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I. **Introduction to Transplantation: Background and ISHLT Registry**
(C H Wigfield MD)  
*P 7*

**Learning Objectives**

1. Background
2. Outcomes in Lung Transplantation
3. Challenges in Lung Transplantation
4. Lung Transplantation Databases and ISHLT Registry

**Selected references and resources**

II. **Evaluation and Management of the Lung Transplant Candidate**
(K M Chan MD)  
*P 8*

**Learning Objectives**

1. Indications for Lung Transplant Referral
2. Transplant Candidate Evaluation and Ongoing Management
3. Special Considerations including Informed Consent
4. Special Considerations: High Panel Reactive Antibody Screen
5. Urgent Inpatient Evaluation

**Minimum Experience Requirement**

**Selected references and resources**

III. **Lung Allograft Donation and Procurement**
(C H Wigfield MD)  
*P 12*

**Learning Objectives**

1. Historical Notes and Background
2. Donor Offer and Evaluation Process
3. Lung Allograft Procurement
4. Additional Lung Allograft Options and Future Directions

**Minimum Experience Requirement**

**Selected references and resources**

IV. **Lung Transplantation: Surgical and Post-operative Management**
(D Mason MD)  
*P 16*

**Learning Objectives**

1. Immediate Post Transplant Management
2. Surgical Conduct
3. Postoperative Complications
4. Special Considerations

**Minimum Experience Requirement**

**Selected references and resources**
V. REJECTION AFTER LUNG TRANSPLANTATION, IMMUNOSUPPRESSION PROTOCOLS AND COMPLICATIONS  
(D J LEVINE MD)  

A. IMMUNOLOGIC CONCEPTS IN LUNG TRANSPLANTATION  

LEARNING OBJECTIVES  
1. DEFINITIONS  
2. NORMAL IMMUNE RESPONSE  
3. IMMUNE RESPONSE TO ALLOGRAFT  
4. TOLERANCE  
5. IMMUNOGENETICS  
6. NON-HLA ANTIGENS  
7. CLINICAL APPLICATIONS OF TRANSPLANT IMMUNOLOGY AND Typing  

MINIMUM EXPERIENCE REQUIREMENT  
SELECTED REFERENCES AND RESOURCES  

B. REJECTION IN THE LUNG TRANSPLANT RECIPIENT  

LEARNING OBJECTIVES  
1. HYPERACUTE REJECTION  
2. ACUTE CELLULAR REJECTION  
3. BRONCHOITIS OBLITERANS SYNDROME (CHRONIC REJECTION)  
4. HUMORAL OR ANTIBODY MEDIATED REJECTION  
5. THE SENSITIZED RECIPIENT  

C. IMMUNOSUPPRESSION REGIMENS POST LUNG TRANSPLANTATION  

LEARNING OBJECTIVES  
1. OVERVIEW OF IMMUNOSUPPRESSIVE AGENTS  

MINIMUM EXPERIENCE REQUIREMENT  
SELECTED REFERENCES AND RESOURCES  

D. HEMATOLOGIC DISORDERS POST LUNG TRANSPLANTATION  

LEARNING OBJECTIVES  
1. THROMBOCYTOPENIA  
2. ANEMIA  
3. LEUKOPENIA OR LEUKOCYTOSIS  

MINIMUM EXPERIENCE REQUIREMENT  
SELECTED REFERENCES AND RESOURCES  

E. GASTROINTESTINAL ISSUES POST LUNG TRANSPLANTATION  

LEARNING OBJECTIVES  
1. FREQENT PROBLEMS AND THEIR POSSIBLE ETIOLOGIES  
2. COLONIC ISSUES  
3. SMALL BOWEL OBSTRUCTION  
4. UPPER GASTROINTESTINAL ISSUES  
5. GERD AND BOS
6. GI BLEED
7. BILIARY DISEASE
8. PANCREATITIS
9. GI COMPLICATIONS OF CYSTIC FIBROSIS PATIENTS
10. HEPATIC TOXICITY SECONDARY TO MEDICATION
11. HYPERAMMONEMIA

MINIMUM EXPERIENCE REQUIREMENT
SELECTED REFERENCES AND RESOURCES

VI. LUNG TRANSPLANTATION PATHOLOGY
(G BERRY MD)

LEARNING OBJECTIVES

1. PATHOLOGY OF COMMON INDICATIONS FOR THORACIC TRANSPLANTATION
2. SPECIMEN ADEQUACY AND HANDLING
3. POST-OPERATIVE AND IMMEDIATE POST-TRANSPLANT GRAFT DYSFUNCTION (WITHIN 7 DAYS)
4. EARLY COMPLICATIONS FOLLOWING LUNG TRANSPLANTATION (1 WEEK – 6 MONTHS)
5. ACUTE CELLULAR REJECTION (ACR)
6. INFECTIONS IN LUNG ALLOGRAFT
7. ACUTE ANTIBODY MEDIATED/HUMORAL REJECTION (AMR)
8. AIRWAY INFLAMMATION/LYMPHOCYTIC BRONCHITIS/BRONCHIOLITIS
9. POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER (PTLD)
10. LATE COMPLICATIONS (BEYOND 6 MONTHS)
11. CHRONIC AIRWAY REJECTION
12. CHRONIC VASCULAR REJECTION (CVR)
13. RECURRENCE OF NATIVE/PRIMARY LUNG DISEASE

