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Luis F. Angel and Stephanie M. Levine

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Stephanie H. Chang, Justin Chan, and G. Alexander Patterson

Lung transplantation remains the only available therapy for many patients with end-stage lung disease. The number of lung transplants performed has increased significantly, but development of the field was slow compared with other solid-organ transplants. This delayed growth was secondary to the increased complexity of transplanting lungs; the continuous needs for surgical, anesthetics, and critical care improvements; changes in immunosuppression and infection prophylaxis; and donor management and patient selection. The future of lung transplant remains promising: expansion of donor after cardiac death donors, improved outcomes, new immunosuppressants targeted to cellular and antibody-mediated rejection, and use of xenotransplantation or artificial lungs.

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Hannah Mannem, Meghan Aversa, Thomas Keller, and Siddhartha G. Kapnadak

Lung transplantation can be lifesaving for patients with advanced lung disease. Demographics are evolving with recipients now sicker but determining candidacy remains predicated on one's underlying lung disease prognosis, along with the likelihood of posttransplant success. Determining optimal timing can be challenging, and most programs favor initiating the process early and proactively to allow time for patient education, informed decision-making, and preparation. A comprehensive, multidisciplinary evaluation is used to elucidate disease prognosis and identify risk factors for poor posttransplant outcomes. Candidacy criteria vary significantly by center, and close communication between referring and transplant providers is necessary to improve access to transplant and outcomes.

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Darya Rudym, Jake G. Natalini, and Anil J. Trindade

Selection of lung transplant candidates is an evolving field that pushes the boundaries of what is considered the norm. Given the continually changing demographics of the typical lung transplant recipient as well as the growing list of risk factors that predispose patients to poor posttransplant outcomes, we explore the dilemmas in lung transplant candidate selections pertaining to older age, frailty, low and high body mass index, preexisting cancers, and systemic autoimmune rheumatic diseases.

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Melanie Subramanian and Bryan F. Meyers

This article examines the existing literature regarding single (SLT) and bilateral lung transplantation (BLT) to help answer the question of which approach is preferable.

Specifically, this review highlights the following subjects: disease-specific indications for SLT versus BLT; the impact of procedure type on posttransplantation functional status; the impact of procedure type on posttransplantation quality of life; chronic rejection after lung transplantation; ethical challenges facing the choice between single and bilateral transplants; and, novel strategies in this arena.

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Wayne M. Tsuang, Erika D. Lease, and Marie M. Budev

The first official donor lung allocation system in the United States was initiated by the United Network of Organ Sharing in 1990. The initial policy for lung allocation was simple with donor lungs allocated based on ABO match and the amount of time the candidates accrued on the waiting list. Donor offers were first given to candidates' donor service area. In March 2005, the implementation of the lung allocation score (LAS) was the major change in organ allocation. International adoption of the LAS-based allocation system can be seen worldwide.

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Melissa B. Lesko and Luis F. Angel

Rates of lung donation have increased over the past several years. This has been accomplished through the utilization of donors with extended criteria, the creation of donor hospitals or centers, and the optimization of lungs through the implementation of donor management protocols. These measures have resulted in augmenting the pool of available donors thereby decreasing the wait time for lung transplantation candidates. Although transplant programs vary significantly in their acceptance rates of these organs, studies have not shown any difference in the incidence of primary graft dysfunction or overall mortality for the recipient when higher match-run sequence organs are accepted. Yet, the level of comfort in accepting these donors varies among transplant programs. This deviation in practice results in these organs going to lower-priority candidates thereby increasing the waitlist time of other recipients and ultimately has a deleterious effect on an institution's waitlist mortality.

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Sahar A. Saddoughi and Marcelo Cypel

Organ shortage remains a limiting factor in lung transplantation. Traditionally, donation after brain death has been the main source of lungs used for transplantation; however, to meet the demand of patients requiring lung transplantation it is crucial to find innovative methods for organ donation. The implementation of extended donors, lung donation after circulatory death (DCD), the use of ex-vivo lung perfusion (EVLP) systems, and more recently the acceptance of hepatitis C donors have started to close the gap between organ donors and recipients in need of lung transplantation. This article focuses on the expansion of donor lungs for transplantation after DCD, the use of EVLP in evaluating extended criteria lungs, and the use of lung grafts from donors with hepatitis C.

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Andrew Courtwright, Carl Atkinson, and Andres Pelaez

Highly sensitized patients, who are often black and Hispanic women, are less likely to be listed for lung transplant and are at higher risk for prolonged waitlist time and waitlist death. In this review, the authors discuss strategies for improving access to transplant in this population, including risk stratification of crossing pretransplant donor-specific antibodies, based on antibody characteristics. The authors also review institutional protocols, such as perioperative desensitization, for tailoring transplant immunosuppression in the highly sensitized population. The authors conclude with suggestions for future research, including development of novel donor-specific antibody-directed therapeutics.

