



International Society for Heart and Lung Transplantation (ISHLT)

# **Lung Transplantation Core Competency Curriculum**

## **(ISHLT LTx CCC)**

Draft Document by

**The Educational Workforce of the  
ISHLT Pulmonary Council**

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**Minimum Experience Requirement**

**Selected references and resources**

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**Minimum Experience Requirement**  
**Selected references and resources**

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**Minimum Experience Requirement**  
**Selected references and resources**

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**Minimum Experience Requirement**  
**Selected references and resources**

## 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.**  
**March 2010**

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

((C H WIGFIELD MD))

## Learning Objectives

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

### 1. Background

Historical Context  
First Lung Transplants  
Advent of Immunosuppression

### 2. Outcomes in Lung Transplantation

Current expected survival rates  
Comparative survival  
Conditional survival after 1 year  
Outcomes dependent on native pulmonary disease process

### 3. Challenges in Lung Transplantation

Donor Scarcity  
Waiting List mortality  
Bronchiolitis Obliterans

### 4. Lung Transplantation Databases and ISHLT Registry

Data Access  
Statistics available  
Data submission

## **Selected hyperlinks for the Background to Lung Transplantation**

<http://www.ishlt.org/meetings/ishltAcademy.asp>

**Overall Lung and Adult Lung Transplantation Statistics**

**Pediatric Lung Transplantation Statistics**

**All Heart/Lung Transplantation Statistics**

<http://www.ishlt.org/registries/quarterlyDataReport.asp>

[www.jhltonline.org](http://www.jhltonline.org)

**Scientific Registry of the International Society for Heart and Lung Transplantation: Introduction to the 2005 Annual Reports**

<http://www.optn.org> (the unified transplant network established by the United States Congress under the National Organ Transplant Act (NOTA) of 1984)

[www.eurotransplant.nl](http://www.eurotransplant.nl)

<http://www.transplant-observatory.org/C18/National%20Transplant%20Organizati/default.aspx>  
(international data on transplantation and multiple links)

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

(K M CHAN MD)

### Learning Objectives

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. 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. 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. A1AT 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. A1AT deficiency (hepatology)
- b. CF (liver disease, DIOS etc)

**I. Special considerations including informed consent**

- i. Hepatitis B or C
- ii. HIV
- iii. Acceptance of high risk donor
- iv. Research participation

**m. Special considerations: high panel reactive antibody screen**

- i. Desensitization therapy
- ii. Prospective and retrospective crossmatching

**n. Urgent inpatient evaluation**

- i. Mechanical ventilation
- ii. ECMO
- iii. Deconditioning

**3. Lung Allocation Systems**

- a. United States
  - i. Lung Allocation Score
- b. Europe
  - i. Eurotransplant allocation
- c. UK
  - i. Lung allocation
- d. Australia
  - i. Lung Allocation
- e. Other Countries
  - i. Lung Allocation

### Minimum Experience Requirement:

(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.

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#### Candidate Selection:

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#### Urgent Transplant Evaluation:

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### Sensitized Patient:

- Colombo MB**, Haworth SE, Poli F, et al. Luminex technology for anti-HLA antibody screening: Evaluation of performance and of impact on laboratory routine. *Cytometry B Clin Cytom* 2007.
- Everly M**, Everly J, Susskind B, et al. Bortezomib provides effective therapy for antibody- and cell-mediated acute rejection. *Transplantation* 2008;86(12):1754-61.
- Fuggle SV**, Martin S. Tools for human leukocyte antigen antibody detection and their application to transplanting sensitized patients. *Transplantation* 2008;86(3):384-90.
- Hadjiiladis D**, Chaparro C, Reinsmoen NL, et al. Pre-transplant panel reactive antibody in lung transplant recipients is associated with significantly worse post-transplant survival in a multicenter study. *J Heart Lung Transplant* 2005;24(7 Suppl):S249-54.
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**Smits JM**, Vanhaecke J, Haverich A, et al. Waiting for a thoracic transplant in Eurotransplant. *Transpl Int* 2006;19(1):54-66.

