



## Preface

# 40 Years in the Making: Lung Transplantation Past, Present, and Future



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The year 2023 has marked historic milestones in the evolution of lung transplantation. Sixty years ago, on June 11, 1963, Dr James Hardy performed the first human lung transplant at the University of Mississippi. It was not until November 7, 1983 that the current modern era of lung transplantation began after a successful single-lung transplantation performed by Dr Joel D. Cooper at the Toronto Lung Transplant Program. Today, 40 years later and with nearly ninety thousand transplant procedures performed worldwide, we confidently feel that lung transplantation has evolved—becoming an excellent alternative for thousands of patients with advanced lung diseases. Due to lung transplantation's challenging nature, perhaps being the most complex of solid organ transplants, these improvements have been incremental—feeling sometimes painfully slow for patients and transplant teams alike.

In this commemorative issue of *Clinics in Chest Medicine*, we highlight some of the major advancements in lung transplantation. To properly recount the history of lung transplantation, Dr Alexander Paterson shared his memories of 40 years of lung transplantation, starting with the very first transplant in Toronto. In addition to looking at the past and present, we also look into the

future of lung transplantation, including an article on Xenotransplantation and Lung Bioengineering, seeing recent major advancements in both early human heart and kidney xenotransplantation. This article provides an updated review on the current state of lung xenotransplantation as we work toward eventually allowing this to be a workable possibility for patients in need of lung transplantation.

Another article focuses on the lung-transplant candidates themselves, describing the major advances that have allowed us to transplant older and sicker patients as well as recommendations for best timing of referral. We also include a more detailed article of some of the most frequent dilemmas faced when listing, including older age, low and high body weight, frailty, preexisting cancers, and systemic diseases. The critical care management of the pre-lung-transplant and post-lung-transplant patients is then reviewed, providing an overview of the intensive management of patients requiring mechanical ventilation and extracorporeal membrane oxygenation (ECMO) support.

Once a patient is approved as a candidate for lung transplantation, the next decision is on what would be the ideal type of transplant procedure

followed by the proper placement on the transplant list. We include an article that elaborates on, in a comprehensive manner, the options of either a single- or a bilateral lung-transplant procedure. The authors support what has become the most widespread practice worldwide of performing bilateral lung transplantation in 80% of the lung-transplant candidates. The discussion about the type of procedure (single-lung transplant vs bilateral lung transplant) now needs to move from the focus on short-term survival to a broader discussion that focuses on the quality of life in patients who are now living longer, and the benefits of having an "extra lung" to provide higher lung capacity and better handling of many of the potential complications of this procedure. In the article on donor management review, the authors share our view that listing for bilateral lungs offers more opportunities to use "not perfect" bilateral lungs for patients who otherwise will be waiting for the ideal single organ while also decreasing the number of discarded organs.

Led in part by the efforts made in the United States, the allocation systems around the world have evolved, now providing more fair distribution of organs. This year a new allocation system based on a continuous distribution of organs was implemented in the United States based on medical urgency, outcomes, efficiency, and patient access. This new allocation system, like other systems around the world, is reviewed in detail. Lung donation has always been considered to be one of the main limitations to the process of lung transplantation; however, the article on donor management and the use of donors after cardiac death, ex vivo lung perfusion, and hepatitis C donors shows how despite the increasing number of lung transplants, the implementation of donor management protocols, and the use of other types of donors offer a hope to close the gap between the number of donors and transplant candidates waiting for transplantation. This gap is now much smaller and could be further closed with a unity in practices among donor procurement organizations and transplant programs. A better understanding of the patient arriving at the donor hospital with no history of lung diseases, normal lung images, and lung mechanics can, despite the common presence of single-lobe pneumonia, atelectasis, and fluid overload, become a "nonperfect" lung donor while still providing comparable results for transplant recipients with the rarely available "perfect" donor lungs.

Major progress has been made in the understanding of both antibody-mediated and T-cell

immunity in lung transplantation. This is unfortunately not yet reflected as a standardized way to prevent and treat both acute and chronic lung allograft dysfunction, but it has established a more solid basis for new and promising therapies for lung-transplant recipients, as reviewed in an article devoted to this topic. The advancements to this approach are more commonly seen in patients who are highly sensitized, presenting alternatives for the diagnosis, listing, and potential management, while also providing a better alternative to allow a successful transplant (now included in the new continuous distribution system for allocation of organs discussed above) and are reviewed in another article. The presence of newly formed or preformed antibodies in the role of acute and chronic rejection is now a routine part of the monitoring of our patients, and these new therapeutic targets are further discussed in an accompanying article. Also, the classic definitions of lung rejection are discussed in a detailed article with a provocative and helpful renaming of acute rejection based more on the actual immunologic mechanisms in the two groups, the antibody-mediated rejection, as discussed above, and the new classification of T-cell-mediated rejection. We also believe that with our better understanding of immunology, better diagnostic tools, and new therapeutic agents, this classification will become the standard in the near future.

The evolution of lung transplantation has now provided a longer survival rate for most patients, in particular, bilateral lung recipients, who are now commonly surviving 8 to 10 years. This improved survival is also related to the better understanding and management of infectious and noninfectious complications for our patients (also reviewed in detail in two articles). Finally, in these unprecedented years of a global pandemic with SARS-CoV-2, we have faced further challenges in both preventing and treating this infection in our lung-transplant patients, as well as a new indication for lung transplantation for severely acute patients with COVID-19 acute respiratory distress syndrome, most on ECMO support. This experience is reviewed in detail in the COVID-19 and lung-transplantation article.

Ultimately, as reviewed in this issue of the *Clinics in Chest Medicine*, we have seen considerable progress in multiple areas. Surviving a lung-transplant surgery and the acute postoperative period is no longer a major limitation, yet we will continue to face challenges for long-term

survival in transplant recipients, and this will continue for the near future as we advance our knowledge about the immune and nonimmune mechanisms associated with chronic lung allograft dysfunction. In the meantime, after these past 40 years of successful lung transplantation, we will focus on better use of our potential lung donors, aiming to perform the best type of procedure, and striving to have more similar practices among donor procurement organizations and lung-transplant programs worldwide, allowing recipients the opportunity of a successful lung transplant regardless of location. We want to sincerely thank all the authors who contributed to writing these excellent reviews, which will, it is hoped, make this issue of the *Clinics in Chest Medicine* a source of information for the hundreds

of health care workers currently taking part in this exciting field.

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