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Laura P. Halverson and Ramsey R. Hachem

Antibody-mediated rejection (AMR) is a form of lung allograft rejection that is emerging as an important risk factor for chronic lung allograft dysfunction and decreased long-term survival. In this review, we provide a brief overview of our current understanding of its pathophysiology with an emphasis on donor-specific antibodies before moving on to focus on the current diagnostic criteria and treatment strategies. Our goal is to discuss the limitations of our current knowledge and explore how novel diagnostic and therapeutic options aim to improve outcomes through earlier definitive diagnosis and preemptive targeted treatment.

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Jake G. Natalini and Emily S. Clausen

Lung transplantation is often the only treatment option for patients with severe irreversible lung disease. Improvements in donor and recipient selection, organ allocation, surgical techniques, and immunosuppression have all contributed to better survival outcomes after lung transplantation. Nonetheless, lung transplant recipients still experience frequent complications, often necessitating treatment in an intensive care setting. In addition, the use of extracorporeal life support as a means of bridging critically ill patients to lung transplantation has become more widespread. This review focuses on the critical care aspects of lung transplantation, both before and after surgery.

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Caroline M. Patterson, Elaine C. Jolly, Fay Burrows, Nicola J. Ronan, and Haifa Lyster

Most therapeutic advances in immunosuppression have occurred over the past few decades. Although modern strategies have been effective in reducing acute cellular rejection, excess immunosuppression comes at the price of toxicity, opportunistic infection, and malignancy. As our understanding of the immune system and allograft rejection becomes more nuanced, there is an opportunity to evolve immunosuppression protocols to optimize longer term outcomes while mitigating the deleterious effects of traditional protocols.

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Hanne Beeckmans, Saskia Bos, Robin Vos, and Allan R. Glanville

Lung transplantation is an established treatment of well-selected patients with end-stage respiratory diseases. However, lung transplant recipients have the highest rates of acute and chronic rejection among transplanted solid organs. Owing to ongoing alloimmune recognition and associated immune-driven airway/vascular remodeling, precipitated by multifactorial, endogenous or exogenous, post-transplant injuries to the bronchovascular axis of the secondary pulmonary lobule, most lung transplant recipients will suffer from a pathophysiological decline of their allograft, either functionally and/or structurally. This review discusses current knowledge, barriers, and gaps in acute cellular rejection and chronic lung allograft dysfunction—the greatest impediment to long-term post-transplant survival.

**Opportunistic Infections Post-Lung Transplantation: Viral, Fungal, and Mycobacterial** 159

Gabriela Magda

Opportunistic infections are a leading cause of lung transplant recipient morbidity and mortality. Risk factors for infection include continuous exposure of the lung allograft to the external environment, high levels of immunosuppression, impaired mucociliary clearance and decreased cough reflex, and impact of the native lung microbiome in single lung transplant recipients. Infection risk is mitigated through careful pretransplant screening of recipients and donors, implementation of antimicrobial prophylaxis strategies, and routine surveillance posttransplant. This review describes common viral, fungal, and mycobacterial infectious after lung transplant and provides recommendations on prevention and treatment.

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Harpreet Singh Grewal, Tany Thaniyavarn, Selim M. Arcasoy, and Hilary J. Goldberg

According to the Scientific Registry of Transplant Recipients, both transplant volume and survival among lung transplant recipients are improving over time. However, the outcomes of lung transplantation remain challenged by multiple thoracic and extra-thoracic complications. With improving lung transplant survival, patients experience prolonged exposure to chronic immunosuppressive agents that can lead to multiple infectious and noninfectious complications. This article focuses on most common noninfectious complications with significant clinical impact.

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Diego Avella, Henry Neumann, and Ankit Bharat

Lung transplant is a life-saving treatment for carefully selected patients with respiratory failure related to the infection with coronavirus disease-2019. Despite a complex pretransplant medical course, the posttransplant outcomes are excellent when performed by experienced centers.

**Future of Lung Transplantation: Xenotransplantation and Bioengineering Lungs** 201

Justin C.Y. Chan, Ryan Chaban, Stephanie H. Chang, Luis F. Angel, Robert A. Montgomery, and Richard N. Pierson III

Xenotransplantation promises to alleviate the issue of donor organ shortages and to decrease waiting times for transplantation. Recent advances in genetic engineering have allowed for the creation of pigs with up to 16 genetic modifications. Several combinations of genetic modifications have been associated with extended graft survival and life-supporting function in experimental heart and kidney xenotransplants. Lung xenotransplantation carries specific challenges related to the large surface area of the lung vascular bed, its innate immune system's intrinsic hyperreactivity to perceived 'danger', and its anatomic vulnerability to airway flooding after even localized loss of alveolocapillary barrier function. This article discusses the current status of lung xenotransplantation, and challenges related to immunology, physiology, anatomy, and infection. Tissue engineering as a feasible alternative to develop a viable lung replacement solution is discussed.