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Bronchiolitis Obliterans Syndrome in Lung Transplantation

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Keith Meyer and Allan Glanville dedicate this book to their families, mentors, and patients.

Keith Meyer especially dedicates this book to his parents-in-law, Wanda and Robert Auerbach, who have provided invaluable and loving support and guidance as he struggled to pursue a career in science and medicine.

Allan Glanville, in particular, dedicates this book to the many patients who have educated him regarding bravery, trust, and fellowship during their combined journey in this amazing field of lung transplantation.

Preface

It has been 50 years since the first successful human lung transplant was reported in 1963 by Hardy and colleagues. However, the success of this first transplant was transient, and outcomes remained poor until the early 1980s, when cyclosporine A (CsA) was first used for clinical immunosuppression. This was associated temporally with improved techniques for donor lung preservation, better surgical techniques, and advances in postoperative management. Most importantly, after an initial experience with dual immunosuppression (CsA and corticosteroids), it was found that a triple drug regimen of CsA, azathioprine, and corticosteroids given post-transplant could prevent acute rejection quite effectively. In the 1990s another calcineurin inhibitor (tacrolimus) and antimetabolite (mycophenolate) became available as alternates to CsA and azathioprine, respectively. Along with improved post-transplantation triple-drug immunosuppression, prophylactic regimens were devised over the past 2 decades to prevent opportunistic infection with viruses (cytomegalovirus and herpes simplex) and fungi (*Candida*, *Aspergillus*, and *Pneumocystis*).

Nonetheless, despite numerous developments in clinical lung transplantation and substantially improved survival statistics from a median survival of approximately 3.9 years in the early 1990s to 5.5 years in the early 2000s, delayed loss of allograft function due to the onset of obliterative bronchiolitis (OB) remains the prime cause of debilitation and recipient death for patients who successfully recover from the transplant and achieve good graft function during the initial recovery period. Because a confident diagnosis of chronic allograft rejection due to OB is difficult to make without a surgical lung biopsy, with its attendant risks of significant morbidity and mortality, a persistent decline of FEV_1 on spirometric testing ($\geq$20 % from baseline) was adopted as a clinical surrogate that is considered highly specific for the development of the syndrome of constrictive bronchiolitis and small airway obliteration that has become known as the bronchiolitis obliterans syndrome (BOS). BOS is generally considered to occur as a consequence of chronic allograft rejection. Attempts to prevent BOS or arrest its progression when it occurs in lung transplant recipients have been ineffective. The identification of risk factors that can be modified, the discovery of interventions that can prevent it from occurring, the

development of sensitive and specific tests to facilitate early detection, and the advent of effective therapies to reverse it or prevent its progression would greatly improve survival and quality of life for lung transplant recipients. Recipients without BOS in particular can survive more than 2 decades post-transplant if significant complications do not occur.

This book is intended to provide readers with a comprehensive understanding of the definition and changing perceptions of the nature of BOS as a clinical and pathologic entity, immune and nonimmune mechanisms that have been identified as risk factors for the development of BOS, and interventions that may prove to be clinically useful for the prevention or treatment of BOS. Chapter 1 reviews observations that lead to the recognition of BOS as a clinical entity, risk factors that have been associated with its appearance, and evolving nomenclature and recognition of chronic lung allograft dysfunction (CLAD) phenotypes. Chapters 2, 3, 4, and 5 examine clinical aspects of BOS and other forms of CLAD. Drs. Lagstein and Myers review the histopathology of obliterative bronchiolitis and related entities that can cause allograft dysfunction in Chap. 2. Drs. Snell, Levvey, and Westall comprehensively review the multitude of abnormalities that can cause CLAD (which must be considered in the differential diagnosis of BOS) in Chap. 3. Dr. Kanne provides a review of the diagnostic capabilities and limitations of thoracic imaging when evaluating patients with suspected CLAD in Chap. 4. Finally, Drs. Brown and Nathan provide a comprehensive discussion of approaches that are currently used to screen for declining lung function and to make a confident diagnosis of BOS when a decline in allograft function is detected.

Chapters 6, 7, 8, 9, 10, and 11 examine the role of allo- and autoimmune responses, infection, and gastroesophageal reflux (GER) in the pathogenesis of BOS. Dr. Martinu thoroughly examines the role of T cell-mediated alloimmunity in OB pathogenesis in Chap. 6. In addition to adaptive immune T-cell response, there is growing recognition that B cells and antibody-mediated immune responses can play a key role in BOS, and Mr. Ainge-Allen and Dr. Glanville examine the expanding knowledge of antibody-mediated rejection (AMR) in the context of lung transplantation and present current recommendations for the diagnosis and treatment of AMR in Chap. 7. There is also increasing awareness that innate immune mechanisms, in concert with adaptive immune responses, play key roles in BOS, and Drs. Todd and Palmer review our current and evolving knowledge of innate immunity and BOS pathogenesis in Chap. 8. In addition to alloimmune responses to lung allograft implantation in human lung transplantation, there is increasing evidence that autoimmunity may develop and play a significant role in BOS pathogenesis, and such autoimmune sensitization may even exist prior to transplant. Drs. Braun, Meyer, and Burlingham review new and evolving knowledge of autoimmune responses that are associated with chronic rejection and BOS, the role of interleukin-17 responses, and the utility of animal models of BOS in Chap. 10. Finally, Chaps. 11 and 12 cover two major risk factors that have been associated with BOS. Dr. Avery provides a comprehensive discussion of the role of various infections in BOS pathogenesis in Chap. 11, and Drs. D'Ovidio and Aramini explore the role of GER with pulmonary aspiration of refluxate in BOS pathogenesis in Chap. 12 and

provide current approaches to the diagnosis and treatment of significant GER in lung transplant candidates and recipients.

Approaches to the diagnosis and management of BOS in infants and small children can vary significantly from what is done for older children and adults, and Drs. Robinson and Aurora give an overview of current approaches to detect and manage BOS in children in Chap. 13. Finally, Chaps. 14, 15, and 16 cover important aspects of BOS prevention and management. Dr. Bhorade provides a comprehensive overview of the role of immunosuppression in the prevention and treatment of BOS in Chap. 14, and Drs. Vos, Stijn Verleden, Ruttens, Vanaudenaerde, and Geert Verleden provide a nicely comprehensive review of the immunomodulatory properties of azithromycin and its role as an agent that can be used to effectively treat and possibly prevent BOS. Lastly, Dr. Hachem provides an up-to-date and comprehensive review of the status of other therapies, such as extracorporeal photopheresis or total lymphoid irradiation, that may provide benefit for patients who have developed BOS in Chap. 16.

We hope that those who read this book will benefit from its contents and that it may stimulate future research endeavors that seek to better understand the pathogenesis of BOS and identify strategies to prevent its occurrence, to detect its onset before significant allograft impairment has occurred to allow therapeutic interventions, and to treat BOS such that further loss of allograft function can be prevented and even possibly restored.

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