SELECTED REFERENCES AND RESOURCES

VII. DIAGNOSIS AND MANAGEMENT OF INFECTIONS FOLLOWING LUNG TRANSPLANTATION
(T L ASTOR MD)

LEARNING OBJECTIVES

1. IMMUNE RESPONSE TO INFECTION
2. EVALUATION OF INFECTION IN THE PRE-TRANSPLANT CANDIDATE
3. SIGNIFICANCE OF INFECTIONS IN THE DONOR
4. IMPAIRED PHYSIOLOGIC MECHANISMS IN THE ALLOGRAFT AND IMPACT ON INFECTION
5. OVERVIEW AND TIMELINE OF INFECTIONS AFTER LUNG TRANSPLANTATION
6. DIAGNOSIS, PROPHYLAXIS, AND MANAGEMENT OF EARLY POST-TRANSPLANT INFECTIONS
7. DIAGNOSIS, PROPHYLAXIS, AND MANAGEMENT OF LATER INFECTIONS
8. NON-INFECTIONAL ALLOGRAFT SEQUELAE OF INFECTION PATHOGENS
9. IMMUNE MONITORING AND INFECTION

SELECTED REFERENCES AND RESOURCES

ADDENDUM
INTRODUCTION

The purpose of this compendium is to provide a curriculum of core competencies in lung transplantation. The ISHLT Academy provides a concise synopsis of clinical knowledge and associated essential professional skills to facilitate the mastery of all surgical and medical aspects involved in the care of patients receiving lung transplantation.

This compendium does not replace a textbook, but intends to provide an outline of essential topics and aims to assist with detailed review. This should be of benefit for both seasoned clinicians and current trainees. The former may find selective revision of complimentary areas in lung transplantation useful, whereas the latter may benefit from a more complete review of all topics during fellowship or other subspecialty training in lung transplantation.

Inevitably, some overlap of clinically related aspects may have occurred. Extensive referencing should assist selective review of published evidence for each topic.

This document also includes active hyperlinks and related multi-media resources. These should be considered during individual study to develop competency in various aspects of lung transplantation.

The core curriculum should also serve programs providing lung transplantation with a tool to review their standards of care, develop protocols and implement guidelines established in lung transplantation.

Wherever possible, specific learning objectives have been defined. Minimal recommended clinical experience has been proposed with the awareness that this may be variable dependent on individual professional background and regional program limitations. The outlines will also serve as a template for a post-graduate course curriculum to be provided by the ISHLT academy at future annual meetings.

The educational workforce of the Pulmonary Council of ISHLT hopes that this compendium will prove to be useful. We would welcome constructive feedback to further develop its scope and accuracy.

On behalf of the Pulmonary Council of ISHLT,

Chris Wigfield MD FRCS
Chicago, IL
May 2010
I. **INTRODUCTION TO LUNG TRANSPLANTATION: BACKGROUND AND ISHLT REGISTRY** (C H WIGFIELD MD)

**Learning Objectives for the Introduction to Lung Transplantation: Background and ISHLT Registry:**

1) To establish context and historic background for lung transplantation.
2) To know indications and expected outcomes in lung transplantation.
3) To appreciate current challenges and limitations associated.
4) To utilize the ISHLT registry report and resources.

1. **Background**
   a. Historical Context
   b. First Lung Transplants
   c. Advent of Immunosuppression

2. **Outcomes in Lung Transplantation**
   a. Current expected survival rates
   b. Comparative survival
   c. Conditional survival after 1 year
   d. Outcomes dependent on native pulmonary disease process

3. **Challenges in Lung Transplantation**
   a. Donor Scarcity
   b. Waiting List mortality
   c. Bronchiolitis Obliterans

4. **Lung Transplantation Databases and ISHLT Registry**
   a. Data Access
   b. Statistics available
   c. Data submission

**Selected Hyperlinks for the Introduction to Lung Transplantation: Background and ISHLT Registry:**

- The Journal For Heart & Lung Transplantation Website: [www.jhiltonline.org](http://www.jhiltonline.org)
- The Unified Transplant Network established by the United States Congress under the National Organ Transplant Act (NOTA) of 1984: [http://www.optn.org](http://www.optn.org)
- Eurotransplant Website: [www.eurotransplant.nl](http://www.eurotransplant.nl)
II. Evaluation and Management of the Lung Transplant Candidate
(K M Chan MD)

Learning Objectives for the Evaluation and Management of the Lung Transplant Candidate:

5) Understand general and disease specific considerations for lung transplant referral
6) Review appropriate and cost effective testing, cancer screening, vaccination, consultation and multidisciplinary support of the lung transplant candidate
7) Understand the importance of “waitlist” management for the transplant candidate
8) Understand the importance of informed consent for transplantation, high risk donor acceptance and research participation
9) Discuss and review risks associated with anti-HLA antibodies, elevated panel reactive antibody screens and desensitization therapies
10) Understand lung donor allocation schemes and the relationship to the urgent inpatient lung transplant evaluation

1. Indications for Lung Transplant Referral
   a. General considerations
      i. End stage lung disease
      ii. Ambulatory
      iii. Maximal medical management
      iv. Minimal or no co-morbid illness
      v. Tobacco cessation
      vi. Strong psychosocial support
      vii. Physiologic age considerations
      viii. Previous or current malignancy
      ix. Systemic disease
      x. Body Mass Index (BMI) considerations
      xi. Colonization with highly resistant organisms (e.g. Burkholderia cepacia genomovar III, M chelonae abscessus)
      xii. Mechanical ventilation
   b. Disease specific listing considerations (including single or double LTx listing)
      i. IPAH
      ii. Emphysema
      iii. CF
      iv. IPF
      v. Other

2. Transplant Candidate Evaluation and Ongoing Management
   a. Respirologist / Pulmonologist
   b. Thoracic Surgeon
   c. Social Worker
   d. Psychiatrist/Psychologist
   e. Pre Transplant coordinator
   f. Financial coordinator
   g. Pharmacist
   h. Nutritionist
   i. Pre transplant education / Patient Support groups
   j. Pulmonary Rehabilitation
   k. Testing
      i. Pulmonary
         1. Pulmonary function tests including ABG
         2. 6MW/Shuttle test
         3. Cardiopulmonary exercise test (CPET)
      ii. Radiographic
         1. High Resolution CT of the chest (HRCT)
2. Perfusion (V/Q) scan
3. Esophagram
4. Bone densitometry

iii. Cardiac
1. EKG
2. Echocardiogram
3. Cardiac stress test
4. Cardiac catheterization
   a. Right
   b. Left

iv. Gastrointestinal
1. EGD, PEG tube placement
2. Colonoscopy
3. 24 hour pH probe and manometry

v. Health Care Screening
1. Dental examination
2. Colon
3. Skin
4. Prostate
5. Breast
6. Cervical/Ovarian

vi. Vaccines
1. Hepatitis B
2. Pneumococcal/Influenza
3. Tetanus etc.

vii. Laboratories and serology
1. Basic labs
   a. Comprehensive panel
   b. CBC
   c. 24 hour creatinine clearance
   d. α1-AT level
   e. ACE level
   f. Nicotine/toxicology screen
2. Infectious Serology
   a. EBV, CMV, HSV, VZV, HIV
   b. Toxoplasma, RPR
   c. Hepatitis A, B, C
3. Blood typing and HLA
   a. PRA
4. Other
   a. PPD skin test or Quantiferon testing

viii. Additional referrals as necessary
1. Cardiology
   a. Coronary artery disease
2. Infectious Disease
3. Gastroenterology
   a. α1-AT deficiency (hepatology)
   b. CF (liver disease, DIOS etc.)

3. Special Considerations Including Informed Consent
   a. Hepatitis B or C
   b. HIV
   c. Acceptance of high risk donor
   d. Research participation

4. Special Considerations: High Panel Reactive Antibody Screen
   a. Desensitization therapy
   b. Prospective and retrospective crossmatching
5. **Urgent Inpatient Evaluation**
   a. Mechanical ventilation
   b. ECMO
   c. Deconditioning

6. **Lung Allocation Systems**
   a. United States: Lung Allocation Score
   b. Europe: Eurotransplant allocation
   c. UK: Lung allocation
   d. Australia: Lung Allocation
   e. Other Countries: Lung Allocation

**Minimum Experience Requirement for Evaluation and Management of the Lung Transplant Candidate:**

*(Modified from UNOS Membership Criteria)*

- Participate in the care of 15 or more lung transplant candidates for a minimum of 3 months from the time of referral to the time of listing and/or transplantation.
- Participate in the care of 3 or more lung transplant candidates with an elevated PRA of > 25% from the time of patient referral to the time of transplantation incorporating desensitization procedures.
- Participate in the care of 3 or more lung transplant candidates undergoing urgent in-hospital evaluation for lung transplantation.

**Selected Hyperlinks for the Evaluation and Management of the Lung Transplant Candidate:**

- International Guidelines for the Selection of Lung Transplant Candidates. The International Society for Heart and Lung Transplantation, the American Thoracic Society, the American Society of Transplant Physicians, the European Respiratory Society: [http://ajrccm.atsjournals.org/cgi/content/full/158/1/335](http://ajrccm.atsjournals.org/cgi/content/full/158/1/335)

**Selected References for Evaluation and Management of the Lung Transplant Candidate:**

**Candidate Selection:**


**Urgent Transplant Evaluation:**


Informed Consent:


Sensitized Patient:


Lung Allocation:


III. LUNG ALLOGRAFT DONATION AND PROCUREMENT (C H WIGFIELD MD)

Learning Objectives for Lung Allograft Donation and Procurement:

11) To develop a clinically relevant understanding of donor brain death, the basic pathophysiology and donor certification issues
12) To differentiate types of donors as relevant to lung transplantation
13) Knowledge of waiting list and donor availability concerns
14) Lung allograft matching criteria
15) Procurement: Procedure and understanding of possible adverse advents
16) Recognize options for donor management and allograft optimization
17) To be aware of future directions in lung allograft procurement

1. Historical Notes and Background
   a. General considerations
      i. Overview and historical Perspective
      ii. Brain Death Definition and Criteria
      iii. Definitions of Donors (DDND v DDCD)
      iv. Donor Scarcity and Waiting List
      v. Definition of Standard v Extended Criteria Donors in LTx (SCD v ECD)

2. Donor Offer and Evaluation Process
   a. Matching Criteria in Lung Transplantation
      i. Serology confirmation
      ii. Size matching
      iii. Laterality Issues
      iv. Organ Procurement Consent
      v. Allocation Scores and recipient matching
   b. Evaluation Process
      i. Procurement Offer
      ii. Provisional Acceptance
      iii. Logistics and Confirmed Acceptance
      iv. Donor Net systems/ IT technology
      v. Etiology of Donor Lung Injury:
         1. Neuroendocrine Dysregulation
         2. Permeability and Pulmonary Edema
         3. Airway, Pulmonary and Pleural Trauma
         4. Aspiration Pneumonitis
         5. Respiratory Infections
         6. Ventilation related Issues
      vi. Modified Evaluation process:
         1. High Risk Donors
         2. Donor type related (DDND v DDCD)
         3. Pediatric Donor
   c. Donor Assessment
      i. Donor Information and Evidence Review
      ii. Verification of Brain Death Certification
      iii. UNOS donor Criteria
      iv. Bronchoscopy of Donor Lungs
      v. Visualization of Donor Lungs
      vi. Additional Investigations
      vii. Dialogue with Recipient Surgeon’s Team
      viii. Multiorgan Procurement Communication
   d. Donor Management and Optimization
      i. Options for Allograft improvement in situ
      ii. Fluid Management and Re-evaluation
iii. Extended Criteria Donors

3. **Lung Allograft Procurement**
   a. Lung Procurement
      i. Preparations and Dissection (with/without Cardiac procurement)
      ii. Antegrade Pulmoplegia Principles
      iii. En Bloc Excision of Allografts: Essentials and Pitfalls
      iv. Backbench Assessment and Retrograde Pulmoplegia
      v. Lung Separation
      vi. Transport Requirements
   b. Planned Ischemia and Reperfusion Preparation
      i. Allograft Ischemia Basics
      ii. Preparation of Donor Lung for Anastomoses
      iii. Re-warming, Re-perfusion and Re-ventilation

4. **Additional Lung Allograft Options and Future Directions**
   a. Additional Lung Allograft Sources
      i. Living Related Lung Donation
      ii. Split Lung Allografts
      iii. DDCD Lung Allografts
   b. Future Directions
      i. Ex Vivo Lung Perfusion
      ii. Xenografts in Lung Transplantation

**Minimum Experience Requirement for Lung Donation and Procurement:**

For recommendations see UNOS Statements on Lung Transplant Surgeon Certification Process: UNOS appendix B; Attachment I—XIII 73 pp.

- Reasonable Minimum experience: “10 or more Lung Allograft Procurements as Primary Surgeon under supervision of qualified lung transplant surgeon”. Case must be documented with Donor UNOS (or equivalent ID Number).
- Nota Bene: Lung Allograft procurement is associated with numerous pitfalls. To prevent adverse outcomes every effort to optimize a procurement surgeons’ skills and judgment is required. This can not be simply quantified in case numbers performed and is best developed in a dedicated thoracic transplant service.

**Selected Hyperlinks for Lung Donation and Procurement:**

- Organ donation information in Europe: [http://www.donoraction.org](http://www.donoraction.org)
- U.S. government organ donation information site: [http://www.organdonor.gov](http://www.organdonor.gov)

**Selected References for Lung Donation and Procurement:**


Weill D et al Donor Criteria in Lung Transplantation An Issue Revisited CHEST 2002; 121:2029–2031


Wigfield CH et al Organ Procurement Data Evaluation of Rejected Marginal Donors in Lung Transplantation Chest 2006 130 (4): 152S


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IV. **LUNG TRANSPLANTATION: SURGICAL AND POST-OPERATIVE MANAGEMENT**
(D MASON MD)

**Learning Objectives for Lung Transplantation: Surgical and Post-Operative Management:**

18) Understand the principles and practice of size matching between donor and recipient
19) Review the differential diagnosis and treatment strategies for graft failure in the early postoperative period
20) Discuss the management of pleural complications after lung transplantation
21) Understand the diagnostic and treatment strategies of bronchial, pulmonary artery and pulmonary venous complications
22) Understand the indications for, management of and contraindications to extracorporeal mechanical support after lung transplantation

1. **Immediate Post Transplant Management**
   a. Surgical Complications of Lung Transplant
   b. Medical Complications post Lung Transplantation
   c. Prophylactic Regimen (antibiotics, anti-fungal and anti-viral)

2. **Surgical Conduct**
   a. Size matching between donor and recipient
   b. Single versus double lung transplant
   c. Coordinating the timing of surgery
   d. Technical aspects of pneumonectomy
   e. Choice of incision- median sternotomy, bilateral anterior thoracotomy, clamshell, anterior vs posterolateral thoracotomy
   f. Use of cardiopulmonary bypass and intraoperative ECMO- disease specific, PAH Anastomotic techniques- running, interrupted, suture choice

3. **Postoperative Complications**
   a. Graft dysfunction- differential diagnosis and treatment (NO)
   b. Anastomotic
      i. Airway- dehiscence, stenosis, bronchovascular fistula, stents
      ii. Vascular- pulmonary vein and artery stenosis
   c. Pleural – acute and chronic effusions; empyema
   d. Renal Failure – prevention and treatment

4. **Special Considerations**
   b. Postoperative ECMO- separation/weaning
   c. Combined cardiac surgery and lung transplantation. Stents vs CABG

**Minimum Experience Requirement for Lung Transplantation: Surgical and Post-Operative Management:**

UNOS Certification criteria for lung transplantation

- Participate in the matching of 15 or more lung transplant donors to recipients
- Participate in 15 or more operative and postoperative lung transplant managements.

**Selected Hyperlinks for Lung Transplantation: Surgical and Post -Operative Management:**

and G. Alexander Patterson, MD)


**Selected References for Lung Transplantation: Surgical and Post-Operative Management:**


V. REJECTION AFTER LUNG TRANSPLANTATION, IMMUNOSUPPRESSION PROTOCOLS AND COMPLICATIONS (D J LEVINE MD)

A. IMMUNOLOGIC CONCEPTS IN LUNG TRANSPLANTATION

Learning Objectives for Immunologic Concepts in Lung Transplantation

23) Review the general concepts and definitions of Basic Immunology
24) Recognize the roles of lymphocytes responsible for immune responses (B v T cells)
25) Discuss the different types of rejection and each of their proposed mechanisms
26) List the causes of HLA allo-immunization
27) Understand the differences in the tests involved in the evaluation of the immune work up prior to transplantation

1. Definitions

2. Normal Immune Response
   a. Innate vs Adaptive Immune System
   b. Molecules and cells of the immune system
      i. T cells
      ii. B cells
      iii. NK cells
   c. Response to foreign antigen

3. Immune Response to Allograft
   a. Mechanism of allorecognition
   b. Humoral vs Cellular Rejection
   c. Proposed mechanism of each type of allograft rejection:
      i. Hyperacute rejection
      ii. Acute rejection
      iii. Chronic rejection
      iv. Humoral rejection

4. Tolerance
   a. Definition
   b. Mechanisms
   c. Clinical Implications

5. Immunogenetics
   a. ABO Blood System
   b. Major Histocompatibility Complex I and II
      i. HLA Nomenclature and HLA genetics
      ii. Causes of HLA-specific alloimmunization
      iii. HLA Antigen Matching in Lung Transplantation
   c. Methods used to detect anti-HLA antibodies
      i. Calculated PRA (c-PRA), Virtual Crossmatch
      ii. Detection of presence of anti-HLA antibodies
      iii. Panel reactive antibodies
      iv. Complement Dependent Cytotoxicity (CDC)
      v. Flow Cytometry
      vi. Solid Phase Assays
         1. Luminex
         2. Flow Cytometry
         3. ELISA
      vii. Screening strategies
6. Non-HLA Antigens

7. Clinical Applications of Transplant Immunology and Typing

Minimum Experience Requirement for Immunologic Concepts in Lung Transplantation:

- Participate in evaluation of the immunologic work up along with immunologist of 15 patients being evaluated for transplantation.

Selected References for Immunologic Concepts in Lung Transplantation:


B. Rejection in the Lung Transplant Recipient

Learning Objectives for Rejection in the Lung Transplant Recipient:

28) Define the different types of lung transplant rejection
29) Discuss the diagnostic approaches to evaluation for each of the different types of rejection post-transplant
30) Discuss surveillance bronchoscopy and pros and cons
31) Define acute cellular rejection per the ISHLT guidelines
32) List the risk factors and outcomes for BOS (chronic rejection)
33) Outline the timeline each type of rejection
34) Understand significance of the sensitized patient
35) Review the histological differences between acute and chronic rejection
36) Explain the treatment options for patients with BOS

1. Hyperacute Rejection
   a. Definition
   b. Mechanism
   c. Pathology
   d. Treatment

2. Acute Cellular Rejection
   a. Definition-(ISHLT guidelines)
   b. Detection, Evaluation and Diagnosis
      i. Surveillance bronchoscopy
         1. Pros and Cons
         2. Table of possible surveillance schedules
      ii. Monitoring
         1. Spirometry
         2. Clinical status
         3. Bronchoscopy
         4. Radiographic changes
   c. Grading of acute cellular rejection
      i. ISHLT Pathologic grading
   d. Type of ACR
      i. Recurrent
ii. Refractory
iii. Lymphocytic bronchiolitis
e. Treatment Options
   i. Modified immunosuppression regimen
      1. Steroid pulse and taper
      2. Change calcineurin inhibitor
      3. Alemtuzumab, antithymocyte globulin, ECP,
      4. Others
f. Outcomes
g. Clinical Implications
h. Risk Factors

3. Bronchiolitis Obliterans Syndrome (Chronic Rejection)
a. Definition (ISHLT guidelines)
b. Evaluation and Diagnosis
   i. Spirometric Diagnosis
   ii. Pathologic diagnosis
   iii. Radiographic findings
   iv. Clinical findings
   v. Grading (ISHLT guidelines)
c. Monitoring
d. Treatment Options
   i. Photopheresis
   ii. Azithromycin
   iii. Augment or change immunosuppression
   iv. Re-transplantation
e. Risk Factors
   i. Acute cellular rejection (ACR)
   ii. Lymphocytic bronchitis/bronchiolitis (LB)
   iii. Organizing pneumonia
   iv. HLA mismatch
   v. GERD
   vi. CMV/respiratory viruses
   vii. Primary Graft Dysfunction (PGD)

4. Humoral or Antibody-Mediated Rejection
a. Definition
b. Evaluation, Screening and Diagnosis
   i. Serologic
   ii. Pathologic
   iii. Immunologic
c. Monitoring
   i. Donor specific antibodies
   ii. C4d monitoring
d. Treatment Options
e. Outcomes
f. Risk Factors

5. The Sensitized Recipient
a. Screening
   i. Types of screening pre-transplant
      1. PRA
      2. V-PRA
   ii. Issues of the sensitized patient
   iii. Treatment and monitoring prior to transplantation
   iv. Treatment and monitoring peri-operatively and post transplant
   v. Risks
Minimum Experience Requirement for Rejection in the Lung Transplant Recipient:

- Review the slides of at least 10 patients with pathologist with acute cellular rejection.
- Diagnose and treat at least 10 patients with acute cellular rejection, humoral rejection and bronchiolitis obliterans syndrome (BOS).
- Perform at least 10 bronchoscopies post transplant to evaluate for ACR.