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

**International Guidelines for the Selection of Lung Transplant Candidates: 2006 Update - A Consensus Report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation**

**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.**

**2009 ESC/ERS Guidelines on the Diagnosis and Treatment of Pulmonary Hypertension**

### III. LUNG ALLOGRAFT DONATION AND PROCUREMENT

(C H WIGFIELD MD)

#### Learning Objectives

- 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) To develop insight into possible donor management and allograft optimization
- 17) Develop a basic insight to 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 DDND)
- 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:
  - a Neuroendocrine Dysregulation,
  - b Permeability and Pulmonary Edema
  - c Airway, Pulmonary and Pleural Trauma,
  - d Aspiration Pneumonitis
  - e Respiratory Infections,
  - f Ventilation related Issues,
  
- vi. Modified Evaluation process:
  - a High Risk Donors
  - b Donor type related (DDND v DDND)
  - c 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 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).

### **Selected references for Lung Donation and Procurement:**

**Novitzky D**, Wicomb WN, Rose AG, Cooper DK, Reichart B. Pathophysiology of pulmonary edema following experimental brain death in the chacma baboon. *Ann Thorac Surg* 1987;43: 288–294.

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**Straznicka M**, Follette DM, Eisner MD, Roberts PF, Menza RL, Babcock WD. Aggressive management of lung donors classified as unacceptable: excellent recipient survival one year after transplantation. *J Thorac Cardiovasc Surg*. 2002;124:250-8.

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### **Selected hyperlinks for Lung Donation and Procurement:**

**A Review of Lung Transplant Donor Acceptability Criteria (a consensus report of the ISHLT Pulmonary Council)**

**Primary Lung Graft Dysfunction Part III: Donor Related Risk Factors and Markers**

**Donor Lung Procurement** 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**

[www.donoraction.org](http://www.donoraction.org) (organ donation information in Europe)

[www.organdonor.gov](http://www.organdonor.gov) (U.S. government organ donation information site)

## IV. LUNG TRANSPLANTATION: SURGICAL AND POST -OPERATIVE MANAGEMENT

(DAVID MASON MD)

### Learning Objectives

- 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

#### **a Immediate Post Transplant Management**

1. Surgical Complications of Lung Transplant
2. Medical Complications post Lung Transplantation
3. Prophylactic Regimen (antibiotics, anti-fungal and anti-viral)

#### **b Surgical Conduct**

Size matching between donor and recipient

Single versus double lung transplant

Coordinating the timing of surgery

Technical aspects of pneumonectomy

Choice of incision- median sternotomy, bilateral anterior thoracotomy, clamshell, anterior vs posterolateral thoracotomy

Use of cardiopulmonary bypass and intraoperative ECMO- disease

specific, PAH Anastomotic techniques- running, interrupted, suture choice

**c Postoperative Complications**

Graft dysfunction- differential diagnosis and treatment (NO)

Anastomotic

Airway- dehiscence, stenosis, bronchovascular fistula, stents

Vascular- pulmonary vein and artery stenosis

Pleural – acute and chronic effusions; empyema

Renal Failure – prevention and treatment

**d Special Considerations**

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

Postoperative ECMO- separation/weaning

Combined cardiac surgery and lung transplantation. Stents vs CABG

**Minimum Experience Requirement:**

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 references for Lung Transplantation: Surgical and Post -Operative Management**

TBC

### **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 and G. Alexander Patterson, MD

**<http://mmcts.ctsnetjournals.org/cgi/content/abstract/2005/0809/mmcts.2004.000984>**

Split lung transplantation with intraoperative extracorporeal membrane oxygenation (ECMO) support  
Gabriel Mihai Marta, Clemens Aigner and Walter Klepetko

**Primary Lung Graft Dysfunction Part I: Introduction and Methods**

**Primary Lung Graft Dysfunction Part II: Definition. A Consensus Statement of the International Society for Heart and Lung Transplantation**

**Primary Lung Graft Dysfunction Part III: Donor Related Risk Factors and Markers**

**Primary Lung Graft Dysfunction Part IV: Recipient-Related Risk Factors and Markers**

**Primary Lung Graft Dysfunction Part V: Predictors and Outcomes**

**Primary Lung Graft Dysfunction Part VI: Treatment**

## V. IMMUNOLOGY AND REJECTION AFTER LUNG TRANSPLANTATION AND IMMUNOSUPPRESSION PROTOCOLS

(D J LEVINE MD)

