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INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION  
(ISHLT)

**LUNG TRANSPLANTATION  
CORE COMPETENCY CURRICULUM**

**(ISHLT LTx CCC)**

**SECOND  
EDITION**

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THE EDUCATIONAL WORKFORCE OF THE  
ISHLT PULMONARY TRANSPLANTATION COUNCIL

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## INTRODUCTION

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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 updated version or second edition of 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,

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**Nice, France 2018**

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# I. INTRODUCTION TO LUNG TRANSPLANTATION: BACKGROUND AND ISHLT REGISTRY

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## 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. Chronic Lung Allograft Dysfunction

### 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:

- ISHLT Academy website: <http://www.isHLT.org/meetings/isHLTAcademy.asp>
- Overall Lung and Adult Lung Transplantation Statistics:  
<http://www.isHLT.org/registries/slides.asp?slides=heartLungRegistry>
- *The Journal For Heart & Lung Transplantation* Website: [www.jhltonline.org](http://www.jhltonline.org)
- Scientific Registry of the International Society for Heart and Lung Transplantation: Introduction to the 2005 Annual Reports: <https://www.srtr.org/reports-tools/srtroptn-annual-data-report>
- The Unified Transplant Network established by the United States Congress under the National Organ Transplant Act (NOTA) of 1984: <http://www.optn.org>
- Eurotransplant Website: [www.eurotransplant.nl](http://www.eurotransplant.nl)
- ONT-WHO Global Observatory on Donation and Transplantation (global database on donation and transplantation):  
<http://www.transplant-observatory.org/>

## Selected References for the Introduction to Lung Transplantation: Background and ISHLT Registry:

- ISHLT Monograph Volume 4: History of International Heart and Lung Transplantation. Published: March 2010 Editors: James K. Kirklind, MD, Mandeep Mehra, MD, and Lori J. West, MD, PhD
- Mendeloff EN. The history of pediatric heart and lung transplantation. *Pediatr Transplant*. 2002 Aug;6(4):270-9.

## II. EVALUATION AND MANAGEMENT OF THE LUNG TRANSPLANT CANDIDATE

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### 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
  - xiii. ECMO
- b. Disease specific listing considerations (including single or double LTx listing)
  - i. IPAH
  - ii. Emphysema
  - iii. CF
  - iv. IPF
  - v. Connective Tissue Disease
  - vi. Other

### 2. Transplant Candidate Evaluation and Ongoing Management

- a. Respiriologist / 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. Renal
  1. 24 hour Creatinine Clearance
  2. Abdominal Ultrasound
- vi. Health Care Screening
  1. Dental examination
  2. Colon - Stool guaiac or FIT test, Colonoscopy
  3. Skin – Full body skin exam
  4. Prostate – PSA
  5. Breast - Mammogram
  6. Cervical/Ovarian – PAP Smear, HPV testing
- vii. Laboratories and serology
  1. Basic labs: Comprehensive panel, CBC, 24 hour creatinine clearance
  2. Infectious Serology: EBV, CMV, HIV, Toxoplasma, RPR, Hepatitis A, B, C
  3. Blood typing x 2 and HLA
  4. HLA testing: PRA and possibly single antigen testing
  5. Others to consider: Quantiferon TB Gold testing, Urine Toxicology, Nicotine or Cotinine
- viii. Vaccines
  1. Hepatitis B
  2. Pneumococcal
  3. Influenza
  4. Tetanus and Pertussis
- ix. Additional referrals as necessary
  1. Cardiology
  2. Gastroenterology
    - a.  $\alpha$ 1-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:

- **A consensus document for the selection of lung transplant candidates: 2014—An update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2015; 34(1): 1-15: [http://www.jhltonline.org/article/S1053-2498\(14\)01181-4/fulltext](http://www.jhltonline.org/article/S1053-2498(14)01181-4/fulltext)**

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### III. LUNG ALLOGRAFT DONATION AND PROCUREMENT

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#### 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 events
- 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:**

- A Review of Lung Transplant Donor Acceptability Criteria (a consensus report of the ISHLT Pulmonary Council) <http://www.jhltonline.org/article/PIIS1053249803000962/fulltext>
- Primary Lung Graft Dysfunction Part III: Donor Related Risk Factors and Markers: <http://www.jhltonline.org/article/PIIS1053249805001348/fulltext>
- Donor Lung Procurement: <http://www.ctsnet.org/sections/clinicalresources/videos/media-81.html> (Cliff K. Choong, MD, Bryan F. Meyers, MD and G. Alexander Patterson, MD)
- Report of the Xenotransplantation Advisory Committee of the International Society for Heart and Lung Transplantation: the Present Status of Xenotransplantation and its Potential Role in the Treatment of End-Stage Cardiac and Pulmonary Diseases: [http://www.isHLT.org/PDF/pdf\\_xeno\\_guidelines.pdf](http://www.isHLT.org/PDF/pdf_xeno_guidelines.pdf)
- Organ donation information in Europe: <http://www.donoraction.org>
- U.S. government organ donation information site: <http://www.organdonor.gov>

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# LUNG TRANSPLANTATION: SURGICAL AND POST-OPERATIVE MANAGEMENT

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## 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
- g. 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

- a. Preoperative ECMO- VA vs VV. Criteria for listing and delisting, status 7.
- 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:

- <http://www.ctsnet.org/sections/clinicalresources/videos/media-90.html> (Cliff K. Choong, MD, Bryan F. Meyers, MD and G. Alexander Patterson, MD)
- <http://www.ctsnet.org/sections/clinicalresources/videos/media-80.html> (Cliff K. Choong, MD, Bryan F. Meyers, MD)

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- Split lung transplantation with intraoperative extracorporeal membrane oxygenation (ECMO) support: <http://mmcts.ctsnetjournals.org/cgi/content/abstract/2005/0809/mmcts.2004.000984> (Gabriel Mihai Marta, Clemens Aigner and Walter Klepetko)
- Primary Lung Graft Dysfunction Part I: Introduction and Methods: <http://www.jhltonline.org/article/PIIS1053249805001889/fulltext>
- Primary Lung Graft Dysfunction Part II: Definition. A Consensus Statement of the International Society for Heart and Lung Transplantation: <http://www.jhltonline.org/article/PIIS1053249804006527/fulltext>
- Primary Lung Graft Dysfunction Part III: Donor Related Risk Factors and Markers: <http://www.jhltonline.org/article/PIIS1053249805001348/fulltext>
- Primary Lung Graft Dysfunction Part IV: Recipient-Related Risk Factors and Markers: <http://www.jhltonline.org/article/PIIS1053249805001361/fulltext>
- Primary Lung Graft Dysfunction Part V: Predictors and Outcomes: <http://www.jhltonline.org/article/PIIS1053249804010526/fulltext>
- Primary Lung Graft Dysfunction Part VI: Treatment: <http://www.jhltonline.org/article/PIIS1053249805001956/fulltext>

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## IV. REJECTION AFTER LUNG TRANSPLANTATION, IMMUNOSUPPRESSION PROTOCOLS AND COMPLICATIONS

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### 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**

## 8. **The Sensitized Recipient**

- a. Screening: Types of screening pre-transplant
  - i. PRA
  - ii. V-PRA
  - iii. Single Antigen / antibody testing
- b. Management of the sensitized patient
  - i. Treatment and monitoring prior to transplantation
  - ii. Treatment and monitoring peri-operatively and post-transplant
- c. Risks

### **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.

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## **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. 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

Risk Factors

### **4. Chronic Lung Allograft Dysfunction (CLAD)**

- a. Update in our understanding of CLAD
- b. Obstructive CLAD: Bronchiolitis Obliterans
  - i. Clinical presentation
  - ii. Spirometric Diagnosis
  - iii. Pathologic diagnosis
  - iv. Radiographic findings
  - v. Grading (ISHLT guidelines)
  - vi. Prognosis
- c. Restrictive CLAD:
  - i. Clinical presentation
  - ii. Spirometric Findings
  - iii. Radiographic Findings
  - iv. Pathologic diagnosis
  - v. Prognosis
- d. Treatment Options
  - i. Photophoresis
  - 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)

### **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.

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- Nicod LP.** Mechanisms of airway obliteration after lung transplantation. . *Proc Am Thorac Soc.* 2006 (5):444-9.
- Christie et al:** The effect of primary graft dysfunction on survival after lung transplantation, *Am J Respir Crit Care Med* 2005;171:1312–1316
- Yates B et al.** Azithromycin reverses airflow obstruction in established bronchiolitis obliterans syndrome. *Am J Respir Crit Care Med* 15 2005;172:772–5.
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- Kumar, et al.** Clinical impact of community-acquired respiratory viruses on bronchiolitis obliterans after lung transplant. *Am J Transplant* 2005;5:2031–6.
- Sharples et al.** Risk factors for bronchiolitis obliterans: a systematic review of recent publications. *J Heart Lung Transplant* 2002;21:271–81.

## **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. Risks and Benefits
  - ii. Agents (For all agents: target, indication, dose, administration, adverse events, monitoring)
    1. Basiliximab (Anti-IL-2)
    2. Alemtuzumab (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 Cellular Rejection
    1. Augmentation of Maintenance Therapy
    2. Adjustment of Maintenance Therapy
  - ii. Chronic Lung Allograft Dysfunction
    1. Augmentation of Maintenance Therapy
    2. Adjustment of Maintenance Therapy
    3. Azithromycin
  - iii. Humoral Rejection
    1. Plasmapheresis
    2. IVIG
    3. Rituximab
    4. Bortezomib or Carfilzomib
- 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. Bortezomib or Carfilzomib

**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:

- Generic Drug Immunosuppression in Thoracic Transplantation: An ISHLT Educational Advisory: [https://www.isHLT.org/ContentDocuments/JHLT\\_July2009\\_Generic\\_Concensus\\_Statement.pdf](https://www.isHLT.org/ContentDocuments/JHLT_July2009_Generic_Concensus_Statement.pdf)

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- Hachem R** et al. A comparison of basiliximab and antithymocyte globulin as induction agents after lung transplantation. J Heart Lung Transplant 2005;24:1320–1326.
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- Diamond D** et al. Efficacy of total lymphoid irradiation for chronic allograft rejection following bilateral lung transplantation. Int J Radiat Oncol Biol Phys 1998;41:795–800.
- Slovic B** et al. . Photopheresis for chronic rejection of lung allografts. N Engl J Med 1995;332:962.
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- Glanville AR** et al. Mycophenolate Mofetil (MMF) vs Azathioprine (AZA) in lung transplantation for the prevention of Bronchiolitis Obliterans Syndrome (BOS): results of a 3 year international randomized trial. 2003;22(1):S207

## **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. Medication effect (including immunosuppression and antimicrobial therapies)
- c. Infection
- d. Treatment options

#### 2. **Anemia**

- a. Evaluation and Diagnostic Work up
- b. Medication effect / Drug Reaction( Immunosuppressive or antimicrobials)
- c. Infection
- d. Iron deficiency
- e. HUS
- f. Treatment options

#### 3. **Leukopenia or Leukocytosis**

- a. Evaluation and Diagnostic Work up
- b. Medication effect / Drug Reaction
- 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. Difficile

#### **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. Cholecystitis

**8. Pancreatitis**

- a. Infection
- b. Medication: Cyclosporine, Azithiprine, Prednisone

**9. GI Complications of Cystic Fibrosis Patients**

- a. DIOS
- b. Pancreatitis
- c. Cholecystitis
- d. Bowel obstruction

**10. Hepatic Toxicity Secondary to Medication**

**11. Hyperammonemia**

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

- Young LR**, Hadjiiladis D, Davis RD, Palmer SM. Lung transplantation exacerbates gastroesophageal reflux disease. *Chest* 2003;124:1689–1693.
- Gilljam M**, et al. GI complications after lung transplantation in patients with cystic fibrosis. *Chest* 2003;123:37–41.
- Paul S**. et al. Heart Lung Transplant. Gastrointestinal complications after lung transplantation 2009 May;28(5):475-9.
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- Robertson AG** et al. Lung transplantation, gastroesophageal reflux, and fundoplication. *Ann Thorac Surg.* 2010 Feb;89(2):653-
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- Morton JR** Distal intestinal obstruction syndrome (DIOS) in patients with cystic fibrosis after lung transplantation. *J Gastrointest Surg.* 2009 Aug;13(8):1448-53. Epub 2009 May 22.
- Corris PA**. Lung transplantation for cystic fibrosis. *Curr Opin Organ Transplant.* 2008 Oct;13(5):484-8.
- Bharat A et al**. Disseminated Ureaplasma infection as a cause of fatal hyperammonemia. *Science Translational Medicine* 2015;7(284):1-7

## V. Lung Transplantation Pathology

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### 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. Bronchioalveolar Lavage
- 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. Adenocarcinoma

### **Selected References for Lung Transplantation Pathology:**

**Stewart S**, Fishbein MC, Snell GI, et al. Revision of the 1996 working formulation for the standardization of nomenclature in the diagnosis of lung rejection. *J Heart Lung Transplant* 2007;26:129-1242.

**Michaels PJ**, Fishbein MC, Colvin RB. Humoral rejection of human organ transplants. *Springer Semin Immunopathol* 2003;25:119-140.

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**Levine DJ et al.** Antibody-mediated rejection of the lung: A consensus report of the ISHLT. *J Heart Lung Transplant* 2016;35:397-406

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## VI. DIAGNOSIS AND MANAGEMENT OF INFECTIONS FOLLOWING LUNG TRANSPLANTATION

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### 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 develop a strategy for recognizing the most common and most challenging bacterial, fungal, and viral pathogens that infect lung transplant recipients.
- 64) 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. Calcineurin 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. **Bacterial Infections**

- a. Prophylaxis and Treatment of Bacterial Pneumonia

### 7. **Atypical Mycobacterial Infections and Nocardia**

- a. Tuberculosis, including donor derived
- b. M. abscessus
- c. Mycobacterium avium
- d. Nocardia

### 8. **Fungal Infections**

- a. Anti-Fungal Prophylaxis
- b. Aspergillus
- c. Mucor / Rhizopus
- d. Scedosporium
- e. Endemic Fungal infections (Coccidioides, Histoplasma, etc.)

### 9. **Viral Infections**

- a. CMV
  - i. Prophylaxis vs. Pre-emptive therapy
  - ii. Disease Manifestations
  - iii. Resistant disease
  - iv. Implications
- b. Respiratory Viral Infections
  - v. RSV
  - vi. Others

## 10. 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

## 11. Immune Monitoring and Infection

- a. Immunosuppressive Drug Levels
- b. Viral DNA
  - i. EBV
  - ii. CMV

## Selected Hyperlinks:

- [The 2015 International Society for Heart and Lung Transplantation Guidelines for the management of fungal infections in mechanical circulatory support and cardiothoracic organ transplant recipients: Executive summary](http://www.jhltonline.org/article/S1053-2498(16)00054-1/pdf) (Guidelines) J Heart Lung Transplant Vol 35, No 3, March 2016: [http://www.jhltonline.org/article/S1053-2498\(16\)00054-1/pdf](http://www.jhltonline.org/article/S1053-2498(16)00054-1/pdf)
- [A 2010 Working Formulation for the Standardization of Definitions of Infections in Cardiothoracic Transplant Recipients](http://www.jhltonline.org/article/S1053-2498(11)00731-5/pdf) (Consensus Document) J Heart Lung Transplant 2011;30:361-374. [http://www.jhltonline.org/article/S1053-2498\(11\)00731-5/pdf](http://www.jhltonline.org/article/S1053-2498(11)00731-5/pdf)

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- De Vlamincck I**, Martin L, Kertesz M, Patel K, Kowarsky M, Strehl C, Cohen G, Luikart H, Neff NF, Okamoto J, Nicolls MR, Cornfield D, Weill D, Valantine H, Khush KK, Quake SR. Noninvasive monitoring of infection and rejection after lung transplantation. Proc Natl Acad Sci U S A. 2015 Oct 27;112(43):13336-41.
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## IV. MALIGNANCIES FOLLOWING LUNG TRANSPLANTATION

### Learning Objectives for Malignancies Following Lung Transplantation:

- 65) To review the high incidence of skin cancer and PTLD in lung transplant recipients.
- 66) To examine why lung transplant recipients are at increased risk for skin cancer and PTLD.
- 67) To discuss skin cancer surveillance and treatment approaches, including certain contraindications for lung transplant recipients.
- 68) To describe how to recognize, diagnose and treat pulmonary and extrapulmonary PTLD.
- 69) To recognize the complicated management of other malignancies that occur in lung transplant recipients, particularly lung cancer.
- 70) To recognize risk factors for malignancies and to develop screening strategies for at risk patients (especially GI malignancies in patients with Cystic Fibrosis and cervical / anal dysplasia in patients with HPV.)
- 71) To consider altered immunosuppression regimens as part of treatment plan for lung transplant patients with malignancies.

#### 1. Incidence of malignancy in lung transplant recipients

- a. Increased rates of Skin Cancer and PTLD
- b. Other Malignancies

#### 2. PTLD

- a. EBV
- b. Location – pulmonary vs. extrapulmonary

#### 3. Skin Cancer

- a. Risk factors (? Role of voriconazole)
- b. Surveillance protocols
- c. Staging
- d. Management

#### 4. Lung Cancer

- a. Incidental at time of transplant
- b. Transplant as therapy
- c. Management

#### 5. Other malignancies

- a. Risk Factors (CF for GI malignancies, ILD / emphysema for lung cancer)
- b. Donor derived malignancies
- c. Locations

#### 6. Cancer Screening in Lung Transplant Candidates

- a. Breast
- b. Lung
- c. Colon
- d. Prostate

#### 7. Modulation of Immunosuppression

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## V. MANAGEMENT OF METABOLIC COMPLICATIONS FOLLOWING LUNG TRANSPLANTATION

### Learning Objectives for Management of Metabolic Complications Following Lung Transplantation:

- 72) To examine the metabolic consequences of prolonged immunosuppression therapy.
- 73) To discuss optimal management of diabetes mellitus following solid organ transplantation.
- 74) To review transplant specific issues regarding management of hypertension.
- 75) To determine an appropriate diagnostic and therapeutic management strategy for steroid induced osteoporosis / osteopenia.

#### 1. Diabetes

- Role of post transplant immunosuppression medications
- Screening
- Therapy

#### 2. Hypertension

- Role of post transplant immunosuppression medications
- Goals of therapy
- Therapy: medical therapies to use or avoid

#### 3. Osteoporosis

- Diagnostic testing
- Therapeutic options- pharmacologic and non-pharmacologic therapies
- When to change or discontinue therapies

#### 4. Metabolic Syndrome in Lung Transplant Recipients

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## **VI. REPRODUCTIVE HEALTH AFTER LUNG TRANSPLANTATION**

### Learning Objectives for Reproductive Health After Lung Transplantation:

- 76) To describe the implications on fertility and pregnancy of lung transplantation.
- 77) To identify the risks to the transplant recipient, the organ and the fetus.
- 78) To determine the medical care considerations during pregnancy in a lung transplant recipient.
- 79) To acknowledge the current outcomes for pregnancies in lung and heart-lung transplant recipients.
- 80) To develop a strategy to increase awareness of family planning options for patients undergoing lung transplantation.
- 81) To be able to counsel lung transplant recipients on contraception with an understanding of potential contraindications.

#### **1. Reproductive implications**

- a. Fertility
- b. Egg Preservation

#### **2. Contraception**

- a. Options for Lung Transplant Recipients
- b. Important considerations / potential contraindications

#### **3. Pregnancy**

- a. Risks to Mother
- b. Risks to Fetus
- c. Obstetric management
- d. Pharmacologic implications for lung transplant recipients

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## ADDENDUM

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