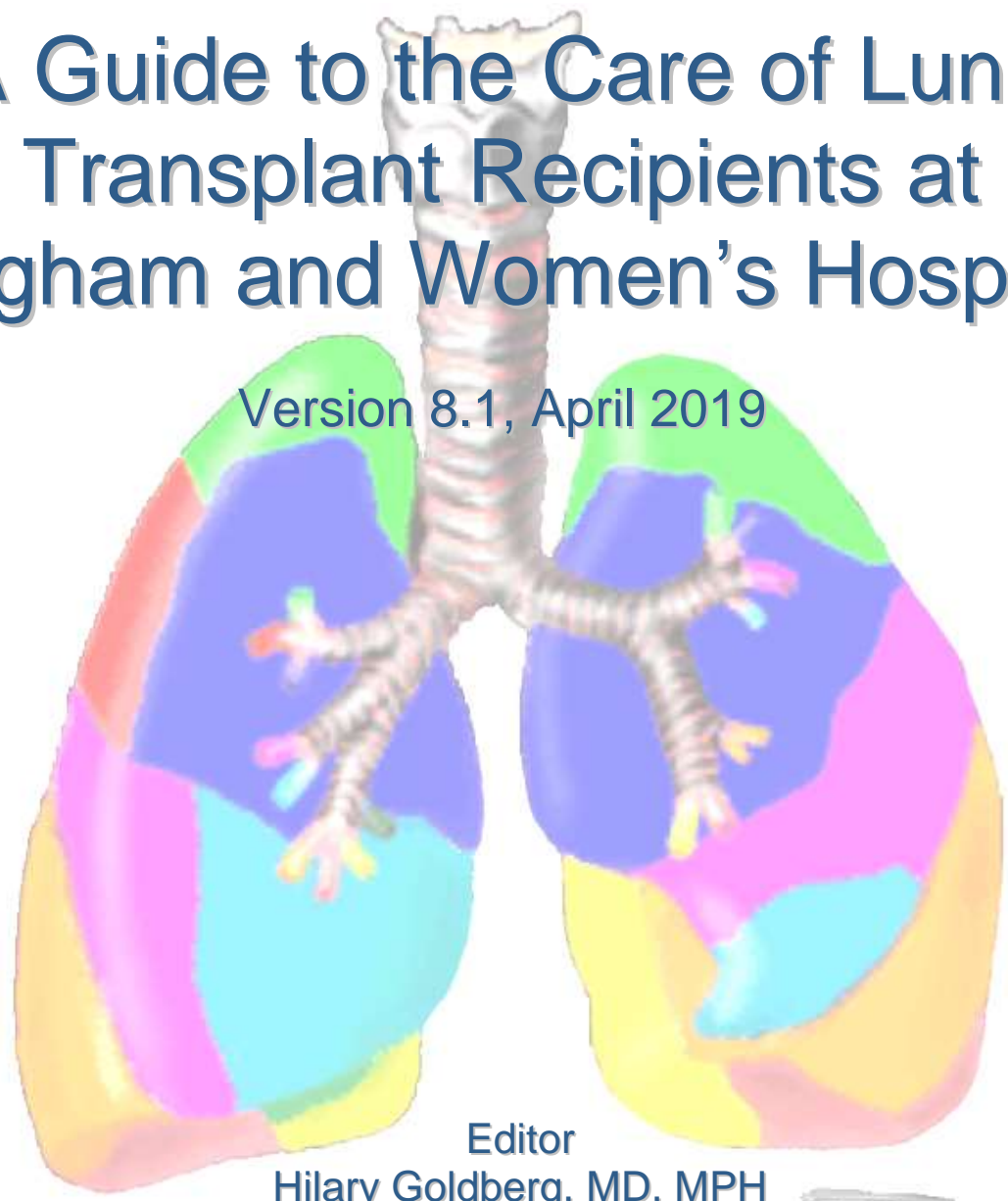


A Guide to the Care of Lung Transplant Recipients at Brigham and Women's Hospital



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Table of Contents

Section 1: Trainee Responsibilities.....	1
Pulmonary Fellow – Outpatient	3
Thoracic Resident – Inpatient	5
Section 2: Pre-operative Evaluation of Transplant Candidates.....	7
Criteria for Referral	7
Initial Consultation	10
Inpatient Evaluation	16
Choice of Procedure	18
Overview of Lung Allocation Score and Lung Offers	19
Survival Statistics.....	20
Section 3: Initial Post-operative Issues.....	21
Fluid Management	23
Implantation Response	24
Mechanical Ventilation.....	26
Post-op Surgical Concerns: Bleeding, Air Leaks, Venous Obstruction, and Bypass.....	27
Diet and Initiating Oral Intake.....	29
Sedation and Analgesia.....	30
Section 4: Bronchoscopy and Airway Management	31
Difficult Bronchoscopies.....	32
Bronchoscopies Outside of the Endoscopy Suite or OR	33
Section 5: Immune Suppression	34
General Overview	34
Induction Immunosuppression	34
Maintenance Immunosuppression	35
Maintenance Immunosuppression	35
Section 6: Infectious Disease Concerns in Transplant.....	36
Pre-transplant Evaluation.....	36
Initial Post-operative Antimicrobial Therapy	38
Post-Transplant Infection Prophylaxis.....	38
Adjustments in Prophylaxis During Episodes of Rejection	41
Common Post-transplant Infections	41
Section 7: Approach to Deteriorating Lung Function	46
General Approach.....	46
Rejection.....	47
Airway Stricture.....	55
Infection.....	56
Native Lung Hyperinflation (Single Lung Transplant Emphysema Patients)	57
Aspiration / GERD	57
Section 8: Long Term Medical Management of Lung Transplant Recipients.....	58
Bone Health.....	58
Hypercholesterolemia	60
Diabetes Mellitus	60
Hypertension	61
Commonly Used Antihypertensives Post Transplant.....	62
Lung Transplant Hypertension Protocol Flowchart.....	63
Gastrointestinal Issues.....	64
Renal Failure	64

Hematological Concerns.....	66
Skin Cancer	69
Section 9: Disease-Specific Management Issues.....	70
Cystic Fibrosis	70
Interstitial Lung Disease.....	73
Lung Transplant for Alpha-1 Antitrypsin Deficiency (AATD)	74
Section 10: Living Lobar and Repeat Lung Transplantation	75
Living Lobar Transplantation.....	75
Repeat Lung Transplantation.....	75
Section 11: Appendices	76
A. Short Telomere Syndrome.....	76
B. Algorithm for Hepatology Evaluation.....	76
C. Pulmonary Hypertension / Right Heart Dysfunction	77
D. Scleroderma.....	78
E. History of Melanoma.....	78
F. DCIS.....	79
G. HIV.....	79
H. Medically Prescribed Marijuana.....	80
I. Height-Weight Tables	81
J. Interpretation of Donor Hepatitis Serologies.....	82
K. Transplant Candidates and Donors with Evidence of Viral Hepatitis Exposure	83
L. Increased Risk Donor Protocol	84
M. Donor CSF Analysis for Meningitis.....	86
N. Prevention of Venous Thromboembolism.....	86
O. Drug Summary.....	87
P. Post-transplant Induction/Prophylaxis Summary.....	91
Q. Steroid Taper	93
R. Lovenox Dosing	94
S. Pancreatic Enzyme Replacement.....	95
T. Leukopenia Algorithm	97
U. ImmuKnow Protocol	98
V. CNI Management Protocol	99
W. Management of Desensitization and Antibody Mediated Rejection.....	101
X. Campath Rejection Protocol	105
Y. ECP (Photopheresis) Protocol.....	107
Z. Nissen Protocol	108
AA. BWH Bone Health Protocol	109
AB. IVIG Replacement Therapy.....	110
AC. Pneumococcal Protection Strategy	110
AD. Antiplatelet/Anticoagulants.....	111
AE. Gabapentin for Chronic Refractory Cough Dose Titration and Renal Adjustments	112

Section 1: Trainee Responsibilities

Pulmonary Fellow – Inpatient

Patient Population

- Post-transplant patients admitted to the medical or surgical services
- Pre-transplant patients on the transplant list admitted to the medical service
- Thoracic surgery consult patients at the discretion of the attending
- Non-transplant pulmonary patients at the discretion of the attending

Duties

- Daily Rounds: rounding with the transplant team daily (location variable –depending on patient location). Rounds begin at 7:30 AM on Monday, Tuesday, Wednesday and Friday, and at 9 AM on Thursday. Afternoon multi-disciplinary table top rounds occur every day at 1:30 PM on 3A.
- The transplant fellow will be responsible for running rounds and formulating a treatment plan in consultation with the attending. This requires a detailed knowledge of the active issues on each patient: recent events, culture results, recent biopsy results, consultation from the previous day.
- PA's are primarily responsible for the management of lung transplant recipients during their index hospital stay for transplant after transfer from ICU and when subsequently readmitted with medical diagnoses after their transplants. PA's perform the same functions as house-staff, including provision of primary coverage for their patients, order entry, communication with consultants, and documentation. As with house-staff, the level of supervision required by PA's is variable, and fellows are responsible for education and supervision of the PA's on the transplant service in consultation with the attending.
- Depending upon the diagnosis, the level of patient acuity and the PA census, some patients may also be admitted to house-staff teams. In this case fellows are responsible for communicating with the medical and surgical housestaff/PA when patients are on those services.
- Consultations: fellows are responsible for providing primary consultative services for patients admitted to the thoracic (e.g. – newly transplanted patients) or other services.
- Admissions: fellows are responsible for completing a full evaluation of all new admissions and formally presenting the patients to the on-service attending. If the admission is planned to occur late in the day, a preliminary management plan may be formulated prior to arrival and formal presentation delayed until the following day, at the discretion of the on-service attending. Fellows are responsible for written admission notes for patients admitted to services other than the PA service, such as the Thoracic ICU, thoracic floor service, and medical housestaff service, at the discretion of the on-service attending.

- Written progress notes: fellows may be responsible for written progress notes for patients admitted to services other than the medical PA or housestaff service, at the discretion of the on-service attending, and are expected to be fully familiar with ongoing issues and changes and to lead the daily care plan, under the supervision of the on service attending, for all patients on the service.
- At the discretion of the on-service attending, fellows may be responsible for evaluating thoracic surgery consultations on the day of request, for presentation to the transplant attending, writing a formal consult note with the attending, and discussing the suggestions with the thoracic surgical team.
- Performing bronchoscopies with the transplant attending on patients either in the ICU or in the bronchoscopy suite; fellows are also encouraged to participate in all OR cases with our surgical staff and if free should plan on performing routine airway procedures in that setting.
- Arranging for attending-level review of special studies such as pathology results and radiology findings.
- Evaluation of Lung Transplant Recipients: the thoracic service performs the initial emergency room assessment of listed patients called in for lung transplantation. The pulmonary fellow is encouraged to participate in this assessment and to observe the transplant surgery in the operating room. Fellows will be expected to scrub in for one transplant operation during their rotation. If more than one transplant is performed during a rotation, they are welcome to scrub in for additional procedures if interested. Fellows are welcome to participate in donor procurement runs as well.
- The pulmonary fellow is expected to perform an in-house assessment of the recipient immediately post-surgery on 11C and to communicate the findings to the on-service attending. This assessment includes writing an admission note, review of acute medical issues related to the transplant, as well as communication with the ICU team regarding immune suppression and antibiotic prophylaxis recommendations. Depending on the level of stability of the recipient post-operatively, this evaluation may be deferred until the next morning at the discretion of the on-service attending.
- Patients are regularly admitted to the thoracic surgery service as part of their evaluation for candidacy for transplant. The transplant fellow is not responsible for these patients, unless otherwise specified by the on-service attending.

Conferences

- Participating in weekly Thursday morning transplant meeting held from 7:30 – 9 AM in the Ingram Library in the Pulmonary Division. ****Please note – Pulmonary Fellows' Conference takes precedence over the Thursday morning transplant conference.**** In general, you should attend the Fellows' Conference on Thursday mornings from 7-7:45 AM.
- Fellows are expected to present current cases at Thursday afternoon Radiology/Pathology Conference as appropriate.

Pulmonary Fellow – Outpatient

Patient Population

- Post-transplant patients (including heart-lung).
- New patients presenting for initial transplant consultation as available.

Duties

- Participation in Wednesday morning post-transplant clinic that starts at 8:00 AM. Dependent upon the inpatient census, the fellow should arrive at clinic between 8-9 am. The fellow performs independent evaluations of patients, and presents each case to one of the transplant attendings in clinic. He/she is responsible for writing a note on each patient seen.
- Performing outpatient consults for the thoracic surgery service in conjunction with the transplant service attending as needed.
- Answering outpatient calls from patients as needed and discussing relevant issues with the transplant attending.
- ED evaluation of lung transplant patients. All transplant patients presenting to the emergency room should be seen by the transplant fellow and evaluated. The case should then be presented to the attending on call and a decision made regarding need for admission. If the patient is to be admitted, the fellow is responsible for developing a management plan with the attending, and communicating with the PA or house-staff. The attending physician of record is the transplant attending. Patients not requiring admission should have a written note outlining the management plan and clinic follow up.

Procedures

- Bronchoscopies:
 - Surveillance bronchoscopies with transbronchial biopsies on post transplant patients performed at 1,3 6, and 12 months and thereafter when clinically indicated.
 - Special procedures – bronchial balloon dilation, stenting, chest tube placements, rigid bronchoscopies, central lines, arterial lines, may be performed in conjunction with the surgical or anesthesia services under supervision.

Pulmonary Fellow – Weekend Coverage

Rounding

Transplant-specific rounds generally start at 7:30 AM (Saturday and Sunday). The pulmonary fellow and transplant attending will round together on the patients not admitted to the medical PA service. Based upon transplant/consult census, a determination will be made by the transplant attending as to whether the fellow should participate in rounds with the medical PA. You should check with the attendings on call to verify the time for morning rounds. You are not responsible for lung offers → *these calls should go to the Thoracic Surgery attending on call.*

Procedures

Weekend bronchoscopies can be performed on the floor if deemed essential. In this case it is the fellow's responsibility to assist the attending. Special issues on the weekend include contacting the Conscious Sedation Service (BB 31469).

Special Days

- Mondays 4:00pm: fellows should attend pulmonary conference and every effort will be made to ensure fellows are free to attend this conference.
- Wednesdays ~9:00am: Post- Transplant clinic. You can use the Epic template for notes if you have access, or copy the old note from Epic and edit it.
- Thursdays: 7:30 am Transplant Listing Meeting. Has breakfast. May be asked to present a patient that you have seen for discussion. – Fellows' conference takes precedence, join listing meeting after fellows' conference is complete.
- Thursdays 12:00: Pulmonary case conference

Thoracic Fellow / Resident – Emergency Dept

Pre-operative Emergency Department Evaluation

Overview:

All calls from the New England Organ Bank regarding potential donor organs are referred to the attending transplant thoracic surgeon on call. Working with the attending transplant pulmonologist, they will screen all potential transplant recipients on the active list. Based on blood group and size, they will select the recipients to notify. The thoracic fellow/resident takes primary responsibility for evaluating potential recipients on presentation to the ED.

Approach to the pre-operative evaluation:

- Our donor coordination service, called "Buckeye," will notify the ED and inform the triage nurse of the patient's anticipated arrival. A computer "expect note" is entered including the requested labs and testing to be performed in the ED.
- The following pre-op labs and tests should be obtained including SMA-20, CBC, PT, PTT, U/A, CXR, EKG, Type and Cross for 4 units. The Thoracic fellow or surgical senior will obtain OR consent from patient. **A separate "Increased Risk Consent" form must be completed if the donor has been designated as increased risk by UNOS, the OPO, or our program.**
- Perform history and physical exam; the admit note should specifically include:
 - Patient's blood type—confirmed from BICS
 - Recommended transplant operation; single, bilateral, single preferred vs. only **and reason why** (V/Q distribution, previous surgery, scarring, nodules, etc.), and if bypass will likely be needed

- Cardiac cath results including right heart pressures if available, review also to assure that no other anatomic defects noted on the cath report will need intra-operative intervention, e.g. PFO
- Recent chest CT results, if over 6 months consider emergent CT in the ED if indicated
- Cardiac echo results-emphasis on pulmonary pressures
- Quantitative V/Q scan results, if performed
- Most recent use of steroids and dose, confirm no use of anticoagulants other than unfractionated heparin or warfarin
- Current medications and allergies
- Last oral intake
- CMV, EBV and Toxoplasmosis status (listed under Labs – Infectious Disease results in computer)
- Check most recent cultures and note them on chart and include ID recommendations when indicated. For CF patients with known history of multi-resistant organisms, synergy studies should be available for review. Document the recommended peri-operative antibiotic regimen. Many patients will have a consultation note from ID for review. Also, if recent synergy studies are not available, the pulmonary team should be able to obtain from the chart, if available.
- Any recent acute illnesses
- BMI
- Conditioning level, most recent 6 min walk distance as well as any recent change in functional status.

Thoracic Resident – Inpatient

- Patients admitted for transplant candidacy evaluations are admitted to the Thoracic Service and coordinated with the Pre-transplant PA.
- Transfer patients from outside institutions for initial evaluation or screening for transplant related diseases, or transferred for disease management prior to full transplant evaluation may be admitted to the thoracic surgery service and subsequent disposition will be determined by the respective attending physicians.
- In general, thoracic residents and/or the Transplant PA write orders on Thoracic Surgery patients including all acute surgical transplant patients. There are occasional exceptions to this. Fellows may write orders on new transplant recipients admitted to 11C. All orders should be coordinated with the lung transplant pulmonary attending and thoracic transplant attending physician.

Patient Care

- Daily Rounds: Rounding with the transplant team daily as needed.
- For those patients newly transplanted or with active surgical issues, the thoracic resident and/or Transplant PA will be responsible for attending rounds and implementing the treatment plan, including immunosuppression, in consultation with the attending physicians and the transplant PA. This requires a detailed knowledge of the active issues on each patient: recent events, culture results, recent biopsy results, consultation from previous day. Coordination with the pulmonary fellow, PA's and nurse coordinator on service will be required.
- Admission Notes: Patients seen in the ER immediately prior to transplant will be seen by the Thoracic Surgery Team who will perform the initial admit note.
- Written progress notes: Thoracic residents and/or the Thoracic PA are expected to write detailed progress notes on patients whom they are actively following. These should include a problem list, events from the past 24 hrs, physical exam, relevant data, and assessment/plan.
- All surgical cases for new or established lung transplant patients will be staffed by the thoracic resident.
- The thoracic resident and/or the Transplant PA is directly responsible for the patient and will coordinate care through the Thoracic Transplant Fellow. Daily sign-out will occur for night-time and weekend coverage and will include detailed plans and communication of expectation for rounds, call, coverage.

Conferences

- Participation in weekly Thursday morning transplant meeting held in the Ingram Library in the Pulmonary Division. These rounds begin weekly at 7:30 in the morning. The thoracic surgery resident is encouraged to attend.

Section 2: Pre-operative Evaluation of Transplant Candidates

Criteria for Referral

Criteria for referral vary based upon the underlying lung disease and clinical considerations determined on a case by case basis.

General Guidelines

- Individuals with advanced lung disease
- Functional status = Some assistance needed with activities of daily living (ADL)
- Unacceptable quality of life
- 50% survival < 3 years despite maximal medical therapy
- Accelerated clinical course
- No significant non-correctable co-morbidity

Disease-Specific Guidelines

1. Chronic Obstructive Pulmonary Disease

Guidelines for Referral

- BODE index exceeding 5

Guidelines for Transplantation

- Patients with a BODE index* of 7 to 10 or at least 1 of the following:
 - History of hospitalization for exacerbation associated with acute hypercapnia (PCO₂ exceeding 50 mm Hg) or persistent hypoxemia (Po₂ < 60mmHg)
 - Pulmonary hypertension or cor pulmonale, or both, despite oxygen therapy.
 - FEV₁ of less than 20% and either DLCO of less than 20% or homogenous distribution of emphysema.
- BODE
 - Body mass index (BMI, B)
 - Airflow obstruction (O) as measured by the post-bronchodilator FEV₁ (% predicted)
 - Dyspnoea (D) assessed by the modified Medical Research Council (MMRC) score.
 - Exercise tolerance (E) measured by 6 minute walking distance

2. Cystic Fibrosis and Other Causes of Bronchiectasis

Guidelines for Referral

- FEV₁ below 30% predicted or a rapid decline in FEV₁.
- In particular in young female patients.
- Exacerbation of pulmonary disease requiring ICU stay.

- Increasing frequency of exacerbations requiring antibiotic therapy.
- Refractory and/or recurrent pneumothorax.
- Recurrent hemoptysis not controlled by embolization.

Guideline for Transplantation

- Oxygen-dependent respiratory failure.
- Hypercapnia.
- Pulmonary hypertension.
- Pretransplant colonization with multi-drug or pan-resistant organisms.
- *Aspergillus fumigatus* is not an absolute contraindication as long as specific therapy regimens can be identified.
- Patients with *Burkholderia cepacia* complex will be considered on a case by case basis.

3. Idiopathic Pulmonary Fibrosis And Non-Specific Interstitial Pneumonia

Guideline for Referral

- Histologic or radiographic evidence of UIP irrespective of vital capacity.
- Histologic evidence of fibrotic NSIP.

Guideline for Transplantation

- Histologic or radiographic evidence of UIP and any of the following:
 - A DLCO of less than 39% predicted.
 - A 10% or greater decrement in FVC during 6 months of follow-up.
 - A decrease in pulse oximetry below 88% during a 6-MWT.
 - Honeycombing on HRCT. (fibrosis score of 2)
- Histologic evidence of NSIP and any of the following:
 - A DLCO of less than 35% predicted.
 - A 10% or greater decrement in FVC or 15% decrease in DLCO during 6 months of follow-up.

4. Pulmonary Fibrosis Associated With Collagen Vascular Disease

Guideline for Referral

- NYHA functional class III or IV, irrespective of ongoing therapy.
- Rapidly progressive disease.

Guideline for Transplantation

- Persistent NYHA class III or IV on maximal medical therapy.
- Low (≤ 350 meter) or declining 6-MWT.
- Failing therapy with intravenous epoprostenol, or equivalent.
- Cardiac index of less than 2 liters/min/m².
- Right atrial pressure exceeding 15 mm Hg.

- Patients with significant Esophageal dysfunction will be considered on a case by case basis.

5. Sarcoidosis

Guideline for Referral

- NYHA functional class III or IV.

Guideline for Transplantation

- Severe impairment in lung function and exercise capacity (e.g., VO₂ max \leq 50% predicted).
- Hypoxemia at rest.
- Pulmonary hypertension.
- Elevated right atrial pressure exceeding 15 mm Hg.

6. Pulmonary Langerhans Cell Histiocytosis (Eosinophilic Granuloma)

Guideline for Referral

- NYHA functional class III or IV.

Guidelines for Transplantation

- Severe impairment in lung function and exercise capacity.
- Hypoxemia at rest.

7. Pulmonary Arterial Hypertension

Guideline for Referral

- NYHA functional class III or IV, irrespective of ongoing therapy.
- Rapidly progressive disease.

Guideline for Transplantation

- Persistent NYHA class III or IV on maximal medical therapy.
- Low (350 meter) or declining 6-MWT.
- Failing therapy with intravenous epoprostenol, or equivalent.
- Cardiac index of less than 2 liters/min/m².
- Right atrial pressure exceeding 15 mm Hg.

Initial Consultation

Patients' initial exposure to the transplant program is through their screening visit in the lung transplant clinic. There are specific criteria that patients must satisfy to be considered for lung transplant. Initial screening occurs in the form of a history and physical, and review of pertinent studies, including radiology, pathology, pulmonary function testing, etc. Patients who meet accepted medical criteria for consideration of lung transplantation and who are without obvious contraindication to transplantation at the time of their initial visit then undergo a series of studies and consultative evaluations (see list below) to further assess their candidacy for transplantation.

Lung Transplantation Selection Criteria - possible contraindications and guidelines for assessment (Criteria for candidacy vary based upon the underlying lung disease and clinical considerations determined on a case by case basis.)

- Solid organ malignancy in the last 5 years, or hematologic malignancy in the last 3 years (exception of cutaneous squamous and basal cell skin cancers, malignant melanoma and ductal carcinoma in situ of the breast as per separate guidelines, or other malignancies based on expert consultation).
- Untreatable advanced dysfunction of another major organ system (e.g., heart, liver, or kidney) that precludes ability to perform transplant safely. Examples include:
 - Coronary artery disease not amenable to percutaneous intervention or bypass grafting, or associated with significant impairment of left ventricular function.
 - Non-curable chronic extrapulmonary infection including chronic active viral hepatitis B, active hepatitis C, and human immunodeficiency virus unresponsive to therapy.
- Significant chest wall/spinal deformity.
- Documented persistent non-adherence or inability to follow through with medical therapy or office follow up.
- Untreatable psychiatric or psychological condition associated with the inability to cooperate or comply with medical therapy.
- Absence of a consistent or reliable social support system.
- Substance addiction (e.g., alcohol, tobacco, or narcotics) that is either active or within the last 6 months. Patients must be able to wean off chronic narcotic use prior to listing. Short term narcotic use (≤ 1 month) for acute injury and chronic narcotic containing cough suppressant syrups are not necessarily considered contraindications to transplantation. Protocol guidelines have been established for evaluation and management of candidates on chronic medical therapy for opioid use disorder. Medically prescribed marijuana use that is not delivered via inhalation in any form is acceptable.
- Overt sepsis.
- An upper age limit is not an absolute contraindication to transplant (recognizing that advancing age alone in an otherwise acceptable candidate with few co-morbidities does not always compromise successful transplant outcomes).
- Untreatable advanced dysfunction of another major organ system (heart, liver, kidney).