### 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

### Immunologic Concepts in Lung Transplantation

#### A. Definitions

#### B. Normal Immune Response

- 1. Innate vs Adaptive Immune System
- 2. Molecules and cells of the immune system
  - T cells
  - B cells
  - NK cells

#### 3. Response to foreign antigen

#### C. Immune response to allograft

- 1. Mechanism of allorecognition
- 2. Humoral vs Cellular Rejection
- 3. Proposed mechanism of each type of allograft rejection:
  - a. Hyperacute rejection
  - b. Acute rejection
  - c. Chronic rejection
  - d. Humoral rejection

#### D. Tolerance

- Definition
- Mechanisms
- Clinical Implications

#### E. Immunogenetics

1. ABO Blood System
  2. Major Histocompatibility Complex I and II
    - A. HLA Nomenclature and HLA genetics
    - B. Causes of HLA-specific alloimmunization
    - C. HLA Antigen Matching in Lung Transplantation
  3. Methods used to detect anti-HLA antibodies
    - A. Calculated PRA (c-PRA), Virtual Crossmatch
    - B. Detection of presence of anti-HLA antibodies
    - C. Panel reactive antibodies
    - D. Complement Dependent Cytotoxicity (CDC)
    - E. Flow Cytometry
    - G. Solid Phase Assays
      1. Luminex
      2. Flow Cytometry
      3. ELISA
    - H. Screening strategies
- F. Non-HLA Antigens
- G. Clinical applications of transplant immunology and typing

### Experience Requirement:

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

### Literature Review for Transplant Immunology

- Hale, D.** Surg Clin N Am 86 (2006) 1103-1125.
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- Fuggle SV et al.** Tools for Human Leukocyte Antigen Antibody Detection and Their Application to Transplanting Sensitized Patients. Transplantation: 2008; 86: 384-390.
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## Rejection in the Lung Transplant Recipient

1. Hyperacute Rejection
  - A. Definition
  - B. Mechanism
  - C. Pathology
  - C. Treatment
2. Acute Cellular Rejection
  - A. Definition-(ISHLT guidelines)
  - C. Detection, Evaluation and Diagnosis
    - a. Surveillance bronchoscopy
      1. Pros and Cons
      2. Table of possible surveillance schedules
    - b. Monitoring
      1. Spirometry
      2. Clinical status
      3. Bronchoscopy
      4. Radiographic changes
  - D. Grading of acute cellular rejection
    - a. ISHLT Pathologic grading
  - E. Type of ACR
    - a. Recurrent
    - b. Refractory
    - c. Lymphocytic bronchiolitis
  - F. Treatment Options
    - a. Modified immunosuppression regimen
      1. Steroid pulse and taper
      2. Change calcineurin inhibitor
      3. Alemtuzumab, antithymocyte globulin, ECP,
      4. Others
  - G. Outcomes
  - H. Clinical Implications
  - I. Risk Factors
3. Bronchiolitis Obliterans Syndrome (Chronic Rejection)
  - A. Definition (ISHLT guidelines)
  - B. Evaluation and Diagnosis
    1. Spirometric Diagnosis
    2. Pathologic diagnosis
    3. Radiographic findings
    4. Clinical findings
    5. Grading (ISHLT guidelines)
  - C. Monitoring

- D. Treatment Options
  1. Photophoresis
  2. Azithromycin
  3. Augment or change immunosuppression
  4. Re-transplantation

- E. Risk Factors
  1. Acute cellular rejection (ACR)
  2. Lymphocytic bronchitis/bronchiolitis (LB)
  3. Organizing pneumonia
  4. HLA mismatch
  5. GERD
  6. CMV/respiratory viruses
  7. Primary Graft Dysfunction (PGD)

### **1. Humoral or Antibody-Mediated Rejection**

- A. Definition
- B. Evaluation, Screening and Diagnosis
  - a. Serologic
  - b. Pathologic
  - c. Immunologic
- C. Monitoring
  1. Donor specific antibodies
  2. C4d monitoring
- D. Treatment Options
- E. Outcomes
- F. Risk Factors

### **2. The Sensitized Recipient**

- A. Screening
  1. Types of screening pre-transplant
    - i. PRA
    - ii. V-PRA
  2. Issues of the sensitized patient
  3. Treatment and monitoring prior to transplantation
  4. Treatment and monitoring peri-operatively and post transplant
  5. Risks

### **Learning objectives of 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

### **Experience Requirement for Rejection in the Lung Transplant Recipient**

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

## Literature Review for Lung Transplant Rejection

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- Nicod**, Mechanisms of airway obliteration after lung transplantation, *Proc Am Thorac Soc* 3 (2006): 444–449
- Christie et al**: The effect of primary graft dysfunction on survival after lung transplantation, *Am J Respir Crit Care Med* 171 (2005), pp. 1312–1316
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- Sharples et al**. Risk factors for bronchiolitis obliterans: a systematic review of recent publications. *J Heart Lung Transplant* 2002;21:271–81. Azithromycin reverses airflow obstruction in established bronchiolitis obliterans syndrome. *Am J Respir Crit Care Med* 15 2005;172:772–5.
- Davis RD** et al. Improved lung allograft function after fundoplication in patients with gastroesophageal reflux disease undergoing lung transplantation. *J Thorac Cardiovasc Surg* 2003;125:533–42.
- Sandrini A** et al. The controversial role of surveillance bronchoscopy after lung transplantation. *Curr Opin Organ Transplant*. 2009 Oct;14(5):494-8.
- Belperio JA** et al. Bronchiolitis obliterans syndrome complicating lung or heart-lung transplantation. *Semin Respir Crit Care Med* 2003;24:499–530.

## Immunosuppression for Lung Transplantation

### Learning Objectives for Immunosuppression 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

- I. Overview of Immunosuppressive Agents
- II. 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
    - a. Pro versus con of induction
    - b. Risks and Benefits
    - c. Agents (For all agents: target, indication, dose, administration, adverse events, monitoring)
      - i. Similect (Basiliximab)
      - ii. Campath (Anti CD-52)
      - iii. Thymoglobulin (rATG)
      - iv. OKT3 (anti-Cd-3)
  - F. Maintenance
    - a. Triple Agent Immunosuppression Regimen

- b. Corticosteroids
  - i. Mechanism of action
  - ii. Pharmacokinetics, dosing and drug monitoring
  - iii. Side effects
  - iv. Drug-drug interactions
- c. Calcineurin Inhibitors  
(Cyclosporine and Tacrolimus)
  - i. Mechanism of action
  - ii. Pharmacokinetics, dosing and drug monitoring
  - iii. Side effects
  - iv. Drug-drug interactions
- d. Anti-proliferative agents  
(Azathioprine and Mycophenolic acid (MMF))
  - i. Mechanism of action
  - ii. Pharmacokinetics, dosing and drug monitoring
  - iii. Side effects
  - iv. Drug-drug interactions
- e. TOR inhibitors  
(Sirolimus and Everolimus)
  - i. Mechanism of action
  - ii. Pharmacokinetics, dosing and drug monitoring
  - iii. Side effects
  - iv. Drug-drug interactions

## G. Rejection

- a. Acute Rejection
  - i. Augmentation of Maintenance Therapy
  - ii. Adjustment of Maintenance Therapy
- b. Chronic Rejection (BOS)
  - i. Augmentation of Maintenance Therapy
  - ii. Adjustment of Maintenance Therapy
  - iii. Azithromycin
- c. Humoral Rejection
  - i. Plasmapheresis
  - ii. IVIG
  - iii. Rituximab
  - iv. Velcade

## H. Trends and Issues in Immunosuppression

### I. Salvage Therapy for Chronic Rejection

- a. Total lymphoid Irradiation (TLI)
- b. Extracorporeal Photopheresis (ECP)

- J. Desensitization
  - i. Plasmapheresis
  - ii. IVIG
  - iii. Rituximab
  - iv. Velcade

## Experience Required for Immunosuppression post Lung Transplantation.

1. Treat 15 patients with immunosuppression post lung transplant and adjust changes and following for side effects or drug drug interactions.

## Literature Review of Immunosuppressants post lung transplantation.

- Taylor A.** Immunosuppressive agents in solid organ transplantation.;Critical Reviews in Oncology/Hematology 56 (2005) 23–46.
- Hallora PF.** Immunosuppressive Drugs for Kidney Transplantation.,N Engl J Med 2004;351:2715-29.
- Bhorade S** et al. Immunosuppression for Lung Transplantation Proc Am Thorac Soc Vol 6. pp 47–53, 2009
- McNeil K** et al. . Comparison of mycophenolate mofetil and azathioprine for prevention of bronchiolitis obliterans syndrome in de novo lung transplant recipients. Transplantation 2006;81:998–1003
- Ailawadi G** et al. Effects of induction immunosuppression regimen on acute rejection, bronchiolitis obliterans, and survival after lung transplantation. J Thorac Cardiovasc Surg 2008;135:594–602.
- 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.
- Burton et al.** . The incidence of acute cellular rejection after lung transplantation: a comparative study of antithymocyte globulin and daclizumab. J Heart Lung Transplant 2006;25: 638–647.
- 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.
- Slovits B** et al. . Photopheresis for chronic rejection of lung allografts. N Engl J Med 1995;332:962.
- Salerno C** et al. Adjuvant treatment of refractory lung transplant rejection with extracorporeal photopheresis. J Thorac Cardiovasc Surg 1999;117:1063–1069.
- Villanueva J**, Bhorade SM, Robinson JA, Husain AN, Garrity ER Jr. Extracorporeal photopheresis for the treatment of lung allograft rejection. Ann Transplant 2000;5:44–47.

**Hyperlinks:**

- [Generic Drug Immunosuppression in Thoracic Transplantation: An ISHLT Educational Advisory \(pdf\)](#)

**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. Immuosuppressive
  - 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

### **Experience Requirements for Hematologic Disorders post lung transplantation**

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

## Non-Pulmonary Medical Complications and Issue Post Lung Transplantation

### I. 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

#### A. Frequent Problems and their possible etiologies

- 1. Nausea/Vomiting
  - a. Medications
  - b. Infection
  - c. Gastroparesis/delayed gastric emptying
  - d. Small bowel obstruction or ileus
  - e. GERD
- 2. Diarrhea
  - a. Medications
  - b. Infection: C.difficile, protozoa, viral, bacterial
  - c. CMV Colitis
  - d. Ischemic Colitis
  - e. Prior co-morbidities
- 3. Abdominal Pain

#### B. Colonic Issues

- 1. Bowel Perforation : multiple risks and etiologies
- 2. Diverticulitis/diverticulosis
- 3. PTLD/Malignancy
- 4. Colitis (viral, fungal or ischemic)
- 5. Pseudo-membranous colitis and C. Diff

C. Small bowel obstruction

- a. Gastroparesis
- b. PTLD
- c. Constipation

D. Upper Gastrointestinal Issues

1. Gastroparesis
2. Esophagitis
3. PUD
4. GERD

E. GERD and BOS

F. GI Bleed

1. Peptic Ulcer Disease
2. Esophagitis
  - a. Candidiasis or fungal
  - b. Malignancy
  - c. CMV or viral

G. Biliary Disease

1. Cholelithiasis pre-transplant
  - a. Timing for cholecystectomy
2. Cholecystitis

H. Pancreatitis

1. Infection
2. Medication: Cyclosporine, Azithiprine, Prednisone

I. GI Complications of Cystic Fibrosis Patients

1. DIOS
2. Pancreatitis
3. Cholecystitis
4. Bowel obstruction

J. Hepatic toxicity secondary to medication.

K. Hyperammonemia

## References Gastrointestinal Issues Post Lung Transplantation

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## **VI. LUNG TRANSPLANTATION PATHOLOGY** (G BERRY MD)

### **Learning Objectives**

- 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. Bronchioloalveolar 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. Lymphangiomyomatosis (LAM)
- c. Diffuse Panbronchiolitis
- d. Giant Cell Interstitial Pneumonia (GIP)
- e. Desquamative Interstitial Pneumonia (DIP)
- f. Langerhans-Cell Histiocytosis
- g. Bronchioloalveolar Carcinoma

**Minimum Experience Requirement:**

TBC

### **Selected references for Lung Transplant Pathology**

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**Wallace WD**, Reed EF, Ross D, et al. C4d staining of pulmonary allograft biopsies: an immunohistochemical study. J Heart Lung Transplant 2005;24:1565-1570.

**Revision of the 1990 Working Formulation for the Classification of Pulmonary Allograft Rejection: Lung Rejection Study Group.**

### **Selected hyperlinks for Lung Transplant Pathology**

TBC

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

(T L ASTOR MD)

### Learning Objectives

- 58) To define the cell populations and humoral/ complement components integral to the host immune response to infection.
- 59) To highlight the specific components of innate and alloimmunity unique to the response to infection in the lung.
- 60) To list the aspects of the host immune response specific to viruses, bacteria, fungi, and parasites.
- 61) To understand the impact of corticosteroids, calcineurin inhibitors, cell cycle inhibitors, and T-cell depleting agents on specific components of the host immune response to infection in the lung allograft.
- 62) To outline the appropriate methods for evaluating the lung transplant candidate's immunity to infection.
- 63) To describe the comprehensive approach to evaluating pulmonary and non-pulmonary infections in the lung transplant candidate.
- 64) To discuss the significance and evaluation of infections in the lung donor.
- 65) 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.
- 66) To describe the timeline, diagnostic methods, prophylaxis, and management of specific early and late post-transplant infections.
- 67) To list the potential non-infectious allograft sequelae resulting from infectious pathogens.
- 68) To discuss the utility of immunosuppressive drug levels, immune function assays, and viral DNA measurements in assessing the lung transplant candidate's susceptibility to infections.

### **3 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

### **4 Evaluation of Infection in the Pre-Transplant Candidate**

- e. Evaluation of Immunity to Infection
  - i. History of Infections

- ii. Serologic Testing
  - iii. Immunoglobulin Testing
  - iv. Vaccinations
- f. 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
- g. Evaluation for Non-Pulmonary Infections
- i. Hepatitis B and C
  - ii. HIV

## **5 Significance of Infections in the Donor**

- h. Diagnostic Approach
- i. History
  - ii. Serologic Testing
  - iii. BAL Gram Stain

- i. Impact of Donor Infections on Early Allograft Function
  - i. Bacterial and fungal pathogens
  - ii. Viral pathogens
    - 1. CMV
    - 2. EBV
    - 3. Community acquired viruses
- j. Impact of Donor Infections on Allograft Prophylaxis Strategies

## **6 Impaired Physiologic Mechanisms in the Allograft and Impact on Infection**

- k. Donor-specific Mechanisms
  - i. Neurogenic edema
  - ii. Ischemic Injury
  - iii. Reperfusion Injury
- l. 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

## **7 Overview and Timeline of Infections Following Lung Transplantation**

## **8 Diagnosis, Prophylaxis, and Management of Early Post-Transplant Infections**

- m. Overview
- n. Prophylaxis and Treatment of Bacterial Pneumonia
- o. Anti-Fungal Prophylaxis
- p. Utility of Inhaled Agents in the Post-Operative Period
- q. CMV Prophylaxis

## **9 Diagnosis, Prophylaxis, and Management of Later Infections**

- r. Overview
- s. Bacterial Pneumonia
- t. Fungal Infections
- u. Community Acquired Viral Pneumonia
- v. CMV
- w. PCP
- x. Nocardiosis
- y. Atypical Mycobacteria (MAC, M. Abscessus, etc.)

## **10 Non-Infectious Allograft Sequelae of Infectious Pathogens**

- z. EBV and the Development of PTLD
- aa. CMV and the Development of BOS
- bb. Community Acquired Respiratory Viruses and the Development of Acute Rejection and BOS
- cc. Fungal and Bacterial Infections and Anastomotic Complications

## **11 Immune Monitoring and Infection**

dd. IS Drug Levels

ee. Immune Function Assays

ff. Viral DNA

i. EBV

ii. CMV

### **Minimum Experience Requirement:**

TBC

### **Selected references for the Diagnosis and Management of Infections Following Lung Transplantation**

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**Selected hyperlinks for the Diagnosis and Management of Infections Following Lung Transplantation**

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**ADDENDUM**

1<sup>st</sup> Edition date

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Thanks and

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