carby, London, UK; Stephen Cassivi, Rochester, MN; Jason Christie, Philadelphia, PA; Paul Corris, Newcastle upon Tyne, UK; Peter Dahlberg, Minneapolis, MN; John Dark, Newcastle upon Tyne, UK; Marc de Perrot, Toronto, ON; Patrick Evrard, Mont Godinne, Belgium; Andy Fisher, Newcastle upon Tyne, UK; David Follette, Sacramento, CA; Reda Girgis, Baltimore MD; Grisha Guenther, Berlin, Germany; Ramsey Hachem, St Louis, MO; Marshall Hertz, Minneapolis, MN; Steven Kawut, New York, NY; Rosemary Kelly, Minneapolis, MN; Shaf Keshavjee, Toronto, ON; Robert M. Kotloff, Philadelphia, PA; David McGiffin, Birmingham, AL; Rebecca Menza, Berkeley, CA; Jonathan Orens, Baltimore, MD; Octavio Pajaro, Jacksonville, FL; Glenda Patterson, Tampa, FL; Masina Scavuzzo, St. Louis, MO; Stephan Schueler, Newcastle upon Tyne, UK; Yaron Shargall, Toronto, ON; Arun Singhal, Philadelphia, PA; Josh Sonett, New York, NY; Dirk Van Raemdonck, Leuven, Belgium; Geert Verleden, Leuven, Belgium; Wickii Vigneswaran, Maywood, IL; Tom Waddell, Toronto, ON; Lorraine Ware, Nashville, TN; David Weill, Denver, CO; Timothy Whelan, Minneapolis, MN.

APPENDIX 2

External Experts Participating in the Review the Working Group on April 23, 2004

Nancy Bridges, Bethesda, MD; John Dark, Newcastle upon Tyne, UK; Alec Patterson, St. Louis, MO; Gregory Snell, Alfred Hospital, Australia.