Selected References for Rejection in the Lung Transplant Recipient:


C. IMMUNOSUPPRESSION REGIMENS POST LUNG TRANSPLANTATION

Learning Objectives for Immunosuppression Regimens Post Lung Transplantation:

37) Discuss the triple agent immunosuppression protocol and which types of agents are typically used
38) Understand the side effects of each of the drug classes
39) Describe the monitoring of levels of the calcineurin inhibitors and what range of levels is appropriate
40) List the possible complications of induction therapy
41) Discuss the laboratory tests to order to evaluate toxicity from the different classes of drugs
42) Discuss drug-drug interactions with the calcineurin inhibitors

1. Overview of Immunosuppressive Agents
   a. Immunosuppressant Action and the Immune Cascade (how all of the agents relate within the cascade where the agent affects the immunologic process).
   b. Induction Agents
   c. Primary Immunosuppressants
   d. Adjuvant agents
   e. Induction
      i. Pro versus con of induction
ii. Risks and Benefits

iii. Agents (For all agents: target, indication, dose, administration, adverse events, monitoring)
   1. Similect (Basiliximab)
   2. Campath (Anti CD-52)
   3. Thymoglobulin (rATG)
   4. OKT3 (anti-Cd-3)

f. Maintenance
   i. Triple Agent Immunosuppression Regimen
   ii. Corticosteroids
      1. Mechanism of action
      2. Pharmacokinetics, dosing and drug monitoring
      3. Side effects
      4. Drug-drug interactions
   iii. Calcineurin Inhibitors (Cyclosporine and Tacrolimus)
      1. Mechanism of action
      2. Pharmacokinetics, dosing and drug monitoring
      3. Side effects
      4. Drug-drug interactions
   iv. Anti-proliferative agents (Azathioprine and Mycophenolic acid (MMF))
      1. Mechanism of action
      2. Pharmacokinetics, dosing and drug monitoring
      3. Side effects
      4. Drug-drug interactions
   v. TOR inhibitors (Sirolimus and Everolimus)
      1. Mechanism of action
      2. Pharmacokinetics, dosing and drug monitoring
      3. Side effects
      4. Drug-drug interactions

g. Rejection
   i. Acute Rejection
      1. Augmentation of Maintenance Therapy
      2. Adjustment of Maintenance Therapy
   ii. Chronic Rejection (BOS)
      1. Augmentation of Maintenance Therapy
      2. Adjustment of Maintenance Therapy
      3. Azithromycin
   iii. Humoral Rejection
      1. Plasmapheresis
      2. IVIG
      3. Rituximab
      4. Velcaide

h. Trends and Issues in Immunosuppression
   i. Salvage Therapy for Chronic Rejection
      i. Total lymphoid Irradiation (TLI)
      ii. Extracorporeal Photopheresis (ECP)
   j. Desensitization
      i. Plasmapheresis
      ii. IVIG
      iii. Rituximab
      iv. Velcaide

Minimum Experience Required for Immunosuppression Regimens Post Lung Transplantation:

- Treat 15 patients with immunosuppression post lung transplant and adjust changes and following for side effects or drug interactions.
Selected Hyperlinks for Immunosuppression Regimens Post Lung Transplantation:


Selected References for Immunosuppression Regimens Post Lung Transplantation:


D. HEMATOLOGIC DISORDERS POST LUNG TRANSPLANTATION

Learning Objectives for Hematologic Disorders Post Lung Transplantation

43) List the major causes of leukopenia post lung transplantation
44) Understand treatment options for drug-induced penias
45) Discuss the reasons for anemia post lung transplantation

1. Thrombocytopenia
   a. Evaluation and Diagnostic work up
   b. Drug reactions
      i. Immunosuppressive
      ii. Antibiotics
   c. Infection
   d. Treatment options

2. Anemia
   a. Evaluation and Diagnostic Work up
   b. Drug Reaction
      i. Immunosuppressive
      ii. Antibiotics
   c. Infection
   d. Iron deficiency
   e. HUS
   f. Treatment options

3. Leukopenia or Leukocytosis
   a. Evaluation and Diagnostic Work up
   b. Drug Reaction
      i. Immunosuppressives
      ii. Antibiotics
   c. Infection
   d. Treatment Options
Minimum Experience Requirement for Hematologic Disorders Post Lung Transplantation:

- Evaluate, monitor and treat 10 patients with leukopenia, thrombocytopenia or anemia post transplant.

E. Gastrointestinal Issues Post Lung Transplantation

Learning Objectives for Gastrointestinal Issues Post Lung Transplantation

46) Discuss the risk factors for bowel perforation post lung transplantation
47) Understand the significance of GERD in lung transplant recipients and its association with BOS (chronic rejection)
48) Identify the gastrointestinal issues that are important to Cystic Fibrosis patients who undergo lung transplantation
49) Understand the etiologies behind the common gastrointestinal symptoms patients have post lung transplantation
50) Discuss the different anti-infective and immunosuppressive agents that typically are associated with gastrointestinal side effects and liver toxicity

1. Frequent Problems and their Possible Etiologies
   a. Nausea/Vomiting
      i. Medications
      ii. Infection
      iii. Gastroparesis/delayed gastric emptying
      iv. Small bowel obstruction or ileus
      v. GERD
   b. Diarrhea
      i. Medications
      ii. Infection: C. difficile, protozoa, viral, bacterial
      iii. CMV Colitis
      iv. Ischemic Colitis
      v. Prior co-morbidities
   c. Abdominal Pain

2. Colonic Issues
   a. Bowel Perforation: multiple risks and etiologies
   b. Diverticulitis/diverticulosis
   c. PTLD/Malignancy
   d. Colitis (viral, fungal or ischemic)
   e. Pseudomembranous colitis and C. Diff

3. Small Bowel Obstruction
   a. Gastroparesis
   b. PTLD
   c. Constipation

4. Upper Gastrointestinal Issues
   a. Gastroparesis
   b. Esophagitis
   c. PUD
   d. GERD

5. GERD and BOS

6. GI Bleed
   a. Peptic Ulcer Disease
   b. Esophagitis
i. Candidiasis or fungal
ii. Malignancy
iii. CMV or viral

7. **Biliary Disease**
   a. Cholelithiasis pre-transplant
      i. Timing for cholecystectomy
   b. Choleycystitis

8. **Pancreatitis**
   a. Infection
   b. Medication: Cyclosporine, Azithiprine, Prednisone

9. **GI Complications of Cystic Fibrosis Patients**
   a. DIOS
   b. Pancreatitis
   c. Choleycystitis
   d. Bowel obstruction

10. **Hepatic Toxicity Secondary to Medication**

11. **Hyperammonnemia**

**Selected References Gastrointestinal Issues Post Lung Transplantation:**


VI. Lung Transplantation Pathology (G Berry MD)

Learning Objectives for Lung Transplantation Pathology:

51) To recognize the common indications and histopathological patterns in combined heart-lung, single lung and double lung transplantation
52) To understand the common pathological complications utilizing a temporal approach
53) To recognize the histopathological grades of acute cellular rejection
54) To understand the current diagnostic challenges of acute antibody mediated rejection
55) To describe the patterns and causes of airway inflammation
56) To recognize the histopathological findings in chronic airway and vascular rejection
57) To outline the pulmonary diseases that can recur in the lung allograft

1. Pathology of Common Indications for Thoracic Transplantation
   a. Congenital Heart Disease/Eisenmenger’s Syndrome
   b. Cystic Fibrosis
   c. Primary Pulmonary Hypertension
   d. Chronic Obstructive Lung Disease
   e. Idiopathic Pulmonary Fibrosis

2. Specimen Adequacy and Handling
   a. Transbronchial Biopsy
      i. Number of Tissue Samples for Adequacy
      ii. Tissue Handling and Fixation
      iii. Processing of Urgent vs. Routine Biopsy
      iv. Basic/Routine Staining
      v. Immunohistochemical/Molecular Studies
   b. Bronchial washes
   c. Endobronchial Biopsy
   d. Video-Assisted Thoracoscopic Biopsy (VATS)

3. Post-Operative and Immediate Post-Transplant Graft Dysfunction (Within 7 days)
   a. Definition
   b. Surgical Technical Complications
      i. Arterial/Venous Obstruction
      ii. Airway Dehiscence/Obstruction
   c. Preservation Injury/Reimplantation Response
      i. Definition
      ii. Histopathological Findings
   d. Hyperacute Rejection
      i. Definition
      ii. Histopathological Findings
      iii. Immunohistochemical/Immunofluorescent Findings
   e. Infection
      i. Bacterial
      ii. Viral
      iii. Fungal
      iv. Other

4. Early Complications Following Lung Transplantation (1 week – 6 months)
   a. Definitions
   b. Classification
   c. Diagnostic Techniques

5. Acute Cellular Rejection (ACR)
   a. Definition
b. Grading of ACR
   i. Minimal
   ii. Mild
   iii. Moderate
   iv. Severe

c. Morphological Mimics of ACR
   i. Bronchial-Associated Lymphoid Tissue (BALT)
   ii. Infection
   iii. Post-Transplant Lymphoproliferative Disorder

6. Infections in Lung Allograft
   a. Bacterial
   b. Viral
   c. Fungal
   d. Parasitic/Protozoan

7. Acute Antibody Mediated/Humoral Rejection (AMR)
   a. Definitions
   b. Histopathological Findings
   c. Immunohistochemical/Immunofluorescent Findings
   d. Ongoing Issues and Controversies

8. Airway Inflammation/Lymphocytic Bronchitis/Bronchiolitis
   a. Definition
   b. Histopathological features
   c. Grading of Acute Airway Rejection
      i. Low Grade
      ii. High Grade
   d. Morphological Mimics
      i. Airway Inflammation Associated with AMR
      ii. Bronchus-Associated Lymphoid Tissue (BALT)
      iii. Prior Biopsy Site
      iv. Ischemic Injury/Organizing Pneumonia
      v. Aspiration Injury
      vi. Infection

9. Post-Transplant Lymphoproliferative Disorder (PTLD)
   a. Definition
   b. Histopathological Patterns
   c. Immunohistochemical/Molecular Markers
   d. Role of EBV Infection
   e. Other EBV-associated Proliferations

10. Late Complications (Beyond 6 months)
    a. Definition
    b. Classification
    c. Diagnostic Techniques

11. Chronic Airway Rejection (CAR)
    a. Definition
    b. Histopathological Findings
    c. Grading of CAR
    d. Role of Transbronchial Biopsy
    e. Differential Diagnosis
        i. Organizing Pneumonia
        ii. Prior Biopsy Site
        iii. Aspiration
12. **Chronic Vascular Rejection (CVR)**
   a. Definition
   b. Histopathological Findings

13. **Recurrence of Native/Primary Lung Disease**
   a. Sarcoidosis
   b. Lymphangioleiomyomatosis (LAM)
   c. Diffuse Panbronchiolitis
   d. Giant Cell Interstitial Pneumonia (GIP)
   e. Desquamative Interstitial Pneumonia (DIP)
   f. Langerhans-Cell Histiocytosis
   g. Bronchioloalveolar Carcinoma

**Selected Hyperlinks for Lung Transplant Pathology:**

- American Lung Association website: [http://www.lungusa.org](http://www.lungusa.org)

**Selected References for Lung Transplantation Pathology:**

Learning Objectives for Diagnosis and Management of Infections Following Lung Transplantation:

58) To highlight the specific components of innate and alloimmunity integral to host immunity to infection in the lung, and the impact of corticosteroids, calcineuren inhibitors, cell cycle inhibitors, and T-cell depleting agents on the immune response in the allograft.
59) To outline the comprehensive approach to evaluating immunity and pulmonary/ non-pulmonary infections in the lung transplant candidate.
60) To discuss the significance and evaluation of infections in the lung donor.
61) To demonstrate the impact of the surgical disruption of the normal pathways of innate lung immunity on the development of infection in the lung transplant recipient.
62) To describe the timeline, diagnostic methods, prophylaxis, and management of specific early and late post-transplant infections.
63) To list the potential non-infectious allograft sequelae resulting from infectious pathogens.

1. Immune Response to Infection
   a. Components of the Immune Response to Infection
      i. Cell Types
      ii. Antibodies
      iii. Complement
      iv. T cell receptors and MHC molecules
   b. Components specific to immune response to infection in the lung
      i. Innate Immunity
      ii. Cellular Immunity
      iii. Humoral Immunity
   c. Immunity Against Specific Infectious Agents
      i. Immunity to Viruses
      ii. Immunity to Bacteria
      iii. Immunity to Fungi
      iv. Immunity to Parasites
   d. Impact of Immunosuppression on Immune Response to Infection
      i. Corticosteroids
      ii. Calcineuren Inhibitors
      iii. Cell Cycle Inhibitors
      iv. T-Cell Depleting Agents

2. Evaluation of Infection in the Pre-Transplant Candidate
   a. Evaluation of Immunity to Infection
      i. History of Infections
      ii. Serologic Testing
      iii. Immunoglobulin Testing
      iv. Vaccinations
   b. Approach to Evaluation of Airway Colonization/Infection
      i. History of Infection
      ii. Diagnostic Modalities
         1. Computed Tomography
         2. Sputum vs BAL
         3. Use of Synergy and Multiple Antibiotic Sensitivity Testing
      iii. Specific Pathogens
         1. Gram Negative Bacteria
         2. Fungi
         3. Mycobacteria
         4. Burkholderia Cepacia
c. Evaluation for Non-Pulmonary Infections
   i. Hepatitis B and C
   ii. HIV

3. **Significance of Infections in the Donor**
   a. Diagnostic Approach
      i. History
      ii. Serologic Testing
      iii. BAL Gram Stain
   b. Impact of Donor Infections on Early Allograft Function
      i. Bacterial and fungal pathogens
      ii. Viral pathogens
         1. CMV
         2. EBV
         3. Community acquired viruses
   c. Impact of Donor Infections on Allograft Prophylaxis Strategies

4. **Impaired Physiologic Mechanisms in the Allograft and Impact on Infection**
   a. Donor-specific Mechanisms
      i. Neurogenic edema
      ii. Ischemic Injury
      iii. Reperfusion Injury
   b. Surgical Disruption of Normal Pathways of Innate Immunity
      i. Lymphatic Drainage
      ii. Atelectasis
      iii. Surfactant Depletion
      iv. Mucociliary Apparatus
      v. Airway Neural Denervation/ Loss of Cough Reflex

5. **Overview and Timeline of Infections Following Lung Transplantation**

6. **Diagnosis, Prophylaxis, and Management of Early Post-Transplant Infections**
   a. Overview
   b. Prophylaxis and Treatment of Bacterial Pneumonia
   c. Anti-Fungal Prophylaxis
   d. Utility of Inhaled Agents in the Post-Operative Period
   e. CMV Prophylaxis

7. **Diagnosis, Prophylaxis, and Management of Later Infections**
   a. Overview
   b. Bacterial Pneumonia
   c. Fungal Infections
   d. Community Acquired Viral Pneumonia
   e. CMV
   f. PCP
   g. Nocardiosis
   h. Atypical Mycobacteria (MAC, M. Abscessus, etc.)

8. **Non-Infectious Allograft Sequelae of Infectious Pathogens**
   a. EBV and the Development of PTLD
   b. CMV and the Development of BOS
   c. Community Acquired Respiratory Viruses and the Development of Acute Rejection and BOS
   d. Fungal and Bacterial Infections and Anastomotic Complications

9. **Immune Monitoring and Infection**
   a. IS Drug Levels
   b. Immune Function Assays
   c. Viral DNA
Selected References for the Diagnosis and Management of Infections Following Lung Transplantation:

Host Immune Response to Infection


Evaluation and Impact of Infection in the Lung Transplant Candidate


Evaluation and Impact of Infection in the Lung transplant Donor


Impaired Physiologic Mechanisms of Host Immunity Following Lung Transplantation


Diagnosis, Treatment, and Prophylaxis of Early and Late Infections Following Lung Transplantation


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ADDENDUM

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