- CrCl \leq 50ml/min.
- Critical or unstable clinical condition.
- Severely limited functional status with poor rehabilitation potential.
- 6 minute walk (6MW) distance less than 450 ft independent of level of oxygen supplementation needed to achieve this:
 - For actively listed patients who were able to ambulate at least 450 feet prior to clinical status change who deteriorate, allowance can be made for one month with a non-ambulatory status.
 - For patients who are able to get out of bed and ambulate, up to one month opportunity to demonstrate that they can achieve a walk distance greater than 450 ft can be considered.
 - For candidates with deteriorating clinical condition, ongoing determination of appropriateness for continued active listing will be made by the team in consideration of overall clinical stability and organ function.
 - Candidates not actively listed who present for urgent evaluation and listing will be assessed by the transplant team, including review of functional status prior to clinical decompensation. Such candidates may be required to demonstrate ability to ambulate at least 450 ft on a 6MWT prior to activation.
 - Candidates who require initiation of mechanical circulatory support will be required to meet functional status criteria as determined by the transplant team prior to (re)activation in the waiting list.
 - See separate functional status requirements for candidates for repeat lung transplantation.
- Colonization with highly resistant or highly virulent bacteria, fungi, or mycobacteria. Can use synergy studies to identify a regimen for treating in the peri-operative period.
- Severe obesity defined as a body mass index (BMI) exceeding 35 kg/m², or significant malnutrition as defined by a BMI below 17 kg/m².
- For persons between BMI 30 and 35kg/m² the decision will be individualized to the patient; we will consider if he/she is exercising, making progress in losing weight and without additional co-morbidities that impact the risk. Similarly, for persons with BMI 17-20, individualized decisions based on ability to gain weight, will be made.
- Severe or symptomatic osteoporosis.
- Mechanical ventilation or Mechanical Circulatory Support: Carefully selected candidates on mechanical ventilation or mechanical circulatory support without other acute or chronic organ dysfunction, who are able to actively participate in a meaningful rehabilitation program, may be successfully transplanted.
- Co-morbid medical conditions that have not resulted in end-stage organ damage, such as diabetes mellitus, systemic hypertension, peptic ulcer disease, or gastroesophageal reflux must be controlled before transplantation.
- Candidates with IPF and co-existent CAD requiring intervention who are above the age of 70 present a unique risk profile for transplantation, particularly if combined lung transplant and surgical revascularization is required. Such patients with single vessel

disease should undergo percutaneous intervention for CAD prior to transplant if possible. Such patients with multivessel CAD or CAD not amenable to PCI likely are susceptible to too high a risk to be considered for transplantation.

- Transplantation for candidates with COPD and co-existent CAD requiring intervention who are above the age of 70 are unlikely to experience significant benefit from transplantation, but will be considered on a case by case basis.

Examples of Potential Exclusion Criteria for Transplantation on Initial Evaluation

- Age in context of patient co-morbidities and case specific clinical status
- History of non-hematologic malignancy (with the exception of basal or squamous cell CA of skin, melanoma skin cancer in situ or early stage, or ductal carcinoma in situ of the breast) within 5 years of referral
- History of hematologic malignancy within 3 years of referral
- CAD: Patients' coronary disease is assessed for amenability to intervention. Pre-existing coronary disease in context of normal LV function does not preclude evaluation
- History of cirrhosis, renal failure
- Significant psychiatric history
- Use of high dose steroids (> 20 mg/day) for more than 7 days
- Continued smoking (any and all tobacco and non-tobacco products) and or continued use of nicotine of any kind (chew, patch, gum, inhaler) (must be off for at least 6 months), significant alcohol, or recreational drug use. Patients with history of tobacco and/or nicotine use within 6 months of referral will have listing deferred until abstinence from tobacco/nicotine for at least 6 months is demonstrated. Random cotinine testing will be performed during this time period. In the event of nicotine replacement use, patients will be given the opportunity to discontinue use over a maximum of three months, and will be expected to demonstrate abstinence for an additional minimum of three months. During this time period, a staged evaluation, beginning with a psychosocial evaluation, can be considered on a case by case basis. Nicotine free support for tobacco cessation will be provided in conjunction with referring physicians if desired by the patient.
- Candidates using medically prescribed marijuana products not administered via inhalation and prescribed for appropriate indications can be considered for transplantation. Candidates using other forms of marijuana will need to abstain from use to be considered for evaluation and listing.
- Candidates are asked to stop alcohol consumption in order to be listed for transplantation.
- History of medical noncompliance
- Poor functional status as manifest by inability to participate in exercise program, marked debilitation
- A 6-minute walk distance < 450 feet

- Poor nutritional status - BMI less than 17 or greater than 35. Patient with BMI between 30 and 35 will be required to develop an exercise and diet program in conjunction with nutrition/pulmonary rehab and to document weight loss before listing. Patient with BMI 17- 18 will be required to demonstrate weight gain before listing.
- Hepatitis Infection:
 - Patients with positive antibody to hepatitis C but with two negative viral load determinations may undergo hepatology evaluation and/or liver biopsy. If no evidence of cirrhosis is documented, such patients may be considered for lung transplantation.
 - Patients who have a positive hepatitis C antibody and are viral load positive should be referred to transplant ID or hepatology for evaluation and treatment prior to lung transplantation listing.
 - Patients who are hepatitis B core antibody positive, hepatitis B surface antigen negative are eligible for lung transplantation. These patients should be referred to transplant ID prior to lung transplantation. There is a low risk of hepatitis B reactivation post-transplantation and they will need to be monitored periodically for this.

Special Considerations

- Short Telomere Syndrome: Short Telomere Syndrome is a syndrome with genetic predisposition associated with pulmonary fibrosis, bone marrow dysplasia, and/or hepatic dysfunction. This syndrome should be suspected in candidates with a family history of pulmonary fibrosis, bone marrow disease, liver disease, or pulmonary fibrosis associated with abnormalities in blood counts or liver function assessment. See appendix A for the evaluation and management of Short Telomere Syndrome.
- Right Ventricular Dysfunction: progressive RV dysfunction can be seen as a consequence of either idiopathic pulmonary hypertension or hypertension associated with advanced parenchymal lung disease. Peri-operative support may be compromised in patients with severe RV dysfunction, and special consideration should be given to RV support such as ECMO, or referral to the Pulmonary Vascular Disease program or the RV Rescue program for initiation of additional therapies as bridge to transplantation. See appendix C for the evaluation and management of RV dysfunction.
- Opioid Use Disorder: regular or habitual use of opioids for chronic pain or other medical conditions >1 month in duration presents an absolute contraindication to listing. However, individuals with a documented opioid use disorder, may be considered candidates if they meet the following criteria:
 - The patient meets diagnostic criteria for opioid use disorder mild, moderate, or severe (F11.XX) over their lifetime.
 - The patient has adhered to an addiction treatment program that has resulted in full remission of their substance use disorder over the 12 months preceding transplant evaluation.

- During the 12 months preceding transplant evaluation, the patient must have demonstrated no use of drugs of abuse (either opioids or drugs in other classes), including use of medications not prescribed the patient for a legitimate medical purpose.
- The 12-month period of sobriety cannot be met solely based on the patient being in a controlled environment, where access to opioids is restricted.
- The patient does not require chronic prescribed opioids (i.e., medication-assisted therapy) to maintain sobriety safely.

-OR-

- The patient can maintain sobriety while consistently taking an oral buprenorphine preparation (e.g., Suboxone™, Subutex™).¹
 - If taking buprenorphine, the patient's total daily dose cannot exceed the customary amount used to treat opioid use disorder (i.e., ≤24 mg of buprenorphine daily).
 - Given the unpredictable timing of transplant, patients taking long-acting buprenorphine preparations including implants (e.g., Probuphine™) or injections (e.g., Sublocade™) cannot be actively listed unless successfully transitioned to an oral agent with demonstrated sobriety over one month.
- The patient must remain in addictions counseling and/or support groups (e.g., NA), whether or not they receive medication-assisted therapy.

The following situations remain absolute contraindications to transplant:

- The inability to remain sober from drugs of abuse despite adherence to buprenorphine and/or other addiction treatment.
- The patient refuses to engage in regular, ongoing addiction treatment as clinically indicated.
- The patient requires chronic (>1 month duration) methadone to treat their opioid use disorder.²
- There is evidence from the patient's medical history and/or home environment that despite ongoing addictions treatment there remains a clear and convincing risk that the patient could overdose, be exposed to infection from intravenous drug use, or experience impairment in judgment sufficient to impair medical adherence.

Considerations for the management of opioid-dependent individuals undergoing lung transplant:

- Management of any medication-assisted treatment prior to transplant remains with the outpatient addictions provider (e.g., Suboxone prescriber). Given the risk of relapse and related sequelae, any taper or modification of opioid replacement for addiction should be solely at the discretion of patient's prescriber.
- At the time that a patient taking buprenorphine-naloxone is called for transplant, they should be instructed to hold any further doses and make note of the time it was last taken. Once in the ED or pre-operative areas, the home buprenorphine-

naloxone should generally be held unless it becomes clear that surgery will not proceed.

- Buprenorphine withdrawal can occur within 24 hours of the last dose and can typically be managed with low-dose opioids (e.g. oxycodone) prior to surgery.
- Due to opioid tolerance, the perioperative pain management needs may be relatively high in individuals with opioid use disorder. Respiratory status requires close monitoring.
- Buprenorphine-naloxone should not be resumed in the immediate post-operative period without prior assessment and recommendations from the Psychiatry (Addictions) Consultation Service. The immediate goal is to manage the patient's post-operative pain with conventional opioids until it is medically feasible to transition to home buprenorphine-naloxone (ideally prior to discharge).
- Any patient with an opioid use disorder and at risk of overdose should be prescribed a naloxone (Narcan™) kit, ideally provided to the family or support team.

¹ The most common medication used for this purpose is Suboxone™, a sublingual film containing buprenorphine and naloxone in a 4:1 ratio. Notably, the naloxone is not bioavailable when taken sublingually, but is included to deter intravenous use. Specific training and DEA waiver (e.g., an “X number”) is required to prescribe buprenorphine-naloxone on an outpatient basis. Buprenorphine can provide a modest degree of analgesia, but does have a ceiling effect, limiting overdose risk, and has a high affinity for the μ -opioid receptor (acting as an agonist-antagonist). As a result buprenorphine will displace any opioids already bound to the receptor and block additional ones from exerting analgesic activity. For this reason, patients beginning buprenorphine must be in at least the early stages of opioid withdrawal before induction.

² Unlike buprenorphine, methadone is a full agonist at μ -opioid receptor, presenting a risk of respiratory suppression at higher doses and when combined with additional opioids or sedatives perioperatively. Methadone can also prolong the QTc interval, a risk for arrhythmia that may be further exacerbated when receiving antibiotics, tacrolimus, and other post-transplant medications. As a practical consideration, patients requiring methadone dosing for addiction require regular (often daily) visits to receive their dose, a schedule patients will be unable to maintain for at least several weeks after transplant. Consider transition from methadone to buprenorphine in candidates pursuing listing for transplantation. Consultations with psychiatry, addictions management specialists, peri-operative pain service, should be obtained as first step in the evaluation process. Thoracic anesthesia should also be involved as indicated.

Inpatient Evaluation

For the majority of patients, the bulk of the transplant evaluation is completed during a 48 hour admission to the BWH thoracic surgical service. The remainder of the testing, including routine age-appropriate cancer screening and confirmation of routine preventive care, is coordinated with the transplant team and patient's referring physicians. Once all pre-transplant screening has been completed, patients are discussed with the entire transplant team during the weekly routine listing meetings, and candidacy for activation on the national transplant waiting list is determined. Patients return to transplant clinic subsequent to this visit, typically with their family, to review their candidacy.

Components of Transplant Evaluation

Forms/Consents

- Initial Receipt of Information
- Acknowledgement of Information
- Educational information
- Donor Selection Consent
- Nicotine Policy
- UNOS Multiple Listing
- Health Care Proxy
- Support Team Worksheet
- Authorization for Release of Information

Evaluations

- Pulmonologist/ Transplant Clinic (candidates should be seen every two months or with any clinical change while listed. Candidates deemed too well for transplant, particularly those with ILD, should ideally be followed every 2-3 months)
- Transplant Coordinator/Provider
- Social Work
- Neuropsych testing: (age 65+ or if applicable)
- Nutrition Consult
- Financial Coordinator (if applicable)
- Pharmacy (may be performed as record review)
- Infectious Disease (CF or if applicable)
- Ear, Nose, Throat (CF or if applicable)

Diagnostic Tests

- ECHO (within 6 months)
- Right Heart Catheterization
- Left Heart Catheterization (if age above 40) (within 5 years is acceptable if no evidence of CAD. If evidence of CAD is present, should be repeated every 2 years.)
- EKG
- Chest X-Ray (within 3 months)
- Chest CT (within 6 months)
- V/Q scan
- RUQ US
- Sinus CT (CF or if applicable)

- Full PFT's
- Updated Spirometry (should be repeated every two months or with any clinical change while listed)
- 6MWT (should be repeated every two months or with any clinical change while listed)
- Lung Allocation Score Components (should be repeated every two months or with any clinical change while listed)
- Impedence PH Probe and esophageal manometry (or appropriate substitute) Gastric Emptying Study (if applicable)
- Bone Densitometry (within 2 years)

Labs

- ABG (should be repeated every two months or with any clinical change while listed)
- Sputum GS and CX with Sensitivities
- Urinalysis
- Urine Culture – if urinalysis suggestive of infection
- Hepatitis Serologies
- Toxoplasma IgG
- CMV IgG
- EBV IgG
- HSV IgG
- VZV IgG
- Coccidioides IgG
- Strongyloides IgG
- HIV
- Comprehensive Metabolic Profile (should be repeated every two months or with any clinical change while listed)
- CBC with Differential (should be repeated every two months or with any clinical change while listed)
- PT/PTT/INR (should be repeated every two months or with any clinical change while listed)
- Hgb A1C if diabetic (should be performed every 4 months while listed)
- Serum/Urine Cotinine
- Toxicology Screen
- Histocompatibility testing (pre screen +/- single antigen testing): Every 2-3 months if negative, monthly for three months, followed by every 2-3 months if positive
- Vitamin D level
- Lipid Profile
- Iron, TIBC, Ferritin
- ABO # 1
- ABO # 2

Routine Health Maintenance

- PAP Smear (within one year for females – may be deferred for 3 years if history of 3 negative PAP smears per guidelines)
- Mammogram (within 1 year for females age greater than 40 or if applicable)

- Colonoscopy (within 10 years if age greater than 45 or as recommended based on testing and/or history)
 - Colonoscopy remains the preferred screening method for the vast majority of candidates, given its ability to detect small and pre-cancerous lesions and to allow for both diagnosis and intervention.
 - If a candidate is too unstable to undergo colonoscopy, CT colonography should be pursued if evaluation is urgent or time sensitive. If not urgent, fecal based testing (FIT or Cologuard) should be obtained.
 - ***Please note that guidelines recommend that CF patients undergoing lung transplantation be screened beginning at age 30***
- Dental Exam (within 1 year)

Specialized testing is indicated for particular disease states, such as systemic sclerosis and sarcoidosis.

For patients living outside the immediate Boston Metropolitan area (more than 3-4 hour travel time with traffic), a thorough travel plan needs to be developed to ensure timely arrival at the hospital when a donor lung becomes available. In addition, a plan to reside locally immediately post transplant may be required.

- Follow-up: Patients who are placed on the active lung transplant waiting list return to clinic one month following listing and every three months thereafter, or as their clinical condition dictates, to assess their clinical status and maintain current pre-operative data.

Choice of Procedure

The decision to offer single versus bilateral lung transplantation is made on a case by case basis. Recipient age, underlying lung disease, previous surgeries and existing comorbidities are analyzed in determining the appropriate procedure for a particular patient. The presence of clinically significant bronchiectasis, colonization with resistant or opportunistic microorganisms, and occasionally severe cough and sputum production typically warrant consideration of bilateral lung transplantation, if appropriate. Similarly, significant pulmonary hypertension is usually best addressed with bilateral lung transplantation, so as to avoid perfusion asymmetry leading to hemodynamic instability at the time of transplant.

Overview of Lung Allocation Score and Lung Offers

In Spring of 2005, the United Network for Organ Sharing (UNOS) moved from a process of organ allocation which had been based on waiting time, to a "Lung Allocation Score" (LAS) System designed to maximize allocation of organs to individuals with the highest risk of death on the waiting list and the greatest likelihood of benefit from transplantation. The individual patient score is determined by an algorithm which incorporates the following objective measurements:

Age	Supplemental Oxygen
BMI	Ventilator Use
Diagnosis	Creatinine
PAP	Diabetes Mellitus
PCWP	pCO ₂
Functional Status	Total Bilirubin
6 MW	
FVC	

Scores range between 0-100. The higher a patient's score, the higher his/her priority for transplantation. As a result, patients with longer waiting times alone no longer receive higher priority in this system, and may be bypassed by newly listed patients with higher LAS scores.

Organs are also matched to recipients based on blood type and size compatibility.

Other issues that can affect a patient's status:

- Use of steroids: at the present time our policy is that use of more than 20 mg of prednisone a day for a week or more, even in an acute setting, precludes transplantation. Patients must be on prednisone at 20 mg/day or less before reactivation occurs. In addition, in the context of chronic management of lung disease, steroids should be tapered below 20 mg daily to the lowest effective/tolerated dose.
- Active infection: active infection precludes transplantation. Exceptions include hospitalizations for clean-out among CF patients. These patients may be transplanted assuming they have no evidence of bacteremia or other acute infection after several days of IV antibiotics.
- Other contraindications: development of organ system dysfunction such as acute hepatitis, acute renal failure, major GI bleed, bowel obstruction, acute pancreatitis, etc, preclude transplantation
- RV dysfunction, as described below
- Sensitized recipients: Sensitization at our institution is defined as the presence of circulating class I or II HLA antibodies in a lung transplant candidate, detected at mean fluorescent intensity (MFI) above 3000. A high degree of sensitization limits the donor pool for such patients, because of the concern that the recipient could mount a donor specific antibody response, which could affect post-transplant graft function.

TABLE 1 HLA diagnostic approach to assign a patient's risk for memory or naïve alloimmune response

Pretransplant donor-recipient HLA laboratory evaluation						
CDC crossmatch	Flow crossmatch	Single antigen bead	History of sensitization	HLA molecular MM	HLA identical	Immune risk assessment
DSA positive	DSA positive	DSA positive				Active memory and at risk for hyperacute rejection
Negative	DSA positive	DSA positive				Active memory and at risk for ABMR and TCMR
Negative	Negative	DSA positive				Active memory and at risk for ABMR and TCMR
Negative	Negative	Negative	Pregnancy or prior transplant with repeat MM			At risk for latent memory with a recall B and T cell response
Negative	Negative	Negative	cPRA with unknown repeat MM			Potential risk for latent memory with a recall B and T cell response
Negative	Negative	Negative	No	High		Increased risk for de novo alloimmune response
Negative	Negative	Negative	No	Low		Baseline risk for de novo alloimmune response
Negative	Negative	Negative	No	0	Yes	Low risk for de novo alloimmune response

MM, Mismatch; DSA, donor-specific antibody; ABMR, antibody-mediated rejection; TCMR, T cell-mediated rejection.

Am J Transplant 2018; 18: 1604

- Recipients with donor specific antibodies (DSA's) require a prospective crossmatch at the time of transplant, further limiting the available donor pool. The role of desensitization protocols deployed in advance of lung remains controversial, and due to evidence of lack of efficacy, such protocols are not typically utilized at our center. See appendix W for the management of sensitized recipients.

Survival Statistics

Patients are given updated information regarding program specific and national graft and patient survival data on a six month basis, as data is released by the SRTR. Up to date information can be accessed at <https://www.srtr.org>.

Section 3: Initial Post-operative Issues

Expedited Pathway

The anesthesia and surgical teams will identify patients appropriate for this pathway at the time of arrival from the OR. General principles include rapid weaning of sedation and the ventilator with a goal of extubation within 6 hours of arrival, early advancement to clear liquids and enteral medication, early mobilization, and early line removal. In general, patients that follow this pathway will spend 24 to 48 hours in the ICU and then be ready for transfer to the TICU.

In more detail:

- Goal initial vent settings: VC 6 ml/kg as per **donor** height with PEEP 10. For single lung recipients with COPD, consider VC 8 ml/kg with PEEP 8. For single lung recipients with pulmonary fibrosis, consider VC 6 ml/kg with PEEP 12.
- Wean sedation aggressively as able after verifying neuromuscular blockade has been reversed or has worn off. Consider dexmedetomidine if needed for behavioral control while weaning to extubate.
- Goal extubation < 6hrs from time of ICU admission (time of day not exclusionary)
Exclusion criteria: active bleeding, escalating level of care
Continued pressor requirement is NOT a contraindication to extubation
If pt on Veletri, consider extubation to Hi-Flow NC with wean post extubation
If unable to extubate, document reason
- Early line removal:
 1. Intraoperatively, patients' vascular access will generally include a left IJ quad lumen catheter. If poor peripheral access is noted, a right IJ cordis will be placed.
 2. If a PA line is needed, the preferred location for placement is via the right IJ. If this is not feasible, a left subclavian line placement is preferred over a "double stick" in the left IJ.
 3. MAC catheters and ipsilateral "double sticks" will be avoided
 4. Remove PA line (if placed) within 12 hrs
 5. Remove PSI (cordis) within 24hrs.
 6. Remove all RIJ lines within 24 hrs (to avoid clotting issues, ideally the morning after arrival to ICU unless PA catheter is in use)
 7. Transition to PIVs within 48 hours post-op;
 8. Remove foley as soon as possible
- In the event of need for volume resuscitation, consider colloid rather than crystalloid; albumin 5% in 250 or 500 ml boluses as indicated by CI or SV in setting of low PAD/CVP
- Out of bed to chair within 6 hours of extubation, ambulate within 12 hours of extubation
- Start clears day of extubation when sitting in chair unless contraindication documented

- Multimodal pain control
 1. Regional anesthesia if present
 2. Acetaminophen
 3. Tramadol
 4. Consider gabapentin (can result in somnolence, start low)
 5. Early transition to oral oxycodone with IV for breakthrough pain
 6. Avoid NSAIDs due to presence of multiple nephrotoxic agents
 7. Use conservative measures such as pillow for cough and inspiratory pain

- Postoperative AF prophylaxis (evidence unclear) and treatment
 1. Aggressive repletion of electrolytes
 2. Beta blockers as preferred prophylactic agent- held if patient requiring vasopressors
 3. Treatment:
 - a) For recipients with pre-op pulmonary hypertension, abnormal RV function, persistent inotrope or vasopressor requirement – amiodarone is preferred agent (except if patient received a Hep C positive lung and is starting immediate treatment for Hep C)
 - b) For other recipients, okay to use beta blockade with low threshold to change to amiodarone. Avoid diltiazem if patient is receiving tacrolimus due to drug-drug interaction

- DVT prophylaxis with lovenox per protocol:
 1. Assess for suitability for initiation by 12 hours post-op on all patients – initiate no later than 72 hours post-op unless clear contraindication identified (see below)
 2. Exclusions for institution of prophylaxis include: need for ECMO support, other indication for therapeutic anticoagulation, frankly bloody chest tube output of large volume, signs of GI or other life threatening bleeding
 3. In the event of creatinine rise of 30% or greater, switch to alternative prophylactic agent

- Delirium management – consider early psychiatry consult

- Transfer to TICU after a minimum of 24 hours in ICU

Fluid Management

General Approach in the Immediate Post-transplant Setting

Volume status should be assessed for each patient and should guide the approach to fluid management. Patients often are maintained euvoletic in the immediate post-transplant period, while simultaneously maintaining urine output at greater than 0.5 ml/kg/hr. Fluid transport in the allograft is abnormal due to severed lymphatics, so excessive hydration can result in very slow clearance of any extra-vascular fluid from the lung parenchyma. Preventing accumulation of interstitial lung fluid and any resulting hypoxemia is accomplished by minimizing intravascular volume and pressure while maintaining adequate end organ perfusion. It may be necessary to use lasix, even if the patient is receiving inotropes or vasopressors, to maintain the goal urine output of 0.5 ml/kg/hr. Once the initial post-op instability is passed, it is desirable to return patients to their dry weight, with diuretics if needed, as quickly as possible while also being very mindful of renal function as multiple nephrotoxic agents are started.

Blood pressure, urine output, acid-base status (pH and base deficit), mental status, cardiac index, and overall peripheral perfusion on physical exam should all be frequently evaluated to assess the adequacy of perfusion. If perfusion is inadequate, and there is evidence of hypovolemia (low PAD or CVP, etc) colloids may be administered to increase venous return and intravascular volume. Albumin is most commonly used for this purpose. Blood products should be given only if there is a primary indication for blood product administration.

Hypotension

Hypotension in the immediate post-transplant setting is common and is generally due to post-CPB vasodilation and intravascular volume depletion. Although these are the most common causes of hypotension, other potentially life-threatening causes of hypotension must be considered in all post transplant patients. These include:

- Uncontrolled post-operative bleeding (often requiring return to the OR)
- Cardiac dysfunction - diagnosed by PA catheter hemodynamics and/or cardiac echo; may require inotropic support or even ECMO in extreme cases
- Cardiac arrhythmia – sustained tachy or brady arrhythmias can adversely impact hemodynamic stability in the post operative transplant patient. Transplant patients undergoing CPB for their transplant may have ventricular rescue pacing wires placed, with a pacing box available in the ICU room. The choice of medication for treatment of tachyarrhythmia should be discussed with the ICU attending and pulmonary attending as there are concerns for both RV depression and drug-drug interactions.
- Pulmonary hypertension – diagnosed by in situ PA catheter and may require inhaled prostanoid administration
- Tamponade - rare but can result from bleeding into the pericardial space
- Tension pneumothorax on the side contralateral to the transplant

- Pulmonary venous obstruction with compromise of venous return: this is best assessed by trans-esophageal echo.
- Torsion
- Dynamic hyperinflation of native emphysematous lung

Evaluation includes assessment of hematocrit, chest tube and drain output, urine output, blood and urine cultures if there is a suspicion for infection, electrocardiogram, chest X-ray, intravascular pressures via pulmonary arterial catheter (usually not in wedge position, but still providing useful measures of pulmonary artery and central venous pressures, mixed venous oxygen saturations, and cardiac output), and cardiac echo. Echo assessment is often helpful in patients with normal or adequate pre-operative cardiac function who develop post-operative reduced cardiac output, hypotension, reduced stroke volume, and apparently normal or elevated pulmonary artery diastolic pressures.

If the cardiac index is low (< 2.2 L/min/m²), or ventricular dysfunction is noted on ECHO, it may be necessary to provide inotropic support. The choice between norepinephrine and epinephrine is made based on an assessment of the relative need for inotropy versus tone. Some patients have an adequate cardiac index but low peripheral vascular tone and hypotension. In this setting, vasopressor therapy may restore adequate perfusion pressure without excessive fluid administration. It may be important to monitor the PA pressures and cardiac index while titrating vasopressor therapy to make sure that any vasoactive agent does not worsen cardiac function and forward flow. Low dose vasopressin (0.04 units/min or less) does not tend to increase PA pressures and may be useful for treating systemic vasodilatation in this patient population. Patients with normal or near normal RV function preoperatively and on the post-CPB TEE may arrive to the ICU without a PA line in place. In this setting, physical exam (perfusion of hands and feet) combined with acid/base status and urine output is usually sufficient to confirm adequate CI. Central venous saturation and lactic acid are other data points that can be useful. Bedside TTE can be performed as needed.

Implantation Response

Low pressure pulmonary edema is fairly common post-transplantation (incidence 15-20% of cases) and is thought to be related to several factors, including mediators released from ischemic tissue within the transplant, activated white blood cells, duration of ischemic time and donor age. This implantation response syndrome is referred to as primary graft dysfunction (PGD). Formal grading of PGD as per published guidelines (Journal of Heart and Lung Transplantation 2017; 36: 1097) should be performed as per Table 4 on the next page at T0 (time of removal of last cross clamp), T24, T48, and T72, all plus or minus 6 hours.

Figure (next page) : Recommendations for grading of PGD (Journal of Heart and Lung Transplantation 2017; 36: 1097)

Table 4 The 2016 International Society for Heart and Lung Transplantation Primary Graft Dysfunction Definition

Grade	Pulmonary edema on chest X-ray	PaO ₂ /FIO ₂ ratio
PGD grade 0	No	Any
PGD grade 1	Yes	> 300
PGD grade 2	Yes	200 to 300
PGD grade 3	Yes	< 200

Grade severity notes: Patients with no evidence of pulmonary edema on chest X-ray are considered grade 0. Absence of invasive mechanical ventilation should be graded according to the PaO₂/FIO₂ ratio, using methods similar to those receiving mechanical ventilation.

FIO₂, fraction of inspired oxygen; PaO₂, partial pressure of arterial oxygen; PGD, primary graft dysfunction.

If PaO₂ is not available for calculation of a PaO₂/FIO₂ ratio, then an oxygen saturation/FIO₂ ratio should be calculated and the 200 and 300 PGD grading cutoffs should be adjusted to 235 and 315. Use of nitric oxide, aerosolized epoprostenol, or other pharmacologic agents that may improve oxygenation should not change grading methods. Use of extracorporeal lung support (ECLS) with bilateral pulmonary edema on chest X-ray image should be graded as grade 3 and ECLS use should be explicitly recorded. The use of ECLS for non-hypoxic indications without pulmonary edema on chest X-ray imaging should be considered ungradable and explicitly recorded separately.

Time window notes: PGD is graded at 4 time-points, every 24 hours, over the first 72 hours after transplantation (T0, T24, T48, and T72 hours). Time starts at reperfusion of second lung. T0, T24, T48, and T72 have time windows ± 6 hours. If multiple blood gas values are available, the worst PaO₂/FIO₂ ratio on a given calendar day should be used.

Other notes: PaO₂/FIO₂ should ideally be measured on positive end-expiratory pressure of 5 cm H₂O at FIO₂ of 1.0 while patients are on mechanical ventilation; however, grading should not be altered for other settings. For altitudes higher than 1,000 m, use of an appropriate correction factor is recommended. For comparative purposes, single lung transplantation is recommended to be reported separately from bilateral lung transplant without change in grading methodology.

PGD is generally managed by judicious use of diuretics and modest application of colloids and PEEP. If a patient requires an $\text{FiO}_2 > 50\%$ with PEEP of > 10 cm H₂O, inhaled Veletri should be started and a discussion should occur with the pulmonary, surgical and critical care attending regarding the potential need for ECMO. Outcomes are generally better if ECMO is started within 24 hours of reperfusion in the case of severe PGD.

Steroids, given in high doses post-transplantation as part of the immunosuppressive regimen, may further blunt the capillary leak syndrome. Occasionally, the pulmonary edema progresses despite these therapies, and leads to progressive hypoxemia and full blown ARDS. Diffuse pneumonia, venous obstruction, pulmonary hemorrhage, transfusion reaction, aspiration, and adverse reaction to induction therapy can all present similarly and should be considered in the differential diagnosis.

Pulmonary hypertension is commonly seen in the peri-operative and occasionally post-operative period following lung transplantation. This occurs most often in association with an implantation response or in patients with long standing right ventricular hypertension and preserved function. Although several agents have been used for this purpose including sodium nitroprusside, prostacyclin, PGE₁ and nitric oxide (NO), inhaled Veletri is most commonly used currently for management of post-operative pulmonary hypertension. The medication is ordered as 30 mcg/ml in sterile water 50 cc for inhalation, and administered at .01 - .05 mcg/kg/min. As pulmonary hypertension improves, the drug is gradually weaned.

Mechanical Ventilation

Typically, a modified lung protective ventilatory strategy is employed post-operatively. Peak inspiratory pressures are ideally maintained below 30 cm H₂O, and a tidal volume of 6 ml/kg (corrected body weight corrected to donor height) is employed with a PEEP of 10. This is to prevent ventilator associated lung injury and in theory to protect the airway anastomosis. Either pressure control or volume control ventilation can be used as long as these goals are met. Post-operative use of PEEP serves a dual purpose. Typically transplanted lungs demonstrate decreased compliance due to ischemic injury and generalized edema. The elevated PEEP (initially 8-10) allows for maintenance of airway recruitment during the early recovery period, while allowing lower FiO_2 which in theory lowers the risk of ischemia-reperfusion injury. Furthermore, in the immediate post-operative period there is often an abundance of raw tissue surface area that is prone to bleeding. The added PEEP allows for improved tissue-graft interface for direct tamponade and decreased bleeding. PEEP is lowered as soon as bleeding is minimized and oxygenation improves. It is also important to recall that the bronchial artery system has been divided in newly transplanted lungs, thus areas of collapse or poor ventilation are prone to ischemic injury and hypoxic vasoconstrictive shunting.

For single lung recipients with COPD, hyperinflation of the native lung is an issue. Tidal volumes of 8 ml/kg (corrected to donor height) and a PEEP of 8 cm H₂O, with lower respiratory rates and extended I:E ratios may work better. Similarly, single lung recipients with pulmonary fibrosis will have the opposite compliance problem and may be best ventilated with 6 ml/kg TV and a PEEP of 12, higher rates, and a normal to shortened I:E ratio.

In the critically ill patient who is requiring full ventilator support, it is reasonable to use a strategy of permissive hypercapnia. Generally speaking, this is well tolerated. It can be dangerous, however, in patients with cardiac arrhythmias, hyperkalemia, increased intracranial pressure, pulmonary hypertension, or hemodynamic instability and must be used cautiously in these settings.

Post-operative Surgical Concerns: Bleeding, Air Leaks, Venous Obstruction, and Bypass

The most important post-operative surgical issues to arise in transplant patients include:

- Bleeding post bypass in the first 24-48 hours
- Large or non-resolving air-leak during the first few weeks
- Large chylous effusions or drainage
- Obstruction of pulmonary venous return suggesting anastomosis site problems such as pulmonary vein obstruction.
- Post-operative Bleeding

Potential causes include:

- Inadequately reversed heparin
- Development of DIC due to bypass, transfusion reaction
- Decreased platelets s/p bypass (due to activation and degradation as a result of passage over membrane oxygenation)
- Fibrinolytic state
- Poor apposition of tissue in the area of raw resection surface
- Presence of undetected bleeding vessels

Patients with bloody chest tube drainage should have the hematocrit of the fluid checked. If > 20% this suggests a significant hemothorax. Most often, bleeding will subside with re-warming, correction of coagulation factors, increased PEEP and pleural cavity drainage. Refractory coagulopathic bleeding may warrant treatment with specific concentrated clotting factors such as Kcnetra (4 factor concentrate), RiaSTAP (fibrinogen) or FEIBA (Activated Prothrombin Complex). This should be discussed early on with the ICU and Surgical attendings. Occasionally, patients require surgical exploration and intervention. Indications for surgical re-evaluation include: > 800 cc bloody drainage for 1 hour, 400 cc/hr unremitting for the first 2 hours, or 200 cc/hr for the first 4 hours.

Persistent Air Leak

Air leaks immediately post-transplantation are not uncommon, but usually resolve within several days. Leaks persisting beyond 72 hours may signify a leak at the anastomotic site, and require further evaluation. Additional studies include:

- Chest CT scan to look for evidence of air in/around the anastomosis site
- Bronchoscopy arranged with one of the surgical attendings present so that a thorough examination of the site can be undertaken by all members of the team.

In patients with new air leaks developing 2 to 4 weeks following surgery, it is important to rule out airway dehiscence and anastomosis site breakdown. This can present as a pneumothorax, and requires immediate evaluation. If evidence of airway dehiscence and/or necrosis is evident, surgical intervention may be required.

Chylous Pleural Effusions

Chylous drainage from the chest tubes or Blake drains (i.e. pleural fluid with a triglyceride level > 110 mg/dl) may signify injury to the thoracic duct or the accessory duct. This usually does not require surgical intervention, but responds to removal of fat from the diet. This may require transient change to TPN with no fat for a week to allow for collapse and healing of the injured duct. Embolization of the thoracic duct by IR can also be considered.

Venous Obstruction

Venous obstruction at the atrial anastomosis site can occur, resulting in pulmonary edema, elevated pulmonary artery pressures, and falsely elevated wedge pressures despite a limitation in left ventricular filling. This is heralded by persistent pulmonary edema despite aggressive diuresis, even to the point of pre-renal azotemia. Diagnosis is based on observation of the appropriate hemodynamic profile, trans-esophageal echo demonstrating lack of Doppler flow in some of the pulmonary veins, and pulmonary arteriography demonstrating venous obstruction. This problem generally requires surgical correction, although consideration could be given to attempted balloon dilation.

Brief Review of Bypass

Cardiopulmonary bypass consists of placement of a venous drainage cannula (to receive deoxygenated blood returning from the body) in the right atrium (single stage cannula), or in both the superior and inferior vena cava (Bicaval cannulas) and an aortic inflow cannula in the aortic root or other major artery (to allow for oxygenated blood from the membrane oxygenator to return to the patient). Femoral or subclavian cannulation can be performed in situations where surgical manipulation of the aortic root is difficult. Full anticoagulation is required for bypass using heparin 300-400 U/kg. The patient is mildly cooled during the bypass procedure however the heart does not require any additional intervention such as being arrested, as it is well perfused and decompressed during CPB. One of the reasons to avoid aortic clamping and arresting the heart is that physical manipulation of the aorta can injure the vessel or dislodge luminal debris. Furthermore, cross-clamp time during bypass is associated with increased risk of myocardial dysfunction on separation from bypass. The need for mechanical or pharmacological cardiac support following bypass is often required and dramatically increases with cross-clamp times in excess of 120 minutes.

Diet and Initiating Oral Intake

General Approach

Often the patient will come to the ICU with an orogastric tube which is removed at time of extubation. If a nasogastric tube is present, it can be likewise be removed upon extubation if no patient-specific concerns such as large volume output, history of significant nausea, etc.

Advancement of diet may proceed as follows:

- Ice chips ONLY with extubation
- Sips of water, clear liquids once tolerating ice chips and when sitting in a chair.
- Advance diet as tolerated including beginning oral medications if no concerns taking clears and when sitting in a chair.

Aspiration is a major cause of post-transplant infection and respiratory compromise. In particular, patients with cystic fibrosis may exhibit significant hypomotility post transplant. If there is concern about the patients' ability to swallow, a formal video-fluoroscopy swallowing study should be performed and a formal speech and swallowing consultation obtained. In addition, as vocal cord dysfunction may occur as a result of intubation or left recurrent laryngeal nerve injury, ENT may need to be consulted to directly assess vocal cord movement. If there is concern regarding gastric emptying, a nuclear medicine emptying study should be performed. Agents that have been useful in treating hypomotility (once obstruction has been ruled out) include metoclopramide, which acts primarily on the upper GI tract to improve gastric motility and increase lower esophageal sphincter tone, and low dose erythromycin 250 mg bid-tid iv or po which stimulates motilin receptors. However, metoclopramide can be poorly tolerated as manifested by mental status changes and should be used with caution. Additionally, early ambulation is likely to improve intestinal function, as will minimizing narcotics.

All transplant patients are presumed to have reflux and are at risk for occult aspiration. Protected micro brush specimens demonstrate oral flora twice as often among transplant patients with pneumonia than among other patients with pneumonia. Therefore, precautions to prevent aspiration are universally implemented and include:

- Raising the head of the bed (30 degrees HOB up)
- Use of H₂-blocker or proton pump inhibitor
- Patients should be out of bed in a chair for all meals

Sedation and Analgesia

Multimodal Pain Control

Most patients will initially require a fentanyl infusion at low to moderate doses (25 to 75 mcg/hr). This should be transitioned to a PCA (fentanyl or hydromorphone) when the patient is able to utilize it. Early transition to enteral narcotics (oxycodone or hydromorphone) is helpful to provide more consistent pain relief. Useful adjuncts include acetaminophen (NG, rectal or PO), neurontin (NG or Po) which should be started low as it can cause somnolence, lidoderm patches, and mechanical measures such as cough pillows. NSAIDS must be avoided due to the multiple other nephrotoxic agents that all patients must receive in the early post-op period. Consider a Post-operative Pain Service consultation for patients with very hard to control pain.

Sedation

The goal for most patients should be “pain first” sedation with fentanyl while intubated. Transplant patients are particularly prone to delirium. Therefore, benzodiazepines and propofol should be avoided if possible. Consider dexmedetomidine if a sedative infusion in addition to fentanyl is required. It is important to review the patient’s pre-operative psychotropic meds and social work and psychiatry evaluations. Many patients have significant pre-operative anxiety or depression and may need some of their baseline medical regimen continued through the perioperative period. There should be a low threshold to involve psychiatry in the setting of difficulty to control anxiety or delirium. Every effort should be made to avoid deliriogenic drugs.

Section 4: Bronchoscopy and Airway Management

Initial Post-transplant Period

Immediate Post Transplant Bronchoscopy

Immediately following change of the patient's endotracheal tube in the OR the patient will routinely undergo bronchoscopy to assess bleeding and integrity of the anastomosis site. Suctioned samples are sent for cultures if not done intraoperatively, or for recurrent significant secretions. If not completed in the OR, or for concern of airway secretions, bleeding, or decreasing respiratory function, bronchoscopy will be performed by the transplant team at the direction of the transplant surgeon or pulmonologist.

Pre-Extubation Bronchoscopy

Prior to planned extubation following transplantation, patients will undergo routine bronchoscopy. Passing the bronchoscope past the anastomosis is perfectly safe and allowed; however, great care must be taken to assure that the scope is not forcefully directed at the healing surgical anastomosis as this can cause significant injury in the early phases of healing.

Bronchoscopies will be performed outside of the standard surveillance schedule as dictated by clinical status. Indications for bronchoscopy in the early post-transplant period include:

- Airway bleeding
- Infiltrates/fever
- Inability to clear secretions
- Persistent oxygen requirement
- Evidence of bronchopleural fistula
- Follow-up cultures to determine the need/duration of antibiotics, anti-fungals, and anti-viral therapy.
- Significant decline in pulmonary function tests.
- Clinical shortness of breath or evidence suspicious for airway narrowing

Subsequent Post-operative Bronchoscopies

Surveillance Bronchoscopy Post-transplant

Bronchoscopy is performed routinely among our post-transplant patients to assess for asymptomatic rejection. While not all transplant centers utilize this approach, we continue to use this method of monitoring for rejection because we frequently detect evidence of rejection in otherwise asymptomatic patients. Published data support this approach since a significant percentage of rejection episodes are asymptomatic, especially during the first 6 months post transplantation.

The current standard for rejection surveillance is transbronchial biopsy, with specific attention to the small end-airways and alveolar tissue. The BWH lung transplant team has adopted a technique for these awake, out-patient procedures that allows for ease of intervention, with maximal patient safety and airway protection. This technique allows for awake intubation with the scope able to move freely. This technique is utilized for planned transbronchial biopsies or when a large amount of airway secretions are expected. The bronchoscopy via the ETT is augmented with a T-piece and 100% flow-by O₂. The nursing staff in the endoscopy suite is familiar with this set-up and can assist you with it.

Surveillance Biopsy Schedule

- 1 month post transplant
- 3 months post transplant
- 6 months post transplant
- 12 months post transplant

During the first year and thereafter, biopsies are also performed as dictated by each patient's clinical status.

Difficult Bronchoscopies

Patients who have a history of significant hypoxemia, bleeding during usual bronchoscopy or poor tolerance of this technique may have a lower risk of complications if the procedure is performed with general anesthesia rather than conscious sedation. Under deep sedation or general anesthesia, the airway and ventilation are easier to control and patient comfort is assured.

Cases can be scheduled with anesthesia support in the OR procedure room. Coordination can also include transbronchial biopsies, as well as advanced airway cases including airway dilation and stenting. Fellows from pulmonary and thoracic surgery both perform these procedures in conjunction with either the surgery or pulmonary staff. Coordination for these cases is generally through the thoracic surgery scheduling team.

Bronchoscopies Outside of the Endoscopy Suite or OR

Bronchoscopies can be performed outside of the endoscopy suite if needed. In general, these are performed in the ICU setting with the assistance of the ICU nursing staff and respiratory therapy. In rare circumstances, bronchoscopy may be performed on the 11th floor. In these cases it is necessary to arrange for appropriate administration of conscious sedation. This is accomplished by contacting beeper 31469 for conscious sedation nurse (week day) or anesthesia resident (weekends) who will administer the medications.

This person will also recover the patient after the procedure, which requires staying with the patient and monitoring vital signs frequently for 1-2 hours.

A mobile video endoscopy cart, including equipment to perform video bronchoscopies, is owned by the hospital and operationally administered by respiratory therapy. Upon request, this cart can be brought to the unit for video bronchoscopy. This resource has most frequently been used in circumstances which require simultaneous visualization of the airway by the fellow and staff member (i.e. airway dilation, transbronchial biopsy). It is important to note that since this equipment is also used by the general surgeons to place PEGs and trachs, it is in high demand and frequently unavailable unless reasonable warning has been given. In this regard, it is a good idea to check on its availability when planning any procedure.

Section 5: Immune Suppression

General Overview

Immunosuppression is critical to the survival of the transplanted lung. Donors and recipients are matched for blood type to prevent hyperacute rejection and candidates are evaluated for circulating anti-HLA antibodies that could potentially cause antibody mediated rejection (AMR). Acute and chronic rejection are prevented and managed pharmacologically using immunosuppressive agents. Patients receive potent induction therapy with basiliximab (IL-2 receptor antagonist) prior to the initiation of maintenance immunosuppression. Our current maintenance protocol consists of tacrolimus (FK506, Prograf®), mycophenolate mofetil (MMF, CellCept®) and steroids. Alternative agents include cyclosporine (CSA, Neoral®, Gengraf®, Sandimmune®) and azathioprine (Imuran®).

Induction Immunosuppression

Basiliximab is a chimeric monoclonal antibody that suppresses the immune system through its actions as an interleukin-2 (IL-2) antagonist. Basiliximab binds to the alpha chain of the IL-2 receptor (CD-25) on the surface of activated T-lymphocytes.

- Induction regimen
 - Two doses of 20 mg
 - First dose: administered within two hours prior to transplantation
 - Second dose: administered on post-operative day four
- Administration
 - Short IV infusion over 20 to 30 minutes
 - No pre-medications required
 - Central or peripheral line
 - Separate IV line required
- Monitoring
 - Typically well-tolerated
 - No increase in adverse effects compared to placebo in clinical trials
 - Possible side effects
 - Hypertension
 - Headache, tremor
 - Acne
 - Constipation, nausea, abdominal pain, vomiting, diarrhea, dyspepsia
 - Urinary tract infections
 - Anemia
 - Hyperkalemia, hypokalemia, hyperglycemia, hypercholesterolemia, hypophosphatemia, hyperuricemia
 - Insomnia
 - Dyspnea, upper respiratory tract infections
 - Surgical wound complications, pain, peripheral edema, fever, and viral infection
 - No therapeutic drug monitoring required
 - No known drug interactions

Steroid Taper: See appendix Q

Maintenance Immunosuppression

Tacrolimus (Prograf®)

- Tacrolimus, a calcineurin inhibitor (CNI), is the preferred agent for initial use, and is begun at the discretion of the transplant team. CNI should be initiated by post-operative day 1-2 for all patients.
- Starting Dose
 - Tacrolimus dose calculation: .025 mg/kg sublingual every 12 hours.
 - Monitoring: Goal Trough Concentration: 8-12 ng/mL
 - Adverse Reactions: hyperglycemia, hypertension, nephrotoxicity, hyperlipidemia, neurotoxicity (headache, tremors, burning sensation in hands/feet), alopecia
- The drug is continued sublingual until the patient is taking PO well. Dosing on conversion may be 1:1 but depends on observed blood levels. To be initiated in first 24 hours post-transplant.
- For patients with pre or peri-transplant RV dysfunction, a lower starting dose of 0.5 mg q12 hours will be initiated to minimize renal toxicity and allow for diuresis as necessary.

Alternative Agent: Cyclosporine

- Suggested starting dose 1-2mg/kg/day IV continuous infusion or 1.5-3 mg/kg q12 hours PO. No sublingual option exists for cyclosporine.
- The conversion from IV to PO is 1:3.
- Monitoring
 - Goal Trough Concentration: 300-350 mcg/L
 - Adverse Reactions: Similar to tacrolimus: hyperlipidemia (CSA>TAC), hypertension (CSA>TAC), hyperglycemia (CSA<TAC), hirsutism- no alopecia

Mycophenolate Mofetil (CellCept®)

- Mycophenolate is our third agent for maintenance immunosuppressive therapy. A single dose of mycophenolate 1000 mg is administered in the operating room at the time of transplant. Scheduled doses are to be initiated immediately post-transplant and are available both orally and intravenously.
- Starting Dose: 1000mg PO BID as tolerated
- Monitoring
 - Adverse Reactions: leukopenia, N/V, diarrhea, hypertension, peripheral edema
- IV:PO Ratio = 1:1

Alternative Agent: Azathioprine

- Starting Dose: Approximately 1-3mg/kg/day PO (rounded to the nearest 50mg). Generally a dose of 100mg/day or less is given.
- Monitoring
 - Adverse Reactions: Leukopenia, N/V, pancreatitis, skin cancer, hepatotoxicity
- IV:PO Ratio = 1:1

Section 6: Infectious Disease Concerns in Transplant

Pre-transplant Evaluation

The initial pre-transplant work up should include serologies for several infectious pathogens as listed below in Table 1. Most of these titers determine the disease risk after transplant and form the basis for certain post-transplant prophylactic or preemptive strategies. For example, the dose and duration of CMV prophylaxis are based on donor and recipient CMV titers as described below. Hepatitis virus serologies and HIV testing are performed in order to detect occult infection. Any patients with a positive HIV test, a positive hepatitis B surface antigen or reactive titers for hepatitis B core antibody, hepatitis C antibody, or Coccidioides antibody should be referred for ID outpatient consultation.

Patients with a history of infection or colonization with resistant Gram-negative bacteria (e.g. MDR pseudomonas, *B. cepacia*), mycobacteria (e.g. *M. abscessus*) or fungal pathogens (e.g. *Aspergillus*, *Scedosporium*) prior to transplant should be seen in the infectious diseases clinic before being listed for determination of the optimal peri-transplant antimicrobial plan.

Serologic Work-Up

Table 1: Serologic work up for patients who are being considered for transplant listing

Pathogen	Serologic test
Herpes simplex	HSV 1 IgG HSV 2 IgG
Varicella zoster	VZV IgG
Epstein-Barr	EBV VCA IgG
Cytomegalovirus	CMV IgG
Toxoplasmosis	IgG
Coccidioides	IgG
Hepatitis B	HBcAb HBsAb HBsAg
Hepatitis C	HCV Ab HCV virus load
HIV1 and 2	HIV ELISA with reflex Western Blot

Pre-Transplant Vaccinations

Table 2: Pre-transplant vaccinations for patients being listed for lung transplantation

Vaccine	When and who to vaccinate	Notes
Influenza	<ul style="list-style-type: none"> All transplant candidates annually 	<ul style="list-style-type: none"> Suggest: injectable vaccine which is not live
<i>S. pneumoniae</i> (Pneumococcal conjugate 23)	<ul style="list-style-type: none"> If never vaccinated If >5 years since previous vaccination 	Must wait one year post PCV13 for administration
<i>S. Pneumoniae</i> (Pneumococcal conjugate 13)	<ul style="list-style-type: none"> If never vaccinated 	Must wait 3 months post PCV23 for administration
Varicella (Varivax)*	<ul style="list-style-type: none"> If no history of chicken pox and varicella titers negative 	<ul style="list-style-type: none"> <u>Live</u> vaccine Two vaccine series given at 0 and 4-8 weeks
Zoster (Shingrix – preferred) (Zostavax - alternative)*	<ul style="list-style-type: none"> A history of chicken pox If varicella titers are positive in the absence of previous varicella vaccination 	<ul style="list-style-type: none"> <u>Zostavax is a live vaccine</u> Single dose
Tetanus / Diphtheria / Pertussis (Tdap)	<ul style="list-style-type: none"> If it has been >2 years since last tetanus booster 	<ul style="list-style-type: none"> Giving Tdap < 2 years from last tetanus booster can result in severe local reaction
Hepatitis B	<ul style="list-style-type: none"> If surface antibody (HBsAb) and surface antigen (HbsAg) are negative 	<ul style="list-style-type: none"> Three vaccine series Administration schedule: <ul style="list-style-type: none"> ○ 0, 2, 4 weeks OR ○ 0, 1, 4-6 months Check HBsAb 2-4 weeks after vaccine series completed If HbsAb negative, repeat series
Hepatitis A	<ul style="list-style-type: none"> If not previously vaccinated or exposed 	<ul style="list-style-type: none"> Two vaccine series given at 0 and 6-12 months
Human Papilloma Virus (Gardasil)	<ul style="list-style-type: none"> If a women between the ages of 9-26 years old 	<ul style="list-style-type: none"> Three vaccine series given at 0, 2, and 6 months

Initial Post-operative Antimicrobial Therapy

The donor airways may demonstrate evidence of purulence at bronchoscopy since most donors are intubated in an ICU prior to organ procurement. Unless the donor airway specimen gram stain is without neutrophils and organisms, transplanted patients should be started on empiric antibacterial treatment pending airway sample culture results. The standard initial therapy we use is ciprofloxacin, metronidazole, and vancomycin. In patients with pre-existing resistant gram-negative colonization (i.e. CF or other forms of bronchiectasis), the choice of antibiotics should be tailored to the pre-operative known bacterial isolates. As described above, patients with a history of multi-drug resistant bacterial or fungal colonization should be seen in ID consultation prior to transplant for determination of an optimal perioperative antimicrobial regimen; this regimen will be documented in the most recent infectious diseases note. Patients undergoing lung transplant should also be treated with perioperative micafungin as described in further detail in the antifungal prophylaxis section.

Culture results from donor specimens must be checked at 24 and 48 hours to further direct therapy. This requires reviewing donor culture results obtained at the hospital of donation and provided by the OPO, or calling the site at which the lungs were procured, or the OPO, and obtaining culture results from the pre-procurement bronchoscopy. Cultures are also obtained from samples collected during the initial bronchoscopy performed in the operating room, and results are available within 24 hours. In cases where no organism is identified and little or no purulence was observed bronchoscopically, broad-spectrum empirical treatment can be discontinued after 72 hours. In cases where significant purulence was observed bronchoscopically, antibacterials are often continued for 7-10 days. Micafungin therapy should also be tailored after 7-10 days when all fungal culture and explant pathology results are available for perioperative samples as described in detail below.

Post-Transplant Infection Prophylaxis

PCP (Pneumocystis jiroveci)

For prophylaxis we use trimethoprim-sulfamethoxazole 1 DS tablet by mouth M/W/F or 1 SS tablet by mouth daily indefinitely. In addition to providing prophylaxis for PCP, trimethoprim-sulfamethoxazole also provides prophylaxis for Listeria, Nocardia, Toxoplasmosis, and UTIs, among other pathogens.

For those patients with documented allergy to sulfa, prophylaxis alternatives include desensitization to trimethoprim-sulfamethoxazole (1 ss tablet po daily), atovaquone 1500mg daily or dapsone 100mg daily. If desensitization to trimethoprim-sulfamethoxazole is needed, consult the allergy service during the evaluation for assessment and planning, and again while the patient is still in the ICU so that the process can occur in a monitored setting. Note that caution should be exercised in choosing either dapsone or inhaled pentamidine as alternatives. Neither provides adequate prophylaxis for Toxoplasma IgG positive recipients. In addition, dapsone has been associated with methemoglobinemia and hemolytic anemia, which can be severe in patients with G6PD deficiency. A G6PD level must be checked prior to dapsone use. In addition, there is significant cross-reactivity between dapsone and trimethoprim-sulfamethoxazole in non-HIV infected patients so dapsone may not be a good alternative in patients with severe sulfa allergy. Inhaled pentamidine has been associated with bronchospasm in susceptible patients (Chest 1994; 105: 417-20.). There have also

BWH Lung Transplant Program- Guide to Management 38

been case reports of extra-pulmonary and upper lobe PCP infection in HIV-positive patients receiving inhaled pentamidine for prophylaxis.

Toxoplasmosis

Patients with positive IgG titres against toxoplasma receive life-long prophylaxis with trimethoprim-sulfamethoxazole one double strength tablet daily.

Viral Prophylaxis

Valganciclovir is our current drug of choice for CMV prophylaxis. The prophylactic valganciclovir regimens based on donor and recipient serologic status are listed in the Table below. Valganciclovir is renally cleared and therefore the dose should be adjusted for creatinine clearance below 60 ml/min (see renal dosing below). The duration of CMV prophylaxis should be extended in the setting of clinically significant rejection as detailed in a later section. After the prescribed valganciclovir prophylaxis course is completed, CMV virus load should be monitored every two weeks for the following 3 months. Note that in addition to preventing CMV, valganciclovir also simultaneously prevents HSV and VZV outbreaks. Patients who are D-/R- do not require valganciclovir prophylaxis for the prevention of CMV, but do require valacyclovir 500 mg po bid after transplant for the prevention of VZV and HSV infections that can be fatal.

In the setting of poor tolerance of or toxicity from valganciclovir, can consider switching Valcyte to Prevymsis (letermovir) 480mg once daily for CMV prophylaxis. Prevymsis has a lower incidence of leukopenia/neutropenia than Valcyte and does not require renal adjustment. It is only approved for CMV prophylaxis, not for treatment. Letermovir has no coverage of HSV, so patients started on it should also be placed on valacyclovir 500mg BID(or renally adjusted) for HSV prophylaxis.

If prophylaxis must be stopped, All CMV D+ or R+ recipients should have CMV VL checked every two weeks for the first two months and at every clinic visit following discontinuation of Valcyte prophylaxis for at least 6 months. In cases of CMV and medication toxicity consider referral to ID clinic for help in management and consideration of alternative anti-CMV agents.

Table 3: CMV, VZV, HSV prophylactic strategy

CMV Donor	CMV Recip	EBV Recip	Prophylaxis PO Month 0 – 6	Prophylaxis PO Month 6 –12
Pos	Neg	Neg	Valcyte 900 mg daily	Valcyte 900 mg daily
Pos	Pos	Pos	Valcyte 900 mg daily	Valcyte 900 mg daily
Pos	Pos	Neg	Valcyte 900 mg daily	Valcyte 900 mg daily
Neg	Pos	Pos	Valcyte 900 mg daily	-
Neg	Pos	Neg	Valcyte 900 mg daily	Valtrex 1 gram tid
Neg	Neg	Pos	Valtrex 500 mg bid	-
Neg	Neg	Neg	Valtrex 1 gram tid	Valtrex 1 gram tid

* Note valganciclovir should be renally dosed for creatinine clearance below 60 ml/min as shown below:

Table 4: Renal dosing guide for valganciclovir

Creatinine Clearance	Valganciclovir Treatment Dose	Valganciclovir Prophylaxis Dose
>60 ml/min	900 mg PO BID	900 mg PO daily
40-59 ml/min	900 mg PO daily	450 mg po daily
25-39 ml/min	450 mg po daily	450 mg po every other day
10-25 ml/min	450 mg every other day	450 mg po twice a week

Fungus

Aspergillus and Candida

All patients are placed on inhaled amphotericin (10 mg BID for two doses, then increased to 25 mg BID if tolerated) post-operatively and remain on treatment for the duration of the initial inpatient stay. The duration of topical prophylaxis may be extended if bronchoscopic cultures reveal evidence of fungal colonization.

In addition, all lung transplant recipients are started on micafungin 100 mg IV daily at the time of transplantation. Antifungal therapy should be tailored after 7-10 days based on final peri-operative donor and recipient lung cultures, explant review and fungal serologies. If cultures are negative for fungus and galactomannan testing is negative on two separate occasions, then micafungin can be stopped. **Note that beta-d-glucan testing should not be obtained to assess for fungal infection in the first week after transplant, as this can be elevated due to the surgical procedure itself. In addition, BAL galactomannan should only be sent if there is clinical concern for an active Aspergillus infection of the lung, not routinely on surveillance samples.** If cultures grow *Candida* sp. that is susceptible to fluconazole, then the patient should be transitioned to oral fluconazole 400 mg po daily for 3-6 months. If cultures grow *Aspergillus*, then the patient should be transitioned to oral voriconazole 200 mg po BID for 3-6 months. For any other fungal isolates, the ID consult team should be contacted for further guidance.

Coccidioidomycosis

All seropositive recipients should be seen by the infectious disease service prior to transplant for determination of the optimal prophylactic strategy. Typically azole antifungal agents are used for prophylaxis.

Gram-Negative Pathogens

Patients who develop or who have pre-existing resistant GNR colonization are generally placed on inhaled antibiotics until discharge, or longer as circumstances dictate. Inhaled antibiotics typically include Tobramycin (300 mg BID) or colistin (50 mg BID with escalation to as high as 150 mg BID if tolerated).

Adjustments in Prophylaxis During Episodes of Rejection

Patients experiencing acute rejection requiring systemic therapy with pulse-dosed steroids are at increased risk for infection. Prophylactic strategies employed in the immediate post-operative period should be extended or reinstated including:

- Amphotericin nebs 25 mg BID
- CMV / VZV / HSV prophylaxis – restart the post-transplant prophylaxis strategy
 - Recipients who are positive for CMV or whose donors were positive for CMV should resume valganciclovir 900 mg po daily x6 weeks, at which point steroids have been tapered back to baseline dosing.
 - D-/R- recipients should resume valacyclovir 500 mg po BID until 6 weeks after the episode of rejection

Common Post-transplant Infections

Etiologies of Post Transplant Infections

- Bacterial pathogens
 - Community-acquired pathogens like *Streptococcus pneumoniae*
 - MSSA and MRSA
 - Resistant Gram-negative bacteria (e.g., Pseudomonas)
- Viral pathogens
 - CMV (including ganciclovir-resistant CMV*)
 - HSV
 - VZV
 - Influenza
 - Adenovirus
 - RSV*
 - Other respiratory viruses (Parainfluenza, Metapneumovirus)
- Fungal pathogens
 - Aspergillus*
 - Cryptococcus*
 - PCP (patients should remain on life-long prophylaxis)
- AFB
 - Rapidly growing mycobacteria such as *M. abscessus* and *M. chelonae**
 - *M. tuberculosis**
- Others
 - Nocardia*
 - Actinomyces*

* Infections due to organisms that are starred are typically co-managed with the Infectious Diseases service

Basic Approach to Specific Pathogens

Bacterial Infections

Bacterial infections of the airway are an important source of morbidity, particularly in the immediate post-transplant setting. The following approach is recommended in the setting of positive airway cultures immediately post-transplant:

MRSA

4 weeks IV vancomycin (or linezolid if intolerant of vancomycin), consider repeat bronchoscopy and chest CT, as needed, before discontinuation of antibiotics.

MSSA

- If donor derived, complicated airway anastomosis or inflammation on bronchoscopy - minimum four weeks of IV cefazolin, consider repeat bronchoscopy and chest CT, as indicated, before discontinuation of abx.
- If none of the above modifiers, po cefadroxil or equivalent for minimum two weeks, even if quinolone sensitive.

Pseudomonas

Minimum two weeks of IV antibiotics based upon sensitivities, consider CT scan and bronchoscopy, as indicated, before discontinuation of antibiotics.

CMV infections and viremia

Multiple centers have reported the existence of a CMV associated mononucleosis-like syndrome with viremia and fever. We have not seen this syndrome among our patients, perhaps because of the use of valganciclovir prophylaxis. CMV infection is not always synonymous with CMV disease since identification of the virus in cultures from immunocompromised patients is not always associated with active tissue injury. Tissue injury is demonstrated by invasion with the presence of intranuclear and intracytoplasmic inclusion bodies. The decision to treat infection without evidence of active disease is usually based on the clinical course of the patient. Gancyclovir/valgancyclovir is our initial treatment agent in the setting of CMV viremia or disease.

- In the setting of reactivation, management recommendations are as follows:
 - Treatment dose Valcyte 900mg bid (to be adjusted for CrCl)
 - Once 2 viral loads are negative, can drop to secondary prophylaxis (valcyte 900mg daily, to be adjusted for CrCl) for **at least 3-6 months**, depending on how well tolerated the medication. Check viral loads at each clinic visit while on treatment.
 - Check viral load every two weeks for the first two months and at every clinic visit following discontinuation of Valcyte prophylaxis for at least 6 months
- If second reactivation occurs:
 - Treatment dose Valcyte 900mg bid (to be adjusted for CrCl)
 - Once 2 viral loads are negative, can drop to secondary prophylaxis (valcyte 900mg daily, to be adjusted for CrCl), likely indefinitely.

Gancyclovir-resistant CMV infection is a well-recognized problem in lung transplant recipients and we have seen gancyclovir-resistant CMV at BWH. Resistant CMV infection should be suspected in patients with persistent CMV viremia or evidence of progressive CMV disease (colitis, pneumonitis, etc.) in the setting of gancyclovir prophylaxis or treatment. ID consultation is recommended for patients in whom resistance is suspected. A CMV genotype from the blood should be sent in patients who are viremic (a send out lab). In addition CMV cultures of urine, stool, and BAL fluid (if bronchoscopy indicated) should be obtained and sent out for viral sensitivity testing if CMV grows. Once cultures and genotype are obtained, patients may be changed to foscarnet 60 mg/kg IV Q8hours (adjust for renal impairment) while genotype and cultures are pending.

RSV

RSV is a relatively common cause of respiratory infection after transplant during the winter. One center reported an infection rate of 16% among 50 lung transplant recipients closely monitored for respiratory illnesses over one winter season. (Eur Respir J 2006; 28: 131-7). Although this is typically a late complication after transplant, it has been reported in patients within the first 90 days of transplant. Lower respiratory tract RSV infection can cause severe illness.

Treatment of severe RSV infection is controversial. Although several centers have described the use of systemic and inhaled ribavirin to treat RSV infections, there are no randomized controlled trials assessing the efficacy of ribavirin (J Heart Lung Transplant 2003; 22: 745-53; J Heart Lung Transplant 2005; 24: 2114-9.). Our standard approach to RSV at BWH is supportive care. Ribavirin is no longer used at BWH for this indication.

Aspergillus

Voriconazole is the antifungal agent of choice to treat proven or probable aspergillosis. As described in the prophylaxis section above, special attention should be paid to drug-drug interactions when initiating or ending voriconazole therapy. Several of the standard immunosuppressants including tacrolimus, cyclosporine, and sirolimus interact with voriconazole and require significant dose adjustments at the initiation and conclusion of voriconazole therapy. In cases of severe, non-resolving *Aspergillus* infection (or other cavitary processes) surgical debridement of necrotic lung may need to be considered. The transplant infectious disease team should be contacted and/or consulted for all cases of confirmed or suspected aspergillosis.

PTLD (See also section 8, Hematological Concerns)

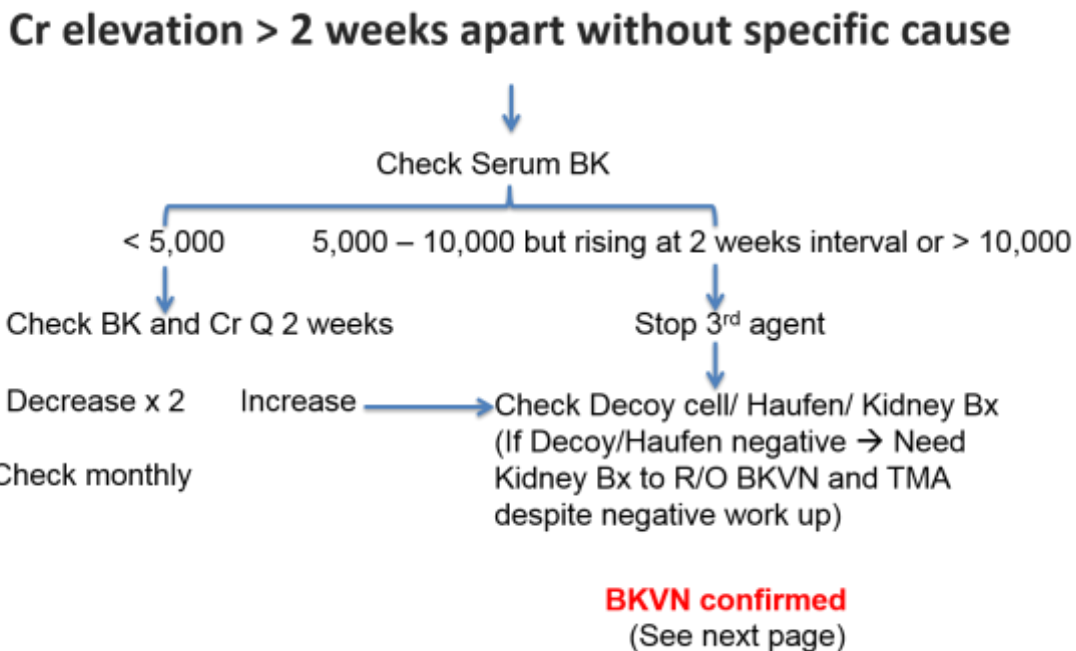
EBV-associated post-transplant lymphoproliferative disorder in lung transplant recipients is a serious complication with a relatively high mortality rate. The incidence reported in the literature is quite variable (2-20%), but the true overall incidence in lung transplant recipients is likely low. One center reported an incidence of 2.5% among 400 lung transplant recipients transplanted over a 10-year period (Chest 2003; 124: 1242-9). Typically PTLT presents as well defined pulmonary nodules in lung transplant recipients (often in the allograft in recipients of single lung transplant). However, extrapulmonary presentations and involvement have been reported. The highest incidence of PTLT is during the first year after transplant, but late PTLT can also be seen.

Diagnosis of PTLD is established by pathologic examination of affected tissue. Because PTLD involves transformed EBV infected cells, treatment is carried out in conjunction with the oncology service. Typically treatment includes reduction in immunosuppression in combination with rituximab therapy (Cancer. 2005; 104: 1661-7). Refractory PTLD is sometimes treated with standard chemotherapeutic regimens such as CHOP. There is no clear evidence that antiviral agents (such as ganciclovir) have any impact on the disease once PTLD is established (Transplantation. 1999; 68:1517-25). In general, antiviral agents are active against the lytic phase of herpes virus infection; because PTLD is caused by lymphocytes that are latently infected with or transformed by EBV, antiviral agents theoretically have no effect.

Per BWH guidelines, in the case of EBV Donor IgG positive organs transplanted into EBV naive (IgG negative) recipients, only ABO identical transplantation will be considered. In addition, in such patients, routine surveillance for EBV viral replication (EBV viral load) should be performed at 1 month post-transplant and every three months thereafter. In the event of development of EBV viremia, referral to Infectious Disease and Ann Lacasce of Hematology/Oncology should be pursued for evaluation for PTLD and consideration of pre-emptive therapy with Rituximab.

BK Virus

BK virus is a rare cause of nephropathy in lung transplant recipients. In the event of BK related nephropathy, published data suggests patients will almost uniformly experience viremia in addition to shedding of BK virus in the urine. Management involves a multi-pronged approach, as outlined in our suggested management algorithm below.



BKVN Confirmed

Start LFM (target trough 50-100) AND/OR IVIG 1g/kg

↓
Check serum BK Q 2 weeks

↓
If rising

├── **Frequent/ Recent rejection
within 3 mo or < 1 y after
TXP**

- Add LFM if not already on OR
- IVIG if not already on or last dose > 2 weeks OR
- Add Everolimus (target 4-6) and reduce CNI target by 30%; check baseline ImmuKnow and F/U at 2-3 months OR
- Compassionate use/ Trial Brincidofovir

IVIG can be given monthly until response seen
If BKV persist → Combination therapy

└── **No frequent/ recent
rejection AND > 1 y after
TXP**

- Reduce CNI target by 30% and check baseline ImmuKnow F/U at 2-3 months AND/OR
- Add LFM if not already on OR
- IVIG if not already on or last dose > 2 weeks OR
- Compassionate use/Trial Brincidofovir

Section 7: Approach to Deteriorating Lung Function

Declining pulmonary function testing in lung transplant recipients can be a manifestation of various problems. These include:

- Acute rejection
- Chronic lung allograft dysfunction
- Antibody-mediated rejection
- Airway stricture
- Infection
- Native lung hyperinflation with compression of the allograft
- Aspiration
- Vascular anomaly with shunt (progressive dyspnea/hypoxemia with stable spirometry)

Symptoms can also be variable or absent in association with an observed decline in PFT's. Patients can present with the following:

- Dyspnea on exertion
- Dyspnea at rest
- Cough
- Wheeze
- Asymptomatic
- Decline in spirometry
- Decline in arterial oxygen saturation

General Approach

The evaluation of declining PFT's in the post-transplant setting should include:

- Spirometry and oximetry to verify results of data recorded at home. All lung transplant patients should have a baseline "best" post-transplant FEV₁ (defined as the average of the two best post-transplant FEV₁ values measured at least three weeks apart) established to be used as a reference value.
- CXR
- CBC and chemistry panel (blood cultures if indicated, etc.)
- Blood for pre-screen/single antigen testing with assessment of donor specific antibody. If strong concern for antibody mediated rejection or urgent need for quick initiation of treatment, request assessment of titers, and consider requesting c1q assessment (see LXMG 05.3).
- Sputum cultures if there is a productive cough (Gram's stain, culture, mycology, AFB if indicated)
- Assessment for ongoing GERD, if not recently performed
- Chest CT scan if the CXR is difficult to interpret, if there are findings that need to be defined further (such as nodular infiltrates), or if native lung hyperinflation is a leading diagnosis. Consider inspiratory/expiratory views to assess for air trapping.

- Bronchoscopy
 - May be performed depending on the results of these tests. Bronchoscopy is indicated to assess for infection, to evaluate airway problems (for example, a stricture) or hemoptysis.
 - BAL is useful to evaluate for infection; and transbronchial biopsies are indicated to diagnose acute rejection, malignancy, and to increase the diagnostic yield for certain infections. Specific indications are discussed in detail below.
 - BAL should be routinely sent for:
 - Gram's stain and aerobic/anaerobic bacterial culture
 - Mycology
 - Viral cultures (CMV, adenovirus, HSV and any other clinically indicated viruses – e.g., RSV, Influenza, Parainfluenza, Metapneumovirus)
 - AFB
 - Modified AFB
 - PCP
 - Cell count (BAL neutrophilia has been shown to correlate with response to treatment of rejection).
 - Transbronchial biopsies (if performed) should be hand-delivered to the pathology laboratory, with RUSH on the requisition only if clinically indicated (this will assure a reading by the next afternoon).

Rejection

Acute Rejection

There are two subcategories of acute cellular rejection: vascular and airway (lymphocytic bronchiolitis/ bronchitis). A history of acute rejection is the most important risk factor for the development of chronic rejection.

Acute rejection is common, occurring in 35% of patients within the first year of transplant. (JHLT. 2013 Oct; 32(10): 965-978 1) Acute rejection usually (but not always) occurs early after transplantation. It is characterized by an acute mononuclear cell infiltrate within the vessels or airways of the allograft (see table). The onset of symptoms is acute to subacute. Clinical features are nonspecific and include any or all of the following: SOB, cough, low-grade fever, infiltrates, reduced oximetry and reduced spirometry. Patients may also be asymptomatic.

Histology is the gold standard for diagnosis of acute rejection. Ground-glass opacities on chest CT are suggestive of acute rejection, but are neither sensitive nor specific for this process.

Biopsies are graded for acute rejection according to the ISHLT guidelines updated in 2007 (see tables below). (JHLT 2007; 26: 1229-1242.)

Histologic Grading Schema

- Acute vascular rejection:

GRADE	Description
A0	No vascular infiltration
A1	Minimal vascular infiltration
A2	Mild vascular infiltration
A3	Moderate vascular infiltration
A4	Severe vascular infiltration

- Acute airway rejection (lymphocytic bronchitis/bronchiolitis):

GRADE	DESCRIPTION
B0	No airway inflammation
B1R	Low grade airway inflammation
B2R	High grade airway inflammation
BX	Ungradable

Treatment of Acute Rejection

Grade A2 or higher and/or any grade B is treated with 3 days of pulse solumedrol 1 gm iv daily followed by a 2.5 week taper back to the patient's baseline prednisone dose. A1 rejection may also be treated based on clinical picture (if lung function is declining). If not treated, repeat biopsy in 6 weeks may be indicated.

- The standard taper employed is:
 - 60 mg x 3 days
 - 50 mg x 3 days
 - 40 mg x 3 days
 - 30 mg x 3 days
 - 20 mg x 3 days
 - 10 mg x 3 days

Due to the increased risk of opportunistic infections during the period of intensified immunosuppression, escalated prophylactic therapy is usually instituted:

- Amphotericin nebs 25 mg bid
- CMV / VZV / HSV prophylaxis – restart the post-transplant prophylaxis strategy:
 - Recipients who are positive for CMV or whose donors were positive for CMV should resume valgancyclovir 900 mg po daily x6 weeks, at which point steroids have been tapered back to baseline dosing.
 - D-/R- recipients should resume valacyclovir 500 mg po BID until 6 weeks after the episode of rejection.

Therapy can be given as an inpatient if potential management issues related to administration of high dose steroids exist in a given patient (hyperglycemia, psychosis), or alternatively can be given as an outpatient by home care companies.

Follow-Up

Repeat bronchoscopy with TBBx is performed 4-6 weeks after solumedrol bolus to assess response. If there is still evidence of acute rejection on follow-up biopsy, or in the event of recurrent acute rejection (s/p 3 steroid pulses) adjunct therapy is considered depending on the patient's clinical and rejection history. If the patient is on CSA/azathioprine, a switch to FK506/MMF is considered. If the 1 year surveillance bronchoscopy demonstrated grade A1 rejection, a repeat biopsy should be performed in 4-6 weeks. In addition, evaluation for causes of recurrent or persistent acute rejection should be performed, including assessment for acid or non-acid reflux (see below).

Adjunctive therapy

If acute rejection is still present on the follow-up bronch or in the event of recurrent acute rejection (s/p 3 steroid pulses) then adjunct therapy is initiated. Repeat biopsies may be performed after adjunct therapy if the patient is a candidate for further therapy. Options include:

- Alemtuzumab: Humanized monoclonal antibody to CD52 antigen on B cells (see reference: AJT 2007; 7: 2802-8)
- Photopheresis: IV treatment with a light-sensitive psoralen (psoralen 8-methoxypsoralen [8-MOP]) which, when exposed to UV light causes apoptosis of activated T cells (see LXMG 05.4). This therapy is administered by the transfusion service. Patients require reliable IV access. The standard protocol is:
 - Treatment on 2 consecutive days weekly for 4 weeks, then
 - Treatment on 2 consecutive days every other week for 4 weeks, then
 - Treatment on 2 consecutive days monthly for 4 months (for a total duration of therapy of 6 months)
 - Consider evaluation for retransplant (see retransplant section).

Chronic lung allograft dysfunction (CLAD)

In lung transplant recipients, chronic lung allograft dysfunction is manifest pathologically as obliterative bronchiolitis (OB)/Bronchiolitis Obliterans Syndrome (BOS) or Restrictive Allograft Syndrome (RAS). In some studies a history of airway rejection has been associated with increased risk of developing OB.

Obstructive CLAD

OB/BOS occurs in up to 50% of lung transplant recipients by 5 years post-transplant. It typically occurs later in the post-transplant course, but according to the ISHLT registry data, 7-10% of patients experienced OB/BOS within the first year of transplant (JHLT. 2018 Oct; 37(10): 1155-1206). Clinical signs and symptoms are nonspecific and include progressive SOB/DOE, cough, reduced oximetry and spirometry, and most characteristically worsening airways obstruction that is refractory to bronchodilators. Fever and pulmonary infiltrates are uncommon. Patients often appear to have a refractory bronchitis. OB/BOS is frequently associated with bronchiectasis and recurrent infections may complicate the course of patients with OB/BOS. Some reports suggest that demonstration of a mosaic pattern of air trapping on

inspiratory and expiratory HRCT is both sensitive and specific for OB, and this may be a helpful adjunctive finding.

Histologic Grading Schema

- Chronic airway rejection (OB):

GRADE	DESCRIPTION
C0	Absent
C1	Present

- Chronic vascular rejection (accelerated vascular sclerosis):
D: present or absent

Bronchiolitis Obliterans Syndrome (BOS)

OB is a pathologic diagnosis and is particularly difficult to diagnose by transbronchial biopsy (TBBx) because of its patchy distribution. Repeated transbronchial biopsy procedures will increase the sensitivity, but the risk of bleeding with TBBx may be higher in patients with OB due to the presence of bronchiectasis. Surgical lung biopsy may be indicated in selected patients, particularly if the differential diagnosis includes infections or other potentially treatable conditions.

Because of the low yield of TBBx and increased risk of repeated procedures in OB, an alternative means of diagnosing this process has been developed, termed “bronchiolitis obliterans syndrome” (BOS). BOS is defined as a reduction in FEV₁ of > 20% of baseline (highest – see definition above) FEV₁ post-transplantation in the absence of any known other cause.

Staging Schema

STAGE	CRITERIA
BOS 0	FEV ₁ > 90% baseline and FEF 25-75 > 75% baseline
BOS 0-p	FEV ₁ 81-90 % baseline and/or FEF 25-75 <= 75% baseline
BOS 1	FEV ₁ 66-80% baseline
BOS 2	FEV ₁ 51-65% baseline
BOS 3	FEV ₁ <= 50% baseline

JHLT 2002; 21: 297-310.

Restrictive Allograft Syndrome (RAS)

Increasing literature suggests that a restrictive form of CLAD can manifest independent from or overlapping with OB/BOS. Patients with RAS tend to have a restrictive decrement in pulmonary function testing (decline in FVC and/or TLC), which may be associated with upper lobe predominant infiltrates/pleural thickening and a decrease in lung volumes. Diagnostic criteria for RAS are not well developed. Comparative clinical characteristics and proposed diagnostic strategies are provided below. Studies generally show that mortality is higher in patients with RAS than those with OB/BOS.

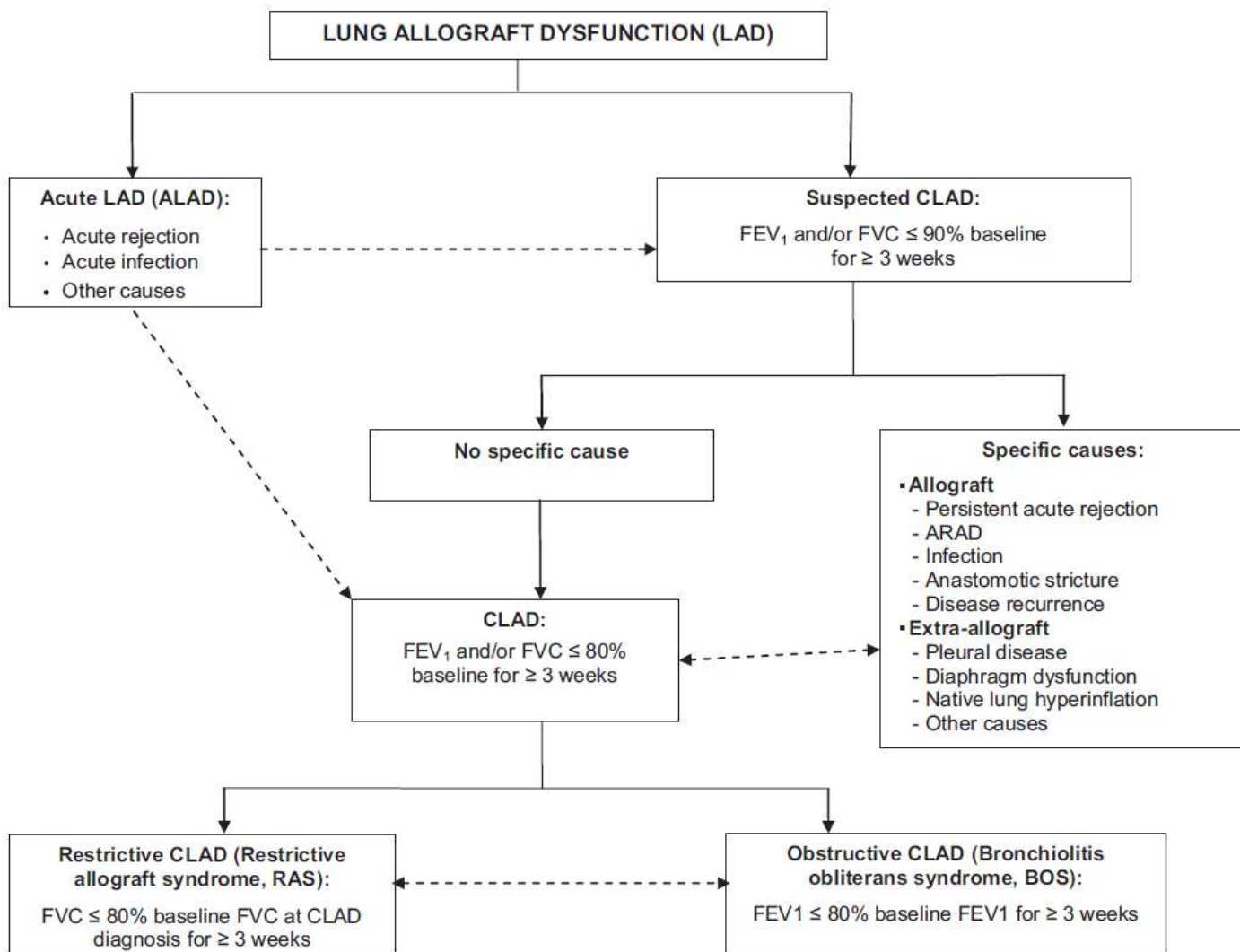
Table 1 Emerging Phenotypes of Chronic Lung Allograft Dysfunction: Key Features^a

Entity	Classic BOS	RAS
Pulmonary function	Obstructive (FEV ₁ ≤ 80% of stable baseline value)	Restrictive (TLC ≤ 90% of stable baseline value) and/or FEV ₁ /FVC normal or increased (with FEV ₁ and/or FVC decline ≤ 80% of stable baseline value)
HRCT thoracic imaging	Air trapping usually present No/minimal infiltrates With/without bronchiectasis	Infiltrates usually present With/without bronchiectasis With/without air trapping
Histopathology	OB (difficult to diagnose by transbronchial biopsy specimen)	Parenchymal/pleural fibrosis with/without OB
Clinical course	Typically progressive but may stabilize Recipients may have coexistent chronic bacterial infection May evolve to RAS	Tends to be relentlessly progressive May start as or coincide with BOS
Other	Usually responds poorly to pharmacologic therapies	Correlates with the presence of early DAD post-transplant

BAL, bronchoalveolar lavage; BOS, bronchiolitis obliterans syndrome; CLAD, chronic lung allograft dysfunction; DAD, diffuse alveolar damage; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; HRCT, high-resolution computed tomography; OB, obliterative bronchiolitis; RAS, restrictive allograft syndrome; TLC, total lung capacity.

^aInfection, other pathologies (e.g., acute cellular rejection, lymphocytic bronchiolitis, antibody-mediated rejection), and/or other causes of allograft dysfunction (e.g., significant gastroesophageal reflux, pleural disorders, anastomotic dysfunction, obesity, thromboembolic disease, recurrent primary lung disease, etc) must be ruled out.

Journal Heart Lung Transplant 2014; 33: 127



Journal Heart Lung Transplant 2014; 33: 127

Treatment of CLAD

CLAD is much less amenable to therapy than acute rejection. Nevertheless, some patients with OB/BOS will experience an improvement or stabilization in their spirometry with therapy. Thus therapy should be considered for any patient in whom OB has been demonstrated by biopsy or in any patient with a decline of > 20% in FEV₁ without another cause (BOS). Data suggest that azithromycin (250 mg 3 x/wk) may have anti-inflammatory properties that lead to improve lung function in established OB. Data are conflicting about the potential benefits of montelukast (10 mg po daily) for stabilization of lung function in CLAD. The long-term success of these therapies are unknown at the present time. Other treatment options are similar to those used for refractory acute rejection:

- Alemtuzumab
- Photopheresis
- Consider evaluation for re-transplantation

The efficacy of treatment in the setting of RAS is poorly studied.

Antibody Mediated Rejection

Antibody Mediated Rejection (AMR) has been best described in the kidney transplant population. Presentations consistent with hyper-acute, acute, and chronic rejection have been described in association with circulating donor specific antibodies. A schema for the diagnosis of AMR follows:

Table 1 Definition and Diagnostic Certainty of Clinical Pulmonary Antibody-mediated Rejection

	Allograft dysfunction	Other causes excluded	Lung histology	Lung biopsy C4d	DSA
Definite	+	+	+	+	+
Probable ^a	+	+	+	-	+
Probable	+	+	+	+	-
Probable	+	+	-	+	+
Probable	+	-	+	+	+
Possible	+	+	+	-	-
Possible	+	+	-	-	+
Possible	+	+	-	+	-
Possible	+	-	+	+	-
Possible	+	-	+	-	+
Possible	+	-	-	+	+

DSA, donor-specific antibodies; +, item present; -, item absent or missing.

^aThere is building evidence that antibody-mediated rejection can be diagnosed confidently in the absence of positive C4d staining, hence this group is recognized separately.

Table 2 Definition and Diagnostic Certainty of Sub-clinical Pulmonary Antibody-mediated Rejection

	Lung histology	Lung biopsy C4d	DSA
Definite	+	+	+
Probable	+	-	+
Probable	-	+	+
Probable	+	+	-
Possible	+	-	-
Possible	-	+	-
Possible	-	-	+

DSA, donor-specific antibodies; +, item present; -, item absent or missing.

J Heart Lung Transplant 2016; 35: 397

The demonstration of circulating donor specific antibody in conjunction with capillaritis should raise the concern for AMR, though the findings are often subtler. The utility of c4d staining in the lung remains controversial.

Consensus has not yet been reached on the best way to manage AMR. Treatment options include plasmapheresis, IVIG, rituximab, and in more severe cases, alternative agents to prevent antibody production or direct complement inhibitors. At BWH the following algorithm is followed for the assessment and management of AMR:

- AMR is suspected in the setting of a decline in PFT's, or other signs of allograft dysfunction, in the presence of circulating donor specific antibody (DSA), or pathologic manifestations consistent with AMR, such as capillaritis, or other manifestations as outlined in published literature (JHLT 2013; 32(1): 14).
- In the setting of acute respiratory failure of unclear etiology, recurrent acute cellular rejection, or chronic lung allograft dysfunction, AMR should be considered in the differential diagnosis.
- Our program does not perform routine surveillance for de novo DSA in the absence of clinical symptoms. All recipients should be assessed for sensitizing events (see appendix W) at every clinic visit and when contacted regarding a change in clinical status. Candidates noted to have sensitizing events should undergo repeat screening for circulating antibodies immediately after identifying the event and then monthly until three assessments have been completed.
- In the setting of concern for AMR, assessment for DSA will be performed by completing prescreen/class I and II single antigen testing.
- If DSA is detected and a decision is made to initiate therapy, request a c1q assay to assess for cytotoxicity and dilutional assessment (titers) to assess response to therapy. Consider c1q assay and dilutional assessment (titers) with the initial request for hospitalized patients, or patients with rapid decompensation in whom a determination to initiate therapy is needed urgently. In these circumstances, contact the tissue typing lab to request urgent completion of testing.
- If tissue samples are obtained in the setting of suspected AMR, consider request for c4d staining. While c4d deposition in the lung is more difficult to interpret than in the kidney, this assessment can support the diagnosis if staining is positive in a pericapillary distribution. c4d staining should also be considered in the setting of high grade (A3 or A4, B2R) or recurrent acute cellular rejection.
- AMR can occasionally occur in the absence of circulating DSA, and strong consideration should be given to treatment in the presence of allograft dysfunction with supporting pathologic changes, even in the absence of DSA.
- After treatment, DSA should be repeated within one week, with dilutional assessment. A follow up schedule for DSA testing will be made on a case by case basis.

Treatment:

- Plasmapheresis Every Other Day x 3 sessions
- IVIG (Gammagard Liquid 10%) 2gm/kg x 1 dose (please use IBW to calculate dose and round to the nearest 5gm), should be given following the final plasmapheresis session. Premedication 30-60 minutes prior to each IVIG infusion is required:
 - Acetaminophen 650mg PO/PR x1
 - Diphenhydramine 50mg PO/IV x1
 - Methylprednisolone 40mg x1 as pre-medication to IVIG. Please see the IVIG Drug Administration Guideline for infusion instructions and adverse reactions to monitor for.
http://www.bwhpikenotes.org/policies/Pharmacy/Drug_Administration/DAG/Igg02DAG.htm
 - Rituximab 375mg/m² x1 following completion of the second dose of IVIG. Please schedule a chemotherapy nurse to infuse the medication at least 24 hours in advance (contact Chemo in the Outfield RN Michaelle Renard [pg 13453]). The patient must have height & weight measured, verified & documented by two of the floor nurses. These measurements are required for accurate calculation of the dose and must be done on the day the order is entered in the chemotherapy order entry system (COE).
 - Rituximab also requires pre-medication with Acetaminophen, diphenhydramine and methylprednisolone at the doses described above.
- Repeat serum screen for HLA 1 week after therapy and consider further therapy with weekly Rituximab, additional plasmapheresis, or alternative therapies such as bortezomib, if indicated. (see appendix W for bortezomib protocol).

Airway Stricture

General Features/ Clinical Presentation

The signs and symptoms of airway stricture are non-specific and include shortness of breath, focal wheeze, reduced spirometry (sometimes with a characteristic flattening of the expiratory limb of the flow-volume loop), reduced exercise tolerance, difficulty with clearance of secretions, and recurrent infections distal to the stricture. Strictures most commonly occur 1-2 centimeters distal to the anastomotic site and often lead to obstruction of the bronchus intermedius. Risk factors may include ischemic time, surgical technique, rejection and infection.

Diagnosis

Bronchoscopy; consider BAL and TBBx given potential associations; Chest CT with airway reconstruction can be helpful for diagnosis, following the stricture, or for planning interventions.

Treatment

Serial balloon dilatations with 6 mm, 8 mm, 10 mm balloons (rarely up to 12 mm) are usually performed in the OR. High dose inhaled steroids may be administered at the same time to decrease local response to the trauma of dilatation. This may decrease the propensity for re-stenosis, although specific data regarding this are not currently available.

Follow-up

Serial PFTs and follow-up bronchoscopy should be performed until the stricture has stabilized at an acceptable diameter. Those patients with refractory stenosis or residual malacia may require stent placement.

Infection (see also Section 6)

General / Clinical Features

Patients with infection may present with cough, sputum production, fever, shortness of breath, chest tightness, wheezing, or focal or diffuse infiltrates on CXR. It is critical to remember that lung transplant patients are immunocompromised and therefore even life-threatening infections may present with relatively minor signs and symptoms. It is also important to note that specific infections may present in unusual ways in these patients, for example bacterial pneumonia may present as nodular infiltrates.

There is a significant degree of overlap in clinical presentation between rejection and infection. The two cannot be differentiated on clinical grounds. A confirmatory diagnostic study is required. Transplant patients with a new pulmonary process should never receive pulse steroids until infection has been convincingly ruled out with bronchoscopy.

Common Etiologies of Infection (see Section 6)

Diagnosis

- Sputum cultures (bacterial, fungal, AFB) may be diagnostic, particularly if the patient is not acutely ill
- Nasal viral swabs for influenza, parainfluenza, adenovirus, RSV
- Bronchoscopy with lavage and TBBx is frequently considered, particularly if the patient is acutely ill or worsening. Biopsy is also useful to rule out allograft rejection or other processes (such as PTLD) that may mimic infection or may be present concomitantly.

In rare instances, surgical lung biopsy may be required to identify an infectious process or to differentiate infection from rejection, malignancy or other processes.

Treatment

Broad-spectrum empiric therapy is generally initiated to cover the most common pathogens, unless previous colonization can help to guide antibiotic choices. Additional empiric antimicrobial coverage is added depending upon the severity of the illness, previous culture results in the specific patient, and specific clinical features such as a history of aspiration, exposures, or suggestive findings such as nodular infiltrates on chest CT. Specific therapy is tailored to the results of cultures or additional diagnostic studies.

Native Lung Hyperinflation (Single Lung Transplant Emphysema Patients)

Patients with native lung hyperinflation may present with SOB, reduced oximetry/spirometry, or reduced exercise tolerance.

Diagnosis may be difficult to make:

- First rule out other causes including infection, rejection (by biopsy)
- Chest CT demonstrating hyperinflation of native lung
- Physiology: spirometry, lung volumes

Treatment

LVRS of native lung should be considered on a case by case basis.

Aspiration / GERD

General Considerations

GERD and aspiration are increasingly recognized as potential co-factors for allograft dysfunction and/or allograft rejection. However, a definitive causal link has not yet been made. The precise etiology of GI dysfunction post-transplant is not clear and may be due to surgical trauma, effects of medication (for example calcineurin inhibitors) or both. Optimal strategies to prevent and/or treat the problem are also unclear.

Diagnosis *Pre-transplant*

All patients undergo impedance 24 hour PH probe and esophageal manometry as part of their pre-transplant screening. Patients may also undergo a gastric emptying study. If these studies confirm significant reflux, gastric emptying is normal and the patient's pulmonary function can tolerate it, Nissen fundoplication will be considered early after lung transplant. If they cannot tolerate the procedure or gastric emptying is abnormal, medical anti-reflux therapy is optimized and the barium swallow is repeated. Particular attention to this evaluation should be paid in patients with scleroderma, in whom esophageal involvement can be profound.

Diagnosis *Post-transplant*

Patients with symptomatic reflux undergo the same diagnostic series of tests as pre-transplant patients.

Treatment

Medical anti-reflux therapy is maximized using H2 blockers, proton pump inhibitors, and pro-motility agents as indicated. Conservative measures including limiting meal size, elevating the head of the bed > 45°, and not eating at least 2 hours before bedtime are stressed. If reflux is significant and/or appears to be impacting lung function then Nissen fundoplication is considered.

Section 8: Long Term Medical Management of Lung Transplant Recipients

Bone Health

General

Bone loss occurs rapidly in the immediate post transplant period, with as much as 4-10% loss in the spine and 3-11 % loss in the hip, in the first 6 - 12 months. This is associated with increased fragility: the rate of spine compression fractures is as high as 50% and the rate of other fractures is also alarmingly high (up to 36%). There have been few studies to identify those at risk for this complication. Those with a lower bone mass pre transplant, women, and those with greater steroid exposure are at greater risk. These transplant recommendations therefore include treatment starting immediately after transplantation with re-evaluation in one year. (J Clin Endocrinol Metab 2005; 90: 2456-65.; J Bone Miner Res 2004; 19: 1919-32; Osteoporos Int 2003; 14: 617-30; N Engl J Med 2004; 350: 767-76)

Evaluation in pre-transplant recipients: prevention

- Identify modifiable risk factors
 - Smoking
 - Alcohol consumption
 - Hyperthyroidism
 - Hypogonadism
- Laboratory work-up in all transplant recipients
 - Evaluate mineral homeostasis
 - Check serum calcium, albumin, phosphate, and magnesium levels
 - Consider ionized calcium if low serum albumin levels are present
 - If calcium level is abnormal, consider checking serum PTH level
 - Check serum 25-hydroxyvitamin D (25-OHD) levels
 - Evaluate kidney function
 - If history of kidney stones or using glucocorticoids check 24 hour urine for total calcium, creatinine to ensure patient is not hypercalciuric and at risk of nephrolithiasis
- Measure bone mineral density, preferably at the time of acceptance to the waiting list
 - If clinically warranted (e.g., back pain), consider spine radiographs or vertebral fracture assessment by dual x-ray absorptiometry to detect prevalent fractures
- Review recommended daily allowance for calcium (1000-1500 mg/day in divided doses) and vitamin D (800-1000 IUs/day) through diet and supplements
 - If using steroids: 1500 mg of calcium
 - Use calcium carbonate, unless patient is on antacids or proton pump inhibitors then use calcium citrate
 - 25-OHD levels should be >30ng/ml
 - If baseline serum levels of 25-OHD < 20ng/ml, then replete with ergocalciferol 50,000 units once a week for eight weeks (re-check levels after repletion).
- Encourage weight bearing and strengthening exercises

- If considering treatment for pre-transplant osteoporosis/osteopenia would refer to endocrinologist/primary care physician for complete work-up: Clinical scenarios that would benefit from a more extensive diagnostic work-up include:
 - History of fractures of the spine, hip or wrist (fragility fractures)
 - Z-score of -1.5 (Z scores are used in clinical management of pre-menopausal women).
 - In a patient with T scores of <-2.0
- Use of combined clinical risk factors and bone mineral density to estimate “absolute” fracture risk are under development.
- Consider treatment of hypogonadism
- Endocrine evaluation
 - Bone mineral density Z score of <-1.5
 - Consideration of treatment in the pre-transplant patient
 - Evidence of hypogonadism and considering replacement

Evaluation Immediately After Transplantation

If using an immunosuppressant regimen that includes high doses of glucocorticoid medications, randomized controlled trials suggest patients at highest risk for rapid bone loss and consequent vertebral fractures are postmenopausal women. However, the lack of reliable clinical predictors to identify patients who will experience bone fractures renders all transplant recipients candidates for the prevention of bone loss seen in the first 6-12 months after transplantation. (J Bone Miner Res 2004; 19: 1919-32; American Society for Bone and Mineral Research, 2006: 296-302)

- Resume calcium and vitamin D replacement as above
- Resume weight-bearing exercise (e.g. organized rehabilitation program)
 - Begin treatment with bisphosphonates either oral or intravenous after surgery; considered first-line therapy in all transplant recipients regardless of bone density test with re-evaluation (including bone density) in one year. Bisphosphonates carry a Category C rating for safety in pregnancy due to toxic effects in rats. Bisphosphonates cross the placenta and accumulate in fetal bones in an experimental rat model:
 - Alendronate 70 mg once a week, patient must be able to sit up for 30-45 minutes; take on an empty stomach with a full glass of water
 - Risedronate 35 mg once a week, patient must be able to sit up for 30-45 minutes; take on an empty stomach with a full glass of water
 - Intravenous agents: must pre-medicate with acetaminophen 650mg for every 4 hours the day of and after the infusion; prior to infusion vitamin D levels must be $\geq 30\text{ng/ml}$, and serum calcium must be within the normal range. Do not use if eGFR is \leq to 30cc/ml. Please review FDA approved infusion instructions:
 - Zoledronic acid 5 mg once a year (given in 100cc over 15 minutes)
 - Pamidronate 30-60 mg every three months
- Consider treatment of hypogonadism (see above section)

Continued Evaluation for the Transplant Recipient: Long-term Care Following Transplantation

- Monitor renal function, calcium homeostasis and 25-OHD levels
- Continue calcium and vitamin D treatments as above
- If not on bisphosphonate would consider initiating a medication. Consider patient risk factors such as:
 - Age
 - Menopausal status
 - Previous fractures (wrist, hip or spine)
 - Bone density
- Follow bone mineral density measurements annually to every two years to re-evaluate if continued therapy with osteoporosis medications is necessary.

Hypercholesterolemia

Hypercholesterolemia has been a common problem post-transplantation among our patients, and is reported as a common problem by other centers as well. It is thought to be related to effects of CNI and prednisone, and unfortunately in most cases it does not improve (and may worsen) with reductions in prednisone doses over time. Increases are often seen in HDL, LDL cholesterol, and triglycerides.

An approach to assessment is as follows:

- Measure total, HDL, LDL, and VLDL cholesterol and TG approximately 1 month post-transplant in the fasting state (after at least 8 hours of fast overnight)
- Patients with values LDL > 100, HDL < 40 mg (men) or 50 mg (women), or triglycerides > 150 mg/dl should have a dietary consult and begin a low cholesterol - low saturated fat diet. The literature suggests this is effective in only a minority of cases.
- Repeat assessment in 1 month.
- If values remain elevated patients should be considered for lipid lowering therapy.

Medical therapy may involve a HMG-CoA reductase inhibitor or a fibrate depending upon the specific lipid profile. Gemfibrozil and the HMG-CoA reductase inhibitors can cause myositis and the risk is increased among patients on CNI. This requires specific monitoring during therapy, and is reversible with discontinuation or decrease in dosage of the medication.

Pravastatin 10 mg per day is a reasonable starting dose. If this is tolerated without difficulty, the dose can be advanced to 20 mg per day and liver function tests and muscle enzyme levels followed. Recent data suggests an additional benefit with regard to bronchiolitis with statin.

Diabetes Mellitus

5-15% of CF patients develop CF-related DM. The median age at diagnosis is 20 years. Many patients have glucose intolerance. Blood glucose values should be monitored carefully in CF patients post-transplant, when corticosteroids and immunosuppressive medications are likely to exacerbate DM or glucose intolerance. In addition, corticosteroids and immunosuppressive medications can cause or exacerbate DM in non-CF lung transplantation patients. Patients on corticosteroids are very insulin resistant during the day, particularly

after they take their prednisone. Therefore, timing NPH administration with Prednisone can be an effective way to control daytime hyperglycemia. In addition, these patients tend to have substantial post-prandial hyperglycemia after breakfast and lunch, and often require short-acting insulin with meals. Blood sugars usually come down in the evenings, as the Prednisone wears off. Patients should be monitored with hemoglobin A1c values every 3 months, with a target of < 7%. DM patients should undergo yearly dilated eye examinations, and have their blood pressure, lipids, and renal function monitored.

Hypertension

Hypertension is very common post transplant, in part from medications. Calcineurin inhibitors (cyclosporine, FK 506) and steroids promote sodium retention and predispose to hypertension. Patients often require treatment for this problem. This is of particular importance since patients on CNI can experience “microvascular” hypertension and intracerebral hemorrhage even with borderline elevations in their blood pressure. This type of CNI neurotoxicity has been observed as early as the third week post transplant, and as far out as 9 months post transplant. MRI scan is the best way to detect this process.

The same criteria are used for initiating anti-hypertensive therapy in the post-transplant patient as in the general population. The following management approach is suggested:

- Document BP elevation on 2 separate occasions.
- Rule out possible relationship to secondary causes.
- Lifestyle Modifications:
 - Weight Reduction- goal = normal BMI 18.5-24.9
 - DASH Diet- Rich in fruits, vegetables, low fat dairy and decreased total and saturated fats.
 - Dietary Sodium Reduction- goal $\leq 100\text{mmol/day} = 2.4\text{g sodium or }6\text{g sodium chloride daily}$.
 - Aerobic Activity
 - Moderation of Alcohol Consumption
- Medical therapy: While there is no consensus in the transplant community regarding the best antihypertensive regimen post transplant, some data suggest that calcium channel blockers and angiotensin converting enzyme inhibitors may be beneficial, thus these agents are generally considered first line. However this should not preclude the use of medications which have been proven beneficial for their respective compelling indications (see chart below).

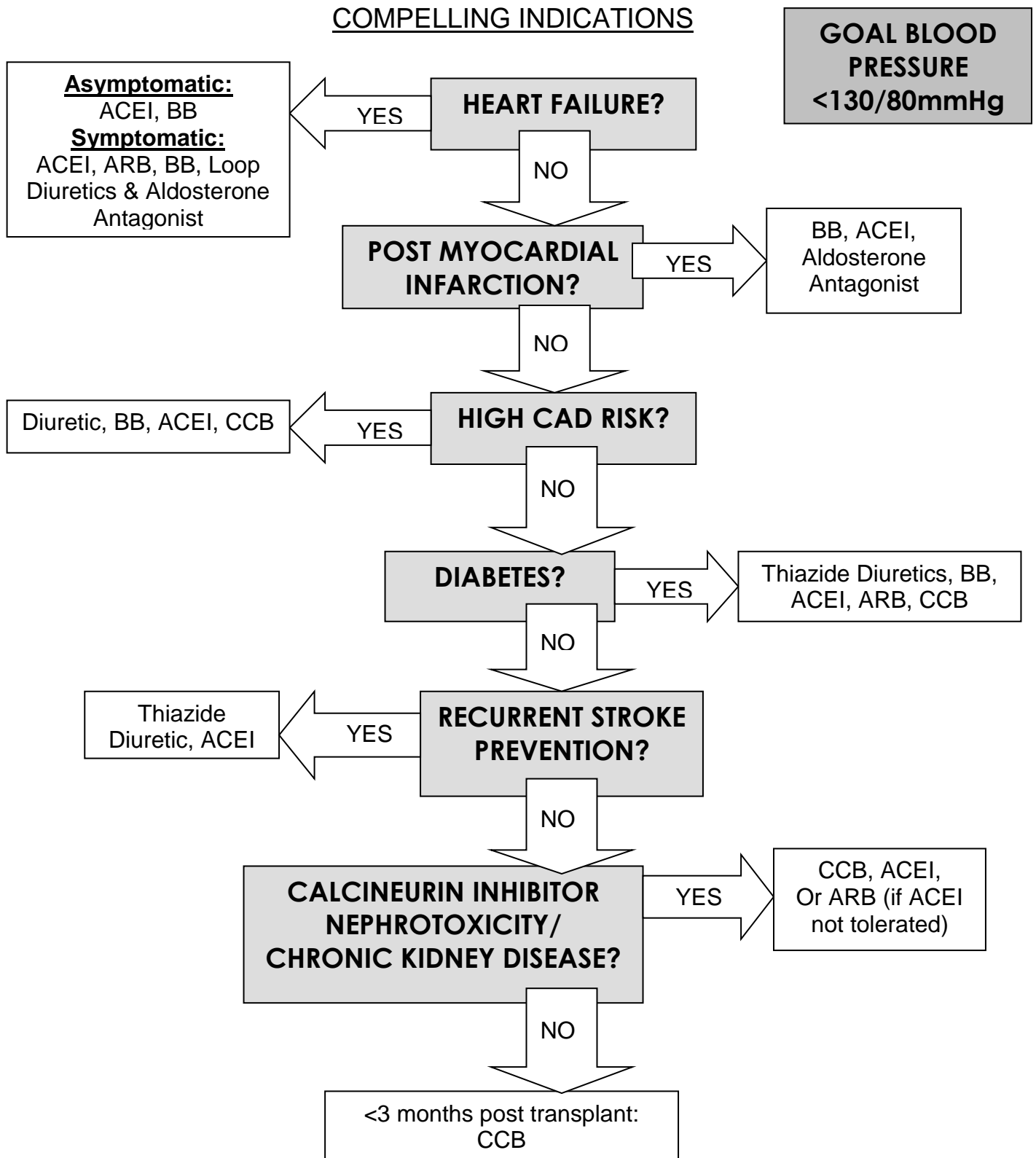
Preferred Agents

- Calcium Channel Blockers (CCB) - There is some evidence that these agents may protect against CSA/TAC related renal dysfunction through counteracting the vasoconstriction caused by CNI. Dihydropyridine CCB (amlodipine, nifedipine) are generally preferred over non-dihydropyridine CCB (diltiazem, verapamil), which are moderate inhibitors of CYP450 3A4 leading to increased levels of CNIs. However diltiazem and verapamil may be used as long as CNI dose is modified and trough levels of CNIs are carefully monitored.

- ACE inhibitors (ACEI) have also shown some benefit in transplant recipients and are known to be beneficial in patients with chronic kidney disease. It is known that ACEI cause efferent arteriole vasodilation and in combination with CNI (which vasoconstrict the afferent arteriole) may decrease creatinine clearance, due to the reduction in intra-glomerular pressure. However, for the majority of patients this increase in serum creatinine is small, and transient. Overall these agents are well tolerated. Potential adverse effects include cough, angioedema and hyperkalemia. When starting an ACEI, initiate at a low dose and monitor blood pressure. Renal function and potassium should be monitored at baseline, one week following and every few weeks thereafter until comfortable that creatinine and potassium are stable.
- Angiotensin Receptor Blockers share many of the same functional effects as ACE inhibitors and may be used as an *alternative* agent in patients intolerant to ACE inhibitors. The side effect profile and monitoring should be considered equivalent to ACEI.
- Other agents
 - β -blockers can be used effectively, even in patients with pre-existing airflow obstruction although exacerbation of bronchospasm is possible and needs to be considered. These drugs can also blunt response to hypoglycemia in CF patients with DM.
 - HCTZ can be used safely but can cause hyperlipidemia and may worsen hyperglycemia, hyponatremia, and may cause marked hypercalcemia among patients on calcium replacement for osteoporosis.

Commonly Used Anti-hypertensives Post Transplant			
Category	Agent	Dose Ranges	Monitoring
CCB	Amlodipine	5-10mg Daily	Edema
	Nifedipine	Initial 30mg Extended Release Daily (Max = 120mg Daily)	Edema, Flushing, Gingival Hyperplasia
ACEI	Lisinopril	Initial = 10mg Daily (Max = 80mg Daily)	Potassium, SCr, Cough, Angioedema
	Enalapril	Initial = 5mg Daily (Max = 40mg Daily)	
ARB	Valsartan (Diovan)	Initial = 80mg Daily (Max = 320mg Daily)	
Beta Blocker	Metoprolol succinate (Toprol XL)	Initial = 25mg Daily Up titrate weekly to effect (Max = 400mg Daily)	Dizziness, dyspnea, fatigue, bradyarrhythmia
Diuretic-thiazide	HCTZ	Initial = 12.5mg Daily Up titrate every 2-3 weeks (Max = 100mg Daily)	Serum electrolytes, glucose, LFTs, Lipids

LUNG TRANSPLANT HYPERTENSION PROTOCOL



Gastrointestinal Issues

Agents that have been useful in treating hypomotility (once obstruction has been ruled out) include metoclopramide, which acts primarily on the upper GI tract to improve gastric motility and increase lower esophageal sphincter tone. Metoclopramide crosses the blood brain barrier and can have CNS side effects (restlessness, drowsiness, fatigue, lassitude, insomnia, headache, confusion, dizziness, or mental depression) and extrapyramidal reactions can also occur.

Domperidone, a dopamine agonist, has effects similar to metoclopramide as a prokinetic agent. It inhibits dopamine at the D1 receptor and inhibits release of neural acetylcholine by blocking D2 receptors leading to facilitation of gastrointestinal smooth muscle activity (inhibiting gastric relaxation and improving gastro-duodenal coordination). One significant difference between domperidone and metoclopramide is that it does not cross the blood brain barrier, thus leading to significantly less neurotoxic effects. It may be possible to use it in patients with severe gastroparesis, however approval from the FDA through an IND (investigational new drug) application is required. Alternatively some patients have received Domperidone through Canada (Canadian pharmacy: Claymen Pharmacy, phone 877-735-7271 and fax 204-261-6390).

Finally low dose erythromycin 250 mg bid-tid iv or po, which stimulates motilin receptors, can also be used as a promotility agent. There are known interactions between erythromycin and calcineurin inhibitors that need to be monitored closely if used.

A gastroparesis diet is also available if requested from dietary services.

Additionally, early ambulation is likely to improve intestinal function.

All transplant patients are presumed to have reflux and are at risk for occult aspiration. Protected micro brush specimens demonstrate oral flora twice as often among transplant patients with pneumonia as among other patients with pneumonia. Therefore, precautions to prevent aspiration are universally implemented and include:

- Raising the head of the bed
- Use of H₂-blocker or proton pump inhibitor

Renal Failure

Drugs: Calcineurin Inhibitors: (FK 506 and Cyclosporine A)

Nephrotoxicity due to calcineurin inhibitors is well described. Their effects can be acute, subacute, or chronic. Acute renal failure can occur with supra-normal levels of FK 506 or CSA. Risk factors include dehydration, pre-existing renal disease, or concomitant treatment with other medications including NSAIDs. Renal failure is due to afferent arteriolar vasoconstriction with reduced glomerular filtration. This results in azotemia, hyperkalemia, and hypertension. Urine electrolytes typically show a low urine U_{Na} and low Fe_{Na}, suggesting a sodium avid, hypoperfused state. Renal function usually returns to normal with adjustment of the drug dosing.

Subacute and chronic renal failure due to CSA or FK 506 toxicity is more difficult to manage since patients may acquire irreversible dysfunction with levels in the therapeutic range after several years of exposure. Lowering of the dose is limited by the problem of organ rejection.

In the absence of volume depletion, fluid boluses should be avoided. In fact diuretics may be required to treat volume overload and/or hyperkalemia.

Interstitial Nephritis

Sulfa drugs, specifically Bactrim, are the most common culprits. Other potential offending drugs include penicillins, cephalosporins, rifampin, and acyclovir. NSAIDs may also cause an interstitial nephritis with associated proteinuria. There may be partial masking of interstitial nephritis by steroids. Interstitial nephritis is suggested by eosinophilia, and urine analysis showing pyuria, sometimes with white cell casts and eosinophiluria. Heavy proteinuria is not a feature of this syndrome, and points towards a glomerular disease.

Pre-renal Disease

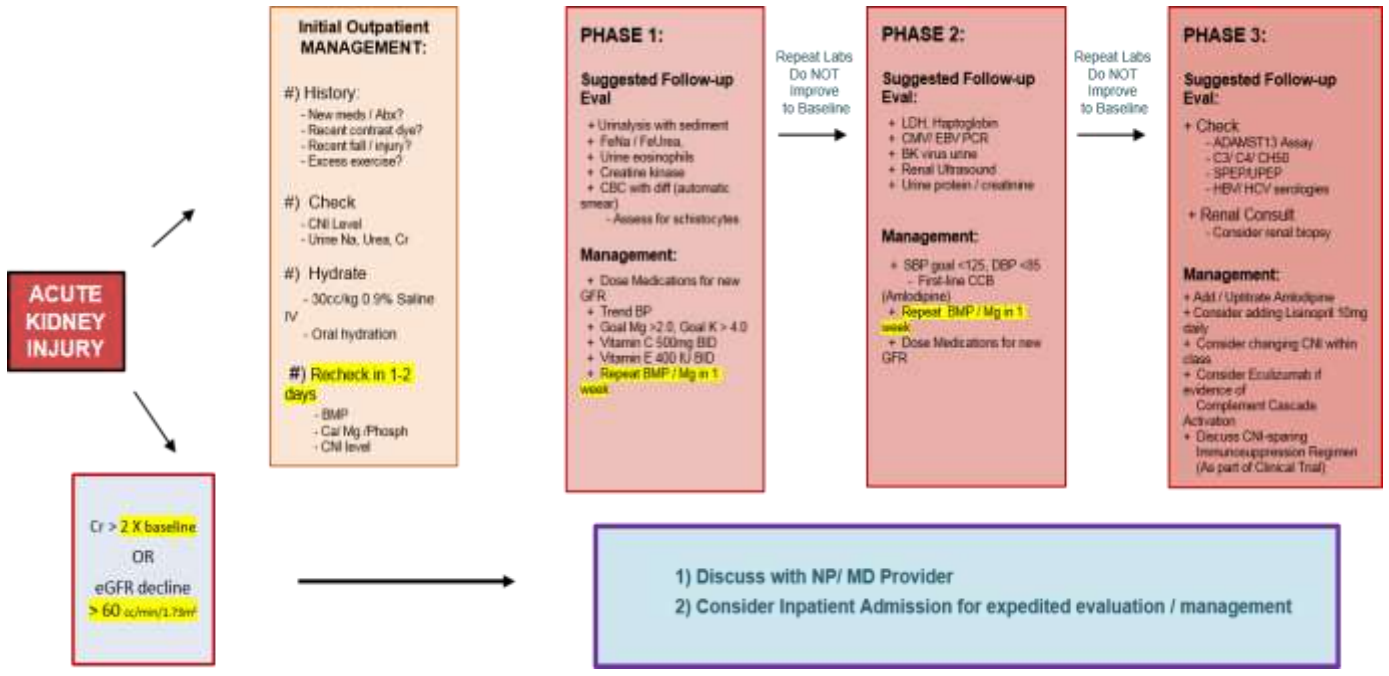
Pre-renal failure commonly occurs with overly aggressive diuresis. The FE_{Na} is the most reliable test to employ in diagnosing pre-renal azotemia, although it may be altered by concomitant CHF, cirrhosis, and CSA use. A single fluid bolus trial with monitoring of renal response may also serve as a useful diagnostic study.

Urinary Tract Obstruction

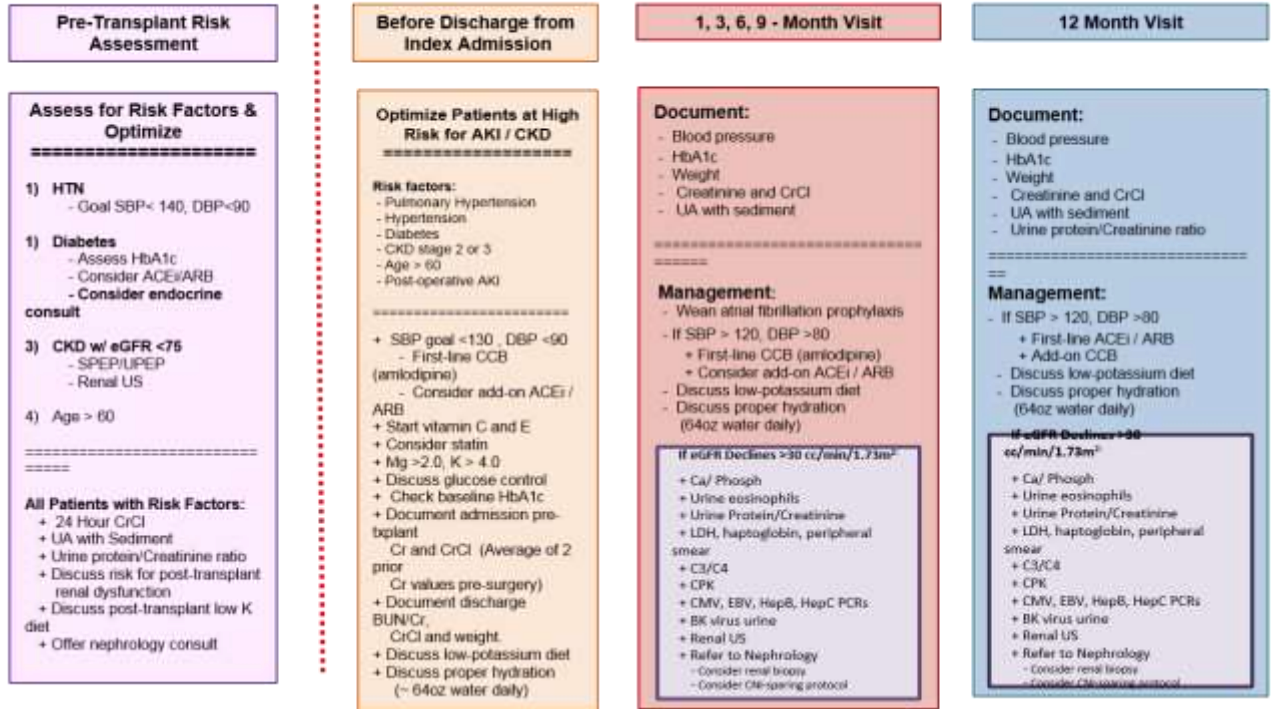
There are no data to suggest an increased risk of urinary tract obstruction among lung transplant recipients. However, patients with new azotemia should have an ultrasound to assess kidney size and rule out obstruction, since obstruction is readily treatable if detected early.

Glomerular and Vascular Disease

Any of the primary GN's can occur de novo in a lung transplant patient and this must be considered. Specifically, HUS is seen with increased frequency among solid organ transplant recipients, particularly those on cyclosporine. This is the most worrisome acute renal failure diagnosis to consider in the post-transplant patient. Typical features include hematuria, hypertension, azotemia, proteinuria, thrombocytopenia, and microangiopathic anemia. Optimal treatment for this syndrome is unknown but likely consists of plasmapheresis plus alternative cytotoxic drugs. Attempts have been made to change from cyclosporine to FK-506, although HUS has also been reported with this agent.



Provider Algorithm to Preserve Renal Function in Lung Transplant Recipients



Hematological Concerns

Leukopenia / Neutropenia

Definitions

- Leukopenia: WBC < 4000/mm³. Post-transplant leukopenia is common and can occur months after transplantation.
- Neutropenia: absolute neutrophil count (ANC) < 1500/mm³. Less common than leukopenia.

Etiologies

- Medications: immunosuppression (cellcept, imuran, azathioprine, sirolimus, antithymocyte globulin), antimicrobials (ganciclovir, valganciclovir, bactrim).
The most common cause of post-transplant leukopenia is marrow toxicity from immunosuppression.
- Infections: CMV, EBV, pneumonia, opportunistic infections, severe infections, sepsis
- Post-transplant lymphoproliferative disorder (PTLD)

Management

- Adjust culprit medications, including cellcept, imuran, and/or ganciclovir/valganciclovir (see section 5 and appendix T).
- Bactrim is discontinued as a last resort (see section 6 for alternative agents for PCP prophylaxis). If there is no response, or if WBC declines, give GCSF qd for 3 days, or in refractory cases for 7 days.
- If patient is neutropenic at any time: GCSF SC qd may be used until neutropenia resolves.
- When WBC > 5000/mm³: restart the withheld drugs one at a time. If high risk for CMV viremia (CMV D+/R-), restart antiviral prophylaxis first. Monitor CMV viral load regularly during the period of leukopenia, and weekly if CMV prophylaxis has been held. **The appropriate test for CMV during leukopenia is CMV viral load, not hybrid capture.**
- If patient has febrile neutropenia: check blood and urine cultures, consider CMV viral load, and start empiric antibiotics with Pseudomonal coverage.

If there is pancytopenia, or if there is no response to GCSF, a hematologic consultation and bone marrow biopsy are indicated to rule out an infiltrative process such as PTLD.

Post transplant lymphoproliferative disorder (PTLD) (See also section 6, Common Post-transplant Infections)

Epidemiology

- Most common malignancy (after skin cancer) in patients following solid organ transplantation, affecting ~10% of all solid organ transplant recipients.
- Incidence (adults): 1-3% of kidney or liver transplant, 1-6% cardiac, 2-6% combined heart/lung, 4-10% lung. (See also Section 6, Common Post-transplant Infections)
- Onset: usually in 1st year after transplant.
- Risk factors: donor/recipient EBV sero-mismatch, donor/recipient CMV sero-mismatch, certain immunosuppressive regimens (OKT3, ATGAM).

The most important risk factor for development of PTLD is donor/recipient EBV seromismatch.

Pathology

- Cellular origin: most cases are B-cell. Rare cases are T-cell (seen in PTLD occurring > 1 year after transplant).
- Pathogenesis of B-cell PTLD: EBV infects B cells and establishes latency. With suppression of T cell immunity from immunosuppression, EBV+ B cells display varying degrees of lymphoproliferative disease depending on balance between T cell immunosuppression and B cell proliferation.
- Histologic classifications (World Health Organization): early lesions (reactive plasmacytic hyperplasia or infectious mononucleosis-like), polymorphic PTLD (polyclonal or monoclonal), monomorphic PTLD (diffuse large B-cell lymphoma, Burkitt's or Burkitt's like lymphoma, plasma cell myeloma, or T cell lymphoma), other rare types (including Hodgkin's-like disease or plasmacytoma-like lesions).
- Histopathology: malignant B cells with positive staining for EBER (EBV RNA).

Clinical Presentation

- < 1 year after lung transplant: lung/allograft involvement. > 1 year after lung transplant: abdominal disease.
- B symptoms: fevers, drenching night sweats, weight loss.
- Hematologic abnormalities: leukopenia, neutropenia, pancytopenia, monoclonal gammopathy
- Local end-organ effects: dependent on anatomic involvement.

Workup

- **In EBV D+/R- transplant, routine surveillance for EBV viral replication (EBV viral load) should be performed at 1 month post-transplant and every three months thereafter.** In the event of development of EBV viremia, referral to Infectious Disease and Ann Lacasce of Hematology/Oncology should be pursued for evaluation for PTLD and consideration of pre-emptive therapy with Rituximab.
- Biopsy of suspicious lesion(s). **If a discrete mass is identified, obtain excisional biopsy, not FNA.**
- Check peripheral blood EBV viral load.
- Bloodwork: CBC/Diff, Comp-12, LDH
- Consult Hematology/Oncology. They will request whole-body PET/CT and will perform bone marrow biopsy for staging.

Management

- Two prognostic scoring systems for PTLD:
 - International Prognostic Index (IPI): age > 60, ECOG performance status ≥ 2 , high LDH, > 1 extranodal site of disease, Stage III-IV. Used for all aggressive non-Hodgkins lymphomas, including PTLD.
 - PTLD-specific prognostic index (PI): age > 60, ECOG performance status ≥ 2 , high LDH. More specific to PTLD than IPI.
- Low-risk disease (IPI = 0-1, or PTLD PI = 0):
 - 1st line treatment: reduction in immunosuppression (RI, see below). Response rates 25-60%, typically occur within 3-4 weeks.
 - If refractory to RI, or if clinical status precludes RI: rituximab 375 mg/m² IV

weekly for 4 doses. Response rates ~40-80% (complete response rate ~20-60%), typically occur at > 4-8 weeks after stopping treatment. If refractory to rituximab: combination chemo-immunotherapy (e.g. RCHOP), clinical trial.

- Intermediate-risk (IPI = 2-3, PTLD PI = 1) or high-risk (IPI = 3-4, PTLD PI = 2-3):
 - RI.
 - Consider combination chemo-immunotherapy before waiting for full effects of RI.
- Burkitt's or Burkitt's-like lymphoma:
 - RI.
 - Intensive chemo-immunotherapy, usually modified Magrath regimen + rituximab.
- Monitoring of response: whole-body PET/CT is checked ~3-4 weeks after completion of treatment. Peripheral blood EBV viral loads may also be monitored serially although correlation with PTLD disease activity is imperfect.

Prognosis

- Overall survival (OS):
 - Low-risk (PTLD PI = 0): 2 year OS 88%
 - Intermediate-risk (PTLD PI = 1): 2 year OS 50%
 - High-risk (PTLD PI = 2-3): 2 year OS 0%
- Responses to therapy:
 - In patients who are about to undergo RI: high LDH, organ dysfunction, or multiorgan PTLD predict poor response to RI.
 - In patients refractory to RI who are about to initiate rituximab: high LDH predicts poor response to rituximab.

Reduction in Immunosuppression (RI)

- For non-critically ill patients:
 - Eliminate azathioprine or cellcept.
 - Reduce cyclosporine or tacrolimus by 50%.
 - Taper prednisone by 50% or as tolerated.
- For critically ill patients:
 - Maximum tolerated reduction of all immune suppression.

Skin Cancer

Risk of skin cancer, particularly squamous cell carcinoma (SCC), is markedly elevated in transplant patients. The risk is higher the longer patients survive after transplant due to cumulative exposure to immunosuppressive drugs. Lung transplant patients are at particularly high risk due to the high doses required to prevent rejection. For light skinned lung transplant patients with a history of sunburn, the lifetime risk of SCC has been estimated to be over 70 percent. All patients are at risk for rare skin cancers such as kaposi's sarcoma due to hhv8 (which can originate in skin and quickly spread internally) and melanoma. Due to the high risk of skin cancer, all organ transplant patients at BWH are seen 6 months post transplant in the immunosuppression and skin cancer (ISC) clinic staffed by Drs. Buzney, Saavedra, and Schmults of dermatology. For appointments, please call or email Rosa Beriguetta at 617-983-4626, option #5. Consider adding in Nicatinamide 500mg Q12 for skin cancer prophylaxis based on NEJM article (Chen, AC, et al. Phase 3 Randomized Trial of Nicotinamide for Skin-Cancer Chemoprevention. N Engl J Med 2015; 373:1618-1626)

Section 9: Disease-Specific Management Issues

Cystic Fibrosis

Pre-transplant Infectious Considerations

All CF patients will be evaluated by an Infectious Disease specialist to review microbiological data and generate an antimicrobial treatment plan prior to listing. If multiple allergies present a challenge to development of a treatment algorithm, Allergy consultation should be considered for allergy testing and consideration of desensitization at the time of transplant if appropriate.

The BWH program will consider patients colonized with pan-resistant *Pseudomonas* for lung transplantation, and will utilize the approach noted above. Similarly, patients colonized with most *Berkholderia* species can be considered for lung transplantation. Colonization with *B. cenocepacia* and *B. dolosa* is currently considered a contra-indication to lung transplantation at our institution.

Pre-transplant CF Pulmonary Exacerbations

CF patients hospitalized for clean outs should be told to notify the transplant office. CF patients receiving greater than 20 mg/day of steroids for more than 7 days are not candidates for transplantation until they are on lower dose steroids.

Patients admitted for subacute exacerbations are generally not inactivated on the waiting list unless there is evidence of a new infection (i.e. acute pneumonia, bacteremia, high fevers). If patients are admitted for acute respiratory symptoms or are febrile, they are usually inactivated for 48-72 hours until the results of the CXR, blood and sputum cultures become available. It is important to determine whether the patient has acquired a new pan-resistant organism, such as *B. cepacia*.

Surgical Issues

CF patients require bilateral lung transplantation because of the presence of chronic airway colonization in both lungs, and risk of spill-over infection into the transplanted lung. This procedure often requires cardiopulmonary bypass. The surgical team makes this determination based upon spirometric and echocardiographic/angiographic data.

Sinus and Airway Infections

Pre-transplant

All patients with CF require an ENT evaluation prior to lung transplantation. The majority undergo endoscopic sinus surgery as a drainage procedure prior to transplantation, since the sinuses can serve as a reservoir of infection with organisms such as *Pseudomonas aeruginosa*, *Staph aureus*, *Haemophilus influenzae*, and *Aspergillus*. The majority of patients are also managed with regular sinus irrigation using either Tobramycin or Gentamicin solution daily with devices such as a Waterpik with nasal adapter or other rinsing mechanisms.

Post transplant

CF patients should

- Continue sinus irrigation with saline, Tobramycin or Gentamicin 200 mg/200 ml of normal saline daily using an irrigation device.
- Undergo sinus CT scan to ensure absence of fluid collections within the sinuses if there is significant purulence or nasal drainage noted in the peri-transplant period.
- Have an ENT consultation for possible drainage procedure if they display evidence of sinusitis on CT scan or develop purulent nasal discharge.
- Receive inhaled tobramycin 300 mg via nebulizer bid immediately post transplant if colonized pre-transplantation with *Pseudomonas*. Inhaled colistin may be useful as an alternative to inhaled tobramycin.
- Receive inhaled Amphotericin (25 mg bid) or alternative via nebulizer if pre-transplant airway or nasal cultures demonstrated colonization with *Aspergillus*. Addition of systemic treatment is performed on a case by case basis.

GI Issues

It has been our experience that CF patients are specifically at risk for several gastrointestinal complications. It is important to identify those patients who may be at increased risk for particular complications (e.g. patients at increased risk for decreased gastric motility due to longstanding CF related diabetes or previous history of bowel obstruction) and managed accordingly pre-transplant. These problems and our approach to management are outlined below:

Decreased Bowel Motility

- May occur post operatively and may last days, weeks, or months.
- Presents with large NG residuals, +/- vomiting and nausea; not due to swallowing problems, but rather to markedly delayed gastric emptying
- Evaluation: nuclear medicine gastric emptying study
- Management
 - Consideration of medical therapy with metoclopramide 10 mg qid, erythromycin 250 mg tid; discontinuation of all nonessential anticholinergics, narcotics, antihistamines, sedatives
 - Evaluation for placement of G/J tube to allow for adequate enteral nutrition and gastric emptying; feeding is done via J tube if possible with gravity drainage of the stomach via G tube
 - Consideration of temporary TPN with stomach drainage if enteral feeding is not tolerated
 - Intermittent evaluation of patient's response to small amounts of enteral feeds with follow-up gastric emptying studies q 1-2 months.

Bowel Obstruction

Usually due to aggregated thick (dry, inspissated) secretions of muco-feculent material. This is termed distal intestinal obstruction syndrome (DIOS). Patients often have prior history of bowel obstruction and it is important to identify those patients at risk prior to transplantation (i.e. previous DIOS, adhesions from previous abdominal surgeries) and manage proactively. When possible, patients presenting for transplantation should be assessed for adequate hydration and receive Miralax (or Glycolax) 17g/8 ounces po q12h preventively or even Golytely po/NG up to 2L (maximum rate 1L/hour) x 1, if any concern for retained fecal matter exists.

Evaluation includes exam, KUB,/upright x-ray, +/- gastrograffin enema (diagnostic and therapeutic), surgical consult.

CF patients who haven't had a bowel movement or gas by the third postoperative day should be started promptly on Miralax (or Glycolax) 17g (1-3x/day) or oral/NG Golytely (maximum 1L/hour) as tolerated by patient PRN, as well as oral N-acetylcysteine 30 mls of a 20% solution qid. Any early evidence of obstruction should be promptly addressed with a gastrograffin enema (keep dilution at 50% with total volume either determined in IR and based on amount of volume necessary to reach cecum or 240 ml for an average sized adult at bedside; monitor electrolytes with volume shift), oral/NG Golytely, as well as addition of lactulose 30 ml qid to this regimen.

Malabsorption

Due to exocrine pancreatic insufficiency. Patients are generally on enzyme replacement with Pancrease, Creon or Ultrase,(see appendix S), and take supplements of the fat soluble vitamins including Vit E (200-400 units bid), Vit D (400-800 units qd), Vit A (5000 units qd), and Vit K (100 mcg qd). Many patients take two ADEK tablets per day. It is important that cyclosporine or FK506 be taken with pancreatic enzymes. An aqueous soluble cyclosporine preparation, Neoral, is usually given to CF patients.

Hepatic Abnormalities

Approximately 15-20% of CF patients have focal nodular cirrhosis of the liver as a result of chronic obstruction of the biliary ducts by inspissated secretions. There is also an increased incidence of gallstones in this patient population, and for this reason all CF patients should undergo a pretransplant abdominal ultrasound to rule out cholelithiasis. Alkaline phosphatase is commonly elevated, and occasionally these patients develop ascites, varices, GI bleeding, and hepatic encephalopathy. Advanced liver disease is a contraindication to lung transplantation.

Endocrine issues

Cystic Fibrosis Related Diabetes Mellitus

5-15% of CF patients develop CF-related DM. The median age at diagnosis is 20 years. Many patients have glucose intolerance. Blood glucose values should be monitored carefully in CF patients post-transplant, when corticosteroids are likely to exacerbate DM or glucose intolerance.

Interstitial Lung Disease

Pre-transplant Considerations

Patients with autoimmune lung disease associated with systemic autoimmune diseases should have limited systemic symptoms that will allow for aggressive rehabilitation and will not impair graft survival or quality of life post-transplant in order to be considered. Specifically, arthritic symptoms should be controlled and should not prevent activity. A complete assessment should be performed for esophageal dysfunction, including PH probe, esophageal manometry and impedance probe. In addition, other potential end-organ dysfunction related to the systemic disease should be evaluated, and bone health should be maintained.

Surgical Considerations

Cough in the setting of interstitial lung disease, particularly in the case of IPF, can be debilitating in the post-transplant setting, and can significantly affect quality of life. For this reason, bilateral lung transplantation has become more routine in such patients at our institution, particularly if patients complain of severe cough before transplant, if they report significant sputum production, or if prominent bronchiectasis is noted in association with fibrosis on chest imaging. In addition, if resistant organisms are cultured in sputum, bilateral lung transplantation is the preferred intervention.

Post-transplant Considerations

In ILD patients who undergo single lung transplantation, progression of fibrosis in the native lung can be observed post-transplant. In this setting, the native lung size may decrease, leading to increasing size of the allograft and potential elongation of the mainstem airway. On occasion, this can contribute to malacia of the airway.

Lung Transplant for Alpha-1 Antitrypsin Deficiency (AATD)

The care of the patient with AATD who has undergone lung transplantation for COPD/emphysema is very similar to the COPD patient without AATD, with a few additional considerations.

Augmentation Therapy

The only cure for AATD is liver transplantation; as such, individuals who have undergone isolated lung transplantation remain deficient in alpha-1 antitrypsin. However, routine inclusion/continuation of AAT augmentation therapy is not supported by the limited data in the literature. Post-transplant, acute and chronic rejection and respiratory infection are accompanied by increased lung elastase activity. Many clinicians support the use of AAT augmentation therapy during these periods of increased lung inflammation. The continuation and/or periodic need to include AAT replacement therapy post-transplant should be discussed on a case by case basis. (Chest 2006; 110:284S-294S; AJRCCM 1994; 149:966-971; Biologics 2009; 3:193-204)

Panniculitis

Panniculitis is a rare but known clinical manifestation of AATD. This dermatologic manifestation includes inflammation of the subcutis of the skin, which includes blood vessels and soft tissue. A thorough dermatologic history is crucial in all patients with AAT deficiency. If individuals develop panniculitis flares with minimal trauma, consideration should be given to pre-treatment prior to thoracotomy. Although many therapies have been used to treat panniculitis, most individuals do respond to treatment with intravenous augmentation therapy. Studies suggest that doses of augmentation therapy used to manage lung disease (~60 mg/kg weekly) are too low for aggressive management of panniculitis and data may support higher dosing (up to 90-130mg/kg weekly) in patients with this rare manifestation of AATD. (Dermatology 2009; 218:370-375)

Liver Disease

Since most lung transplant recipients do not also undergo liver transplantation, they remain at high risk for liver cirrhosis and likely are at higher risk for hepatic manifestations of drug side effects. Pre-transplant, all patients with AATD should have hepatic evaluation, with strong consideration towards the establishment of routine, longitudinal care by a hepatologist.

Section 10: Living Lobar and Repeat Lung Transplantation

Living Lobar Transplantation

Living lobar lung transplantation in adult recipients involves removal of a recipient lung and transplantation of lower lobes from two adult donors. The most common indication for this procedure is bilateral sequential transplantation in the setting of CF. In this instance, lower lobes from 2 donors are used to replace both recipient lungs. The literature suggests that the results from living donor transplantation are comparable to those obtained with cadaveric transplants when performed at experienced centers. However, given the potential risk to the donors, this option has typically been performed in patients too sick to await cadaveric lung donation. Since the institution of the Lung Allocation Score, the waiting time for cadaveric lung transplantation and the number of deaths on the waiting list have declined considerably. As a result, living lobar lung transplantation has been performed rarely since 2005. Patients being considered for living donor transplantation are required to meet the same criteria for transplantation as those seeking cadaveric donors.

Repeat Lung Transplantation

Repeat lung transplantation can be considered in the post-transplant patient with declining lung function. While results from repeat lung transplantation have improved in recent years, the one, three and five year survival rates remain lower than for primary transplant recipients. As a result, the BWH reserves this intervention for patients who meet strict criteria as supported by the available literature pending unusual circumstance:

- 2 years or more since initial lung transplant
- PFT decline secondary to OB/BOS
- Absence of need for mechanical ventilatory support (unless able to fully rehabilitate on ventilator or mechanical circulatory support)
- Able to ambulate 450 feet or more on 6MWT
- EGFR > 50 (unless a suitable candidate for renal transplant)
- Completes full evaluation and meets all requirements for candidacy as outlined for initial lung transplant procedure
- Initial transplant performed at BWH (or CHB if age appropriate) – candidates declined for repeat transplantation at their initial transplanting center are considered on a case by case basis
- Specific attention will be paid to candidates with Restrictive Allograft Syndrome or other potential technical concerns, prior to acceptance for repeat transplant.
- In addition, candidates listed for repeat lung transplant who deteriorate to the point that they cannot meet our 450 foot threshold on 6 minute walk testing may be inactivated (in contrast to our recently updated walk test criteria for primary lung transplant)
- Similarly, candidates may be inactivated if they require any form of mechanical support

Section 11: Appendices

A. Evaluation of Patients with Suspected Short Telomere Syndrome

1) Patients with Interstitial Lung Disease

AND

2) Any of the following:

- a. WBC, HCT or Platelets below lower limit of normal
- b. MCV or RDW above upper limit of normal
- c. Abnormal liver function tests
- d. Abnormal coagulation profile in the absence of anticoagulants
- e. History or evidence of hepatomegaly
- f. History or evidence of splenomegaly
- g. History or evidence of varices
- h. Abnormal liver contour on abdominal ultrasound

Proceed to measurement of telomere length

(Note the patient should be informed of the implications of testing on family members, and that they will incur an approximately \$500 cost for this testing)

If telomere length is abnormal:

Hematology and hepatology consultations, with strong consideration of bone marrow biopsy. Consider liver biopsy if clinical or laboratory evidence of liver dysfunction.

B. Algorithm for Hepatology Evaluation in Solid Organ Transplant

After a multidisciplinary discussion involving the Medical Directors of each of the solid organ transplant programs at BWH, as well as Dr. Hashemi from Hepatology and Dr. Baden from the Transplant Infectious Disease Service, the following algorithm was drafted to address the indications for, and elements of, hepatology evaluation in solid organ transplant candidates:

1) Indications for hepatic evaluation:

- a. Known liver disease, including fatty liver
- b. Abnormal liver function tests or imaging (e.g., abnormal liver contour, unexplained ascites)
- c. Systemic disease which can involve the liver
- d. Known telomeropathy
- e. History of exposure to Hepatitis B or C virus
- f. History of chronic/heavy alcohol use
- g. Other conditions specific to end-organ disease (e.g., chronic right heart failure, restrictive cardiomyopathy, Fontan circulation)

- 2) Recommended hepatic evaluation for above transplant candidates:
 - a. Fibrosure
 - b. Fibroscan
 - c. Viral load testing for candidates with hepatitis B or C exposure
 - d. Hepatology consultation at the discretion of the transplant team –Consider liver biopsy in consultation with GI/hepatology, particularly for patients with suspected cirrhosis not verified by noninvasive modalities and/or if portal pressure measurements are required. The transjugular approach for biopsy is considered for patients with need for transhepatic pressure gradient assessment, coagulaopathy, ior thrombocytopenia. Otherwise consider percutaneous liver biopsy. (if transjugular, measure transhepatic pressure gradient).
 - e. Evidence of moderate to severe fibrosis (F3-F4) or cirrhosis is generally considered to present a high risk for transplantation.

C. Evaluation of Transplant Candidates with Pulmonary Hypertension / Right Heart Dysfunction

- 1) Consider referral to Pulmonary Hypertension Group; this is indicated for any patient with:
 - a. TR jet > 2.5 m/s
 - b. Moderate or severe RV dilation, with or without RV dysfunction
 - c. Evidence of RV dysfunction
 - d. Evidence of RA dilation
 - e. mPA > 25
 - f. PVR >3 Wood's Units or 240 dynes
- 2) Patients requiring right heart catheterization without the need for coronary artery assessment/left heart catheterization should be referred to Aaron Waxman for procedure.
- 3) For patients with clinical or echocardiographic/cath evidence of worsening right heart function who require urgent assessment, contact Aaron Waxman directly and he will help us to facilitate admission for evaluation and management.

D. Evaluation and Management of Scleroderma Patients

- 1) Consider pre-existing conditions that could contribute to hemodynamic instability or low flow state in evaluating candidacy
- 2) All candidates with scleroderma may have combined Cardiology and Rheumatology assessment or evaluation in Raynaud's clinic with incorporation of disease severity score as part of evaluation, as clinically indicated
- 3) Candidates will undergo PH probe, esophageal manometry, and abdominal CT angiogram to better assess for evidence of GI ischemia/dysfunction
- 4) Candidates with scleroderma will be routinely reassessed for evidence of progression of systemic manifestations of disease, and referred to subspecialists for re-evaluation as indicated
 - a. All scleroderma candidates should have PVD consult immediately post-operatively for assistance with vasodilator management: Consider peri-operative continuation of IV prostacyclines or initiation of vasodilators
 - b. All efforts will be made to maintain a positive fluid balance in the operating room for these candidates

E. Evaluation and Candidacy of Patients with History of Melanoma

- 1) History of melanoma in situ: not exclusionary, plan full dermatology screen as part of evaluation process.
- 2) T1a and T1b melanoma: 1.0 mm deep or less in which either sentinel node is not indicated or is negative if done: not exclusionary, plan full dermatology screen as part of evaluation process.
- 3) T2a lesions: >1.0 but <2.0 mm thick, negative sentinel node biopsy: Require 2-year disease-free interval before eligible for transplant.
- 4) T2b lesions: >1.0 but <2.0mm thick, negative sentinel node: 4 year disease-free interval before eligibility.
- 5) >T2b: non-candidate, node negative: 6 years disease-free survival allows individual consideration for eligibility.
- 6) Otherwise >T2b: non-candidate
- 7) For melanoma of any depth with a positive sentinel or other clinical metastasis, non-candidate.

F. Evaluation of Candidates with DCIS

- 1) DCIS is considered stage 0 breast cancer. It is confined to the ducts. Survival after a DCIS diagnosis is greater than 99%. The diagnosis of DCIS may be increasing at least in part due to increased breast cancer screening.
- 2) In the non-transplant setting, the main risk from DCIS is of local recurrence. This risk is less than 1% after mastectomy and 5-6% in a 15 year period after lumpectomy and radiation therapy.
- 3) Recurrence is most common in the first 3-5 years after intervention. Half of recurrences present as invasive disease and half as recurrent DCIS.
- 4) The risk of local recurrence decreases with advancing age.
- 5) Given the above information, DCIS of the breast is not considered a contraindication to lung transplantation.
- 6) Useful information in the evaluation of candidates with DCIS includes the size of the lesion, the grade, and the margin size on resection (2 mm considered a clear margin).
- 7) Consultation should be considered if recipients have DCIS which has not been treated, as this carries a 40% risk of progression to invasive cancer, or if treatment consisted of lumpectomy alone.

*** Consider coordinated evaluation with dermatology for any question regarding thickness, staging or concern for metastases.

G. Evaluation of Candidates with HIV

Candidates with a history of HIV infection will be considered, evaluated, and managed using the following guidelines:

1. Candidates should have demonstrated at least 6 months of a stable response (defined as a negative viral load) to a single antiretroviral regimen (the regimen cannot have been changed due to lack of effect over that 6 month period).
2. CD4 count should be > 200 cells/mm³.
3. An ID consult will be obtained for all HIV positive patients undergoing evaluation. The purpose of this consult will be to assess the current anti-retroviral regimen and determine if the candidate can be transitioned to a regimen more easily managed in the context of post-transplant medications.
4. If the anti-retroviral regimen is changed, the candidate will be followed for at least three months for stability on the new regimen before listing.

5. Once listed, in addition to standard donors, HIV positive donors may be considered for HIV positive recipient candidates. The anti-retroviral regimen of the donor would need to be known and ID will be consulted when such a transplant is being considered.
6. The decision to give induction immune suppression will be made on a case by case basis. Induction should be considered unless a clear contraindication exists.

H. Evaluation of Candidates Using Medically Prescribed Marijuana

In light of changes to the legal status of medically prescribed marijuana in Massachusetts, the Lung Transplant Team has developed the following guidelines for consideration of candidates using tetrahydrocannabinol (THC) or marijuana for medicinal purposes:

- 1) The Lung Transplant Team will accept candidates who are using THC/marijuana for consideration of candidacy only in the setting of medically prescribed marijuana and will require documentation of a prescription by a physician caring for the candidate as part of the evaluation process. The supporting documentation will include the appropriate indication for the prescription, as well as evidence of appropriate dosing.
- 2) Due to potential injury to the allograft, the Lung Transplant Team will not consider candidates using inhalational marijuana.
- 3) If use of THC/marijuana is not prescribed, this will be considered a contraindication to transplant. In this instance, candidates will need to abstain from marijuana to be considered for listing.

I. Height-Weight Tables

1959 Metropolitan Height and Weight Tables

Men							
Height		Small	Mean #	Medium	Mean #	Large	Mean #
Feet	Inches	Frame		Frame		Frame	
5	1	112-120	116	118-129	123.5	126-141	133.5
5	2	115-123	119	121-133	127	129-144	136.5
5	3	118-126	121.5	124-136	130	132-148	140
5	4	121-129	125	127-139	133	135-152	143.5
5	5	124-133	128.5	130-143	136.5	138-156	147
5	6	128-137	132.5	134-147	140.5	142-161	151.5
5	7	132-141	136.5	138-152	145	147-166	156.5
5	8	136-145	140.5	142-156	149	151-170	160.5
5	9	140-150	145	146-160	153	155-174	164.5
5	10	144-154	149	150-165	157.5	159-179	169
5	11	148-158	153	154-170	162	164-184	174
6	0	152-162	157	158-175	166.5	168-189	178.5
6	1	156-167	161.5	162-180	171	173-194	183.5
6	2	160-171	165.5	167-185	176	178-199	188.5
6	3	164-175	169.5	172-190	181	182-204	193

Weight in pounds according to frame in indoor clothing weighing 7 lbs. for men.

1959 Metropolitan Height and Weight Tables

Women							
Height		Small	Mean #	Medium	Mean #	Large	Mean #
Feet	Inches	Frame		Frame		Frame	
4	8	92-98	95	96-107	101.5	104-119	111.5
4	9	94-101	97.5	98-110	104	106-122	114
4	10	96-104	100	101-113	107	109-125	117
4	11	99-107	103	104-116	110	112-128	120
5	0	102-110	106	107-119	113	115-131	123
5	1	105-113	109	110-122	116	118-134	126
5	2	108-116	112	113-126	119.5	121-138	129.5
5	3	111-119	115	116-130	123	125-142	133.5
5	4	114-123	118.5	120-135	127.5	129-146	137.5
5	5	118-127	122.5	124-139	131.5	133-150	141.5
5	6	122-131	126.5	128-143	135.5	137-154	145.5
5	7	126-135	130.5	132-147	139.5	141-158	149.5
5	8	130-140	135	136-151	143.5	145-163	154
5	9	134-144	139	140-155	147.5	149-168	158.5
5	10	138-148	143	144-159	151.5	153-173	163

Weight in pounds according to frame in indoor clothing weighing 4 lbs. for women.

J. Interpretation of Donor Hepatitis Serologies

<i>Interpretation of the Hepatitis B Panel</i>		
<i>Tests</i>	<i>Results</i>	<i>Interpretation</i>
HbsAg anti-HBc anti-HBs	negative negative negative	Susceptible
HbsAg anti-HBc anti-HBs	negative positive positive	Immune due to natural infection
HbsAg anti-HBc anti-HBs	negative negative positive	Immune due to hepatitis B vaccination **
HbsAg anti-HBc IgM anti-HBc anti-HBs	positive positive positive negative	Acutely infected
HbsAg anti-HBc IgM anti-HBc anti-HBs	positive positive negative negative	Chronically infected
HbsAg anti-HBc anti-HBs	negative positive negative	Four interpretations possible *

* Four Interpretations:

1. Distant resolved infection (most common)
2. Recovering from acute infection
3. False positive anti-HBc
4. Might be undetectable level of HBsAg present in the serum and the person is actually chronically infected

** Antibody response (anti-HBs) can be measured quantitatively or qualitatively. A protective antibody response is reported quantitatively as 10 or more milliinternational units (≥ 10 mIU/mL) or qualitatively as positive. Post-vaccination testing should be completed 1-2 months after the third vaccine dose for results to be meaningful.

Definitions

- **Hepatitis B Surface Antigen (HBsAg):** A serologic marker on the surface of HBV. It can be detected in high levels in serum during acute or chronic hepatitis. The presence of HBsAg indicates that the person is infectious. The body normally produces antibodies to HBsAg as part of the normal immune response to infection.
- **Hepatitis B Surface Antibody (anti-HBs):** The presence of anti-HBs is generally interpreted as indicating recovery and immunity from HBV infection. Anti-HBs also develops in a person who has been successfully vaccinated against hepatitis B.
- **Total Hepatitis B Core Antibody (anti-HBc):** Appears at the onset of symptoms in acute hepatitis B and persists for life. The presence of anti-HBc indicates previous or ongoing infection with hepatitis B virus (HBV) in an undefined time frame.
- **IgM Antibody to Hepatitis B Core Antigen (IgM anti-HBc):** This antibody appears during acute or recent HBV infection and is present for about 6 months.

K. BWH Policy for Evaluation of Transplant Candidates and Donors with Evidence of Viral Hepatitis Exposure

Hepatitis C Virus—for patients who are HCV antibody positive

- Viral load testing X 2
 - If negative, consider assessment of liver function with fibroscan or biopsy. Obtain hepatology evaluation.
 - If biopsy not indicated, or is negative for evidence of cirrhosis, proceed with full evaluation
 - If biopsy suggests cirrhosis – Not a candidate for transplant

Hepatitis B Virus

- *Donor Issues*
 - Hep B Core Ab positive, surface Ag negative:
 - Negative NAT testing:
 - Risk < 1% of transmission – offer to all recipients, discuss risk of transmission with those recipients who are Hep B surface antibody negative
 - NAT Positive:
 - Donor is infected
 - Surface Ag positive, Core antibody positive:
 - Donor is infected
- *Recipient Issues*
 - Vaccinate potential recipients using accelerated protocol, followed by quantitative titer
 - Vaccine options and schedule of administration:
 - 3-dose hepatitis B vaccine schedule of administration
 - Vaccinate at day 0, 1 month, and 6 months (Engerix-B or Recombivax HB)
 - Or preferably administer via the accelerated protocol
 - Engerix-B: Vaccinate at day 0, 1 month, 2 months, and 12 months
 - Twinrix (combined Hep B and Hep A vaccine): Vaccinate at day 0, day 7, day 21-30, and 12 months
 - 2-dose hepatitis B vaccine schedule of administration (Heplisav-B or Dynavax)
 - Vaccinate at day 0 and 1 month
 - Check titer for HBsAb 1-2 months after the vaccination series is complete (a false positive result may occur if Hep B surface antigen is checked prior to 4 weeks after Hep B vaccination)
 - If the patient is not immune to HBV, then repeat the vaccination series
 - Hep B core antibody positive recipients: Check viral load and Hep B surface Ag, if both are negative, indicates prior resolved infection, can proceed. If positive – not a candidate.

L. BWH Increased Risk Donor Protocol

Goal: Safely increase utilization of increased risk donor organs and to minimize risk of potential transmission of HIV, HCV and HBV to transplant recipients

<p>Increased Risk Donors</p>	<ul style="list-style-type: none"> • People who have had sex with a person known or suspected to have HIV, HBV, or HCV infection in the preceding 12 months • Men who have had sex with men (MSM) in the preceding 12 months • Women who have had sex with a man with a history of MSM behavior in the preceding 12 months • People who have had sex in exchange for money or drugs in the preceding 12 months • People who have had sex with a person who had sex in exchange for money or drugs in the preceding 12 months • People who have had sex with a person who injected drugs by intravenous, intramuscular, or subcutaneous route for nonmedical reasons in the preceding 12 months • A child who is 18 months of age and born to a mother known to be infected with, or at increased risk for, HIV, HBV, or HCV infection • A child who has been breastfed within the preceding 12 months and the mother is known to be infected with, or at increased risk for, HIV infection • People who have injected drugs by intravenous, intramuscular, or subcutaneous route for nonmedical reasons in the preceding 12 months • People who have been in lockup, jail, prison, or a juvenile correctional facility for more than 72 consecutive hours in the preceding 12 months • People who have been newly diagnosed with, or have been treated for, syphilis, gonorrhea, <i>Chlamydia</i>, or genital ulcers in the preceding 12 Months • People who have been on hemodialysis in the preceding 12 months (HCV only) • People with positive testing for hepatitis, syphilis, and other chronic infections • People from whom we are unable to obtain the appropriate history or blood testing 	
<p>Management</p>	<p>As appropriate, consult BWH Transplant Infectious Disease before or immediately after transplantation of an increased risk donor organ for assessment and ongoing peri-operative management and post-transplant monitoring.</p>	
<p>Recommended Recipient Serological Testing</p>	<p>Post Transplant</p>	<p>Follow-up testing should be completed at 1 month post-transplant (+/- 2 weeks), with 2 additional tests within 12 months of the transplant date (preferred schedule: 1 month, 3 months, 6 months).</p> <ul style="list-style-type: none"> • For HIV: HIV 1/2 Ag/Ab, HIV-1 VL • For HBV: HBsAg, HBcAb, HBV VL • For HCV: HCV Ab (if no prior history of HCV in recipient), HCV VL

RISK ASSESSMENT FOR RECIPIENTS

**NAT testing estimates infection up to 7-14 days prior to testing.
The overall risk of transmission of HIV, HCV, or HBV is less than 1%.**

The information below is provided to you as a reference.

The decision to accept an increased risk donor organ can be difficult for transplant candidates. They are trying to weigh the possibility of contracting a transmissible disease and their prognosis/projected survival with a failing organ. Patients are often seeking concrete numerical figures from clinicians in order to understand the risks associated with transplantation of an increased risk organ. The references below can be used to assist with these discussions.

The highest risk of window period infection to organ recipients from any of the increased risk donor populations for the following infections is estimated to be:

- **HCV: 0.3%**
- **HIV: 0.05%**

Kucirka et al. AJT 2011

Hepatitis B Virus

- Hep B core Ab positive, surface Ag negative:
 - Negative NAT testing:
 - Risk < 1% of transmission – offer to all Hep B surface antibody positive recipients, consider for others after discussion of risk of transmission
- Hep B surface Ag positive, core Ab positive:
 - Donor has acute or chronic infection

Huprikar et al. AJT 2015

Risk per 10,000 donors	HCV NAT	HIV NAT
IV drug user	32.4	4.9
Men who have sex with men	3.5	4.2
Prostitutes	12	2.7
Incarceration	0.8	0.9

Kucirka et al. AJT 2011

M. Donor CSF Analysis for Meningitis

Please navigate to the GlobalRPH site:

http://www.globalrph.com/cerebrospinal_fluid.htm

N. Prevention of Venous Thromboembolism

- 1) The program will make an effort to identify candidates with a history of DVT/PE. We will document the date of the event, location of the thrombus, method of treatment, and whether the candidate remains on anticoagulation for this indication. The plan for post-transplant management will be discussed at the presentation of the candidate to the multidisciplinary team for listing. Consultation with cardiology and/or the VTE service will be obtained as needed.
- 2) Intraoperative vascular access will avoid multiple indwelling catheters in the same vein (see guidance in section 3).
- 3) The default choice for DVT prophylaxis in transplant recipients is low molecular weight heparin. When low molecular weight heparin cannot be used, unfractionated heparin will substitute.
- 4) DVT protocol:
 - a. Assess for suitability for initiation by 12 hours post-op on all patients – initiate no later than 72 hours post-op unless clear contraindication identified (see below)
 - b. Exclusions for institution of prophylaxis include: need for ECMO support, other indication for therapeutic anticoagulation, frankly bloody chest tube output of large volume, signs of GI or other life threatening bleeding
 - c. In the event of creatinine rise of 30% or greater, switch to alternative prophylactic agent
- 5) Transplant recipients will continue on prophylaxis at least through their one month post-transplant surveillance bronchoscopy. At that time, a decision regarding discontinuation will be made by the transplant team. If a recipient is too ill to undergo the one month post-transplant bronchoscopy, the determination for discontinuation of VTE prophylaxis should be discussed, as this level of illness may warrant continuation of prophylaxis.

O. Drug Summary

Medication	Dosage	Site of Metabolism	Adverse Effects
Simulect (R) (basiliximab)	20mg on POD#0 prior to implantation followed by 20mg on POD4	N/A	HTN Tachycardia Abdominal pain Vomiting Dizziness Rare hypersensitivity Edema
Tacrolimus (Prograf / FK506)	Starting Dose .025 mg/kg (or 0.5 mg for patients with RV dysfunction) sublingual every 12 hours. Once patient is tolerating orals, tacrolimus may be transitioned to PO/PNGT at the discretion of the transplant team. Target Levels: 8-12 ng/ml	Liver, 98-99% via CYP450 3A4, active metabolites	Alopecia, Hepatotoxicity, Hyperglycemia, Hyperkalemia, Hyperlipidemia, Hypertension, Hypomagnesemia, Myelosuppression, Nephrotoxicity, N / V / D, Stroke/Seizures, Tremors
Cyclosporine (Gengraf, Neoral, Sandimmune)	IV: 2 mg/kg/day as continuous infusion PO: 3 x IV Dose (or approximately 2-5mg/kg/bid) Target levels: First Year: 250-350 ng/ml Later: 150-250 ng/ml	Intestine wall, by CYP450 3A4 isozyme Liver, extensive, by CYP450 3A4, Active metabolites Kidney	Gingival hyperplasia, Hemolytic Uremic Syndrome (HUS), Hepatotoxicity, Hirsutism, Hyperkalemia, Hyperlipidemia, Hypertension, Hyperuricemia, Hypomagnesemia, Myelosuppression, Nephrotoxicity, Seizures, Stroke, Tremors

Drug - Drug Interactions	Drug - Food Interactions	Special Instructions
(Simulect (R)) N/A	N/A	Basiliximab does NOT require premedication. Administer over 20-30 minutes as a short IV infusion via a separate peripheral or central line (no compatibility data available). Follow the infusion with a 25mL NS flush.
<p>(Tacrolimus) <u>Increased levels:</u> Amiodarone, Azole antifungals, Contraceptives, Macrolide Antibiotics, Metoclopramide, Methylprednisolone, Non-Dihydropyridine Calcium Channel Blockers <u>Decreased levels:</u> , Anticonvulsants, Dexamethasone, Rifamycins, St. John's Wort <u>Other:</u> Nephrotoxic agents</p>	<p><u>Increased levels:</u> Grapefruit juice</p>	<p>Switch from IV to PO Tacrolimus: Oral dose is 5 times IV dose. Switch from oral Cyclosporine to Tacrolimus: Both are dosed every 12 hours so replace Cyclosporine with Tacrolimus and continue dosing Q12 hours. Should reach steady state in 5 doses (~3 days). Start FK506 at 0.075mg/kg PO BID</p>
<p>(Cyclosporine) <u>Increased levels:</u> Amiodarone, Azole antifungals, Contraceptives, Macrolide Antibiotics, Metoclopramide, Methylprednisolone, Non-Dihydropyridine Calcium Channel Blockers <u>Decreased levels:</u> Anticonvulsants, Dexamethasone, Rifamycins, St John's Wort <u>Other:</u> Nephrotoxic Agents</p>	<p><u>Increased levels:</u> Alcohol (heavy dose), Grapefruit juice, High fat meals (Sandimmune only) <u>Decreased levels:</u> low fat meals (Sandimmune only)</p>	<p>Switch from IV to PO Cyclosporine: Oral dose is 3 times the IV dose divided Q12 Hours. Switch from Tacrolimus to Cyclosporine: Both are dosed every 12 hours so replace Tacrolimus with Cyclosporine and continue dosing Q12 hours. Should reach steady state in 5 doses (~3 days). Start Cyclosporine at 2-5mg/kg PO BID</p>

O. Drug Summary (continued)

Medication	Dosage	Site of Metabolism	Adverse Effects
Mycophenolate (Cellcept, Myfortic)	<u>CellCept:</u> 1000 mg PO/IV BID <u>Myfortic:</u> 720mg PO BID	Liver	Birth defects (Pregnancy Cat. D), Dyspepsia, Gastritis, Myelosuppression, N / V / D
Azathioprine (Imuran)	<u>Maintenance:</u> 1-3 mg/kg PO QDAY	Liver, with active metabolites	Alopecia, Gastritis, Hepatotoxicity, Myelosuppression N / V / D, Pancreatitis
Sirolimus (Rapamycin/ Rapamune)	Loading Dose 6mg X1, then 2mg PO QDAY Target Levels: 5-8ng/mL Check level one week after initiation If discontinuing CNI, cut to half dose until sirolimus level at goal, then stop.	Intestine wall, by CYP450 3A4 Liver, extensive, by CYP450 3A4	Arthralgias, Bronchial Anastomotic Dehiscence, DVT/ VTE, Dyspnea, Headache, Hyperlipidemia, Hypertension, Increased SCr, Interstitial Pneumonia, Nephrotic Syndrome, Peripheral Edema
Corticosteroids (Prednisone, methylprednisolone)	Methylprednisolone 250 mg prior to implant, 250 mg post- reperfusion, then 125 mg IV q8 hours on POD 1, 1 mg/kg methylprednisolone or prednisone daily for one week, then 0.5mg/kg/day x 14 days. If FEV1 remains stable and no AR on biopsy then wean to 5mg/day by 4 months. See 'Immunosuppression Section' for exact details on wean	Mainly Liver, some renal and tissue	Glaucoma, Hyperglycemia, Hypertension, Impaired Wound Healing, Increased Appetite, Insomnia, Osteoporosis, Stomach Ulcers

Drug - Drug Interactions	Drug - Food Interactions	Special Instructions
<p>(Mycophenolate) <u>Increased levels:</u> Acyclovir, Ganciclovir, Probenecid, Salicylates, Valacyclovir, Valganciclovir <u>Decrease levels:</u> Antacids (Ca and Mg), Cholestyramine, Cyclosporine</p>	N/A	<p>Abd. pain, cramping, diarrhea are the most common side effects.</p> <p>Myfortic may be beneficial for upper GI complaints due to mycophenolate. <u>Conversion:</u> 500mg CellCept = 360mg Myfortic</p>
<p>(Azathioprene) <u>Increased Levels:</u> Allopurinol</p> <p><u>Increased Adverse Events:</u> ACE inhibitors, Anticoagulants, Cyclosporine</p>	N/A	<p>May take with food or in divided doses to decrease GI intolerance</p>
<p>(Sirolimus) <u>Increased levels:</u> Amiodarone, Azole antifungals, Contraceptives, Macrolide Antibiotics, Metoclopramide, Methylprednisolone, Non-Dihydropyridine Calcium Channel Blockers <u>Decreased levels:</u> Anticonvulsants, Dexamethasone, Rifamycins, St John's Wort</p>	<p><u>Increased Levels:</u> Grapefruit Juice</p> <p>High fat meals increase total drug exposure- so take drug consistently with or without food.</p>	<p>May have a positive effect in those patients with skin cancer, lymphoma or renal cell carcinoma.</p> <p>Not recommended early post transplant due to bronchial anastomotic dehiscence.</p> <p>Administration- Dose must be separated by 4 hours from Cyclosporine.</p>
<p>(Corticosteroids) <u>Increased Levels:</u> Azole Antifungals Estrogens Oral Contraceptives</p> <p><u>Decreased Levels:</u> Rifampin, Phenytoin, Barbiturates</p> <p>Increases risk of side effects on many drugs (ex. Increased risk tendon rupture with quinolones)</p>	N/A	<p>Administer as a pre-medication to Thymoglobulin</p>

P. Post-transplant Induction/Prophylaxis Summary

BWH Lung Transplant Immunosuppressive Protocol	
POD # 0 Given in OR Day of Transplant	<ul style="list-style-type: none"> • Simulect (Basiliximab): <ul style="list-style-type: none"> ○ Dose = 20mg x 1 ○ Administration: <ul style="list-style-type: none"> ▪ Infuse over 20-30 minutes through a central or peripheral line. Basiliximab should not be infused with other medications. ▪ To be infused prior to implantation of first lung • Mycophenolate 1000 mg • Methylprednisolone: <ul style="list-style-type: none"> ○ Dose = 250 mg ○ Administration: <ul style="list-style-type: none"> ▪ First dose prior to implant. Please give prior basiliximab ▪ Second dose after reperfusion
POD # 1	<ul style="list-style-type: none"> • Anti-Infectives: <ul style="list-style-type: none"> ○ Micafungin 100mg IV Daily ○ Nystatin Suspension 5mL every 6 hours ○ Vancomycin 15 mg/kg IV Q12 hours ○ Flagyl 500mg IV Q8 hours ○ Ciprofloxacin 400mg IV Q12 hours ○ Amphotericin Nebs 10mg INH Q12 x 2 doses, then increased to 25mg INH Q12 if tolerated, (or alternative) to be administered until discharge ○ Consider starting antiviral (acyclovir, gancyclovir, valacyclovir, or valgancyclovir) based on donor/recipient CMV/EBV status as per anti-viral prophylaxis protocol. • Methylprednisolone: <ul style="list-style-type: none"> ○ Dose = 125 mg IV q8 hours • Tacrolimus: <ul style="list-style-type: none"> • To be initiated within the first 24 hours post-transplant. Starting Dose .025 mg/kg sublingual (For patients with pre or peri-transplant RV dysfunction, a lower starting dose of 0.5 mg q12 hours will be initiated to minimize renal toxicity and allow for diuresis as necessary) every 12 hours. Please order daily tacrolimus levels once initiated. Once patient is tolerating orals, tacrolimus may be transitioned to PO/PNGT at the discretion of the transplant team. • Mycophenolate: <ul style="list-style-type: none"> ○ To be initiated immediately post-transplant. Starting Dose = 1000mg IV/PO/PNGT Q12 hours
POD # 2	<ul style="list-style-type: none"> • Anti-Infectives: <ul style="list-style-type: none"> ○ Continue as above and tailor to cultures, sensitivities and patient's clinical condition ○ Order Galactomannan Test Today • Methylprednisolone or Prednisone: <ul style="list-style-type: none"> ○ Dose = 1mg/kg POD #2-8 • Tacrolimus: <ul style="list-style-type: none"> ○ To be initiated within the first 24 hours post-transplant. Starting Dose .025 mg/kg sublingual every 12 hours. Please order daily tacrolimus levels once initiated. Once patient is tolerating orals, tacrolimus may be transitioned to PO/PNGT at the discretion of the transplant team. • Mycophenolate <ul style="list-style-type: none"> ○

BWH Lung Transplant Immunosuppressive Protocol	
POD # 3	<ul style="list-style-type: none"> • Anti-Infectives: <ul style="list-style-type: none"> ○ Continue as above and tailor to cultures, sensitivities and patients clinical condition. • Methylprednisolone or prednisone: <ul style="list-style-type: none"> ○ Dose = 1mg/kg POD #2-8 • Tacrolimus: <ul style="list-style-type: none"> ○ To be initiated postoperatively at the discretion of the lung transplant team based on the patients clinical condition. Starting Dose .025 mg/kg sublingual every 12 hours. Please order daily tacrolimus levels once initiated. Once patient is tolerating orals, tacrolimus may be transitioned to PO/PNGT at the discretion of the transplant team. • Mycophenolate: <ul style="list-style-type: none"> ○
POD # 4	<ul style="list-style-type: none"> • Anti-Infectives: <ul style="list-style-type: none"> ○ Continue as above and tailor to cultures, sensitivities and patient's clinical condition. ○ Once patient is tolerating orals, start Bactrim DS QMon-Wed-Fri as PCP prophylaxis. ○ If patient is allergic to sulfa, use Atovaquone 1500mg QDAY • Simulect (Basiliximab): <ul style="list-style-type: none"> ○ Dose = 20mg x 1 ○ Administration: <ul style="list-style-type: none"> ▪ Infuse over 20-30 minutes through a central or peripheral line. Basiliximab should not be infused with other medications. • Methylprednisolone or Prednisone: <ul style="list-style-type: none"> ○ Dose = 1mg/kg POD #2-8 • Tacrolimus: <ul style="list-style-type: none"> ○ To be initiated within the first 24 hours post-transplant. Starting Dose .025 mg/kg sublingual every 12 hours. Please order daily tacrolimus levels once initiated. Once patient is tolerating orals, tacrolimus may be transitioned to PO/PNGT at the discretion of the transplant team. • Mycophenolate <ul style="list-style-type: none"> ○
POD # 5+	<ul style="list-style-type: none"> • Anti-Infectives: <ul style="list-style-type: none"> ○ Continue as above and tailor to cultures, sensitivities and patients clinical condition ○ Once patient is tolerating orals, start Bactrim DS QMon-Wed-Fri as PCP prophylaxis. ○ If patient is allergic to sulfa, use Atovaquone 1500mg QDAY • <i>Order Galactomannan Test Today</i> • Methylprednisolone or Prednisone: <ul style="list-style-type: none"> ○ Dose = 1mg/kg POD #2-8 • Tacrolimus: <ul style="list-style-type: none"> ○ To be initiated within the first 24 hours post-transplant. Starting Dose .025 mg/kg sublingual every 12 hours. Please order daily tacrolimus levels once initiated. Once patient is tolerating orals, tacrolimus may be transitioned to PO/PNGT at the discretion of the transplant team. • Mycophenolate

Q. Steroid Taper

Day	Steroid Dose	70kg Individual Example
POD # 0	Methylprednisolone 250 mg - First dose prior to implant, second dose after reperfusion	500 mg solumedrol
POD # 1	Methylprednisolone 125 mg IV q8 hours	375 mg methylprednisolone
POD # 2 - 8	1 mg/kg/day prednisone or IV equivalent	70 mg/day prednisone
POD # 9 - 30	Prednisone 0.5 mg/kg/day	35 mg/day prednisone
If FEV1 drops no more than 10% and no AR on 1 month bronchoscopy		
POD # 31 - 90	Wean to 0.3 mg/kg/day by 8 weeks post-op	Wean by 5mg every 2 weeks to 20mg/day prednisone by 6-8 weeks
IF FEV1 drops no more than 10% and no AR on 3 month bronchoscopy		
POD # 91	Wean to 10mg/day prednisone by 3 months	Wean by 2.5mg every week to 10mg/day prednisone by 3 months
POD # 120	Wean to 5mg/day prednisone by 4 months	Wean by 2.5mg every 2 weeks to 5mg/day prednisone by 4 months

R. Lovenox Dosing

Lovenox Renal Dosing

CrCl (ml/min)	Lovenox Dose	Anti-Xa Monitoring (Heparin Level)
> 70	1 mg/kg Q12h	None
35 – 69	0.75 mg/kg Q12h	3 – 6 hrs after the 3 rd Injection
< 35	1 mg/kg Q24h	3 – 6 hrs after the 3 rd injection

Lovenox Dosing in Obesity

Weight	Lovenox Dose	Anti-Xa Monitoring (Heparin Level)
< 100 kg	1 mg/kg Q12h	None
100 - 130 kg	1 mg/kg Q12h	3– 6 hrs after the 1 st Injection
> 130 kg	130 mg Q12h	3– 6 hrs after the 1 st injection

S. Pancreatic Enzyme Replacement

Enzyme	Company Tel #	Bead size (mm)	Optimal Dissol- ution pH	Lipase USP Units	Protease USP Units	Amylase USP Units	Micro- Tablets	Micro- Spheres
Enteric Coated								
Creon® 5	Solvay 800-241-1643	<1.7	>5.5	5,000	18,750	16,600		√
Creon® 10	Solvay	<1.7	>5.5	10,000	37,500	33,200		√
Creon® 20	Solvay	< 1.7	>5.5	20,000	75,000	66,400		√
Lipram™ (generic)	Global 215-289-2220	?<1	>5.5	Company carries substitutions for Creon (CR5, CR10, CR20), Ultrase (4500, UL12, UL18, UL20), and Pancrease (4500, PN10, PN16, PN20)				
Pancrearb® MS-4*	Digestive Care 610-882-5959	0.4 – 0.8	6-7	4,000	25,000	25,000		√
Pancrearb® MS-8*	Digestive Care	0.6 – 1.5	6-7	8,000	45, 000	40,000		√
Pancrearb® MS- 16	Digestive Care	0.6- 1.5	6-7	16,000	52,000	52,000		√
Pancrease®	Ortho-McNeil 800-682-6532	<3	>5.5	4,500	25,000	20,000		√
Pancrease® MT4	Ortho-McNeil	<3	>5.5	4,000	12,000	12,000	√	
Pancrease® MT10	Ortho-McNeil	<3	>5.5	10,000	30,000	30,000	√	
Pancrease® MT16	Ortho-McNeil	<3	>5.5	16,000	48,000	48,000	√	
Pancrease® MT 20	Ortho-McNeil	<3	>5.5	20,000	44,000	56,000	√	
Ultrase®	Axcan Scandipharm 800-472-2634	1.3	>5.5	4,500	25,000	20,000		√
Ultrase® MT 12	Axcan Scandipharm	2.0	>5.5	12,000	39,000	39,000	√	
Ultrase® MT 18	Axcan Scandipharm	2.0	>5.5	18,000	58,500	58,500	√	
Ultrase® MT 20	Axcan Scandipharm	2.0	>5.5	20,000	65,000	65,000	√	
Viokase® 16 tablet	Axcan Scandipharm	n/a	n/a	16,000	60,000	60,000	n/a	n/a

S. Pancreatic Enzyme Replacement (continued)

Enzyme	Company Tel #	Bead size (mm)	Optimal Dissol- ution pH	Lipase USP Units	Protease USP Units	Amylase USP Units	Micro- Tablets	Micro- Spheres
<i>Non-Enteric Coated</i>								
Viokase® powder (0.7 gm or ¼ tsp)	Axcan Scandipharm	n/a	n/a	16,800	70,000	70,000	n/a	n/a

*Buffer capacity: 1.5 mEq/L bicarbonate

Recommended starting dosage of Pancreatic Enzymes

8,000 USP units Lipase/meal or snack
Max of 32,000 USP units Lipase per meal

T. Leukopenia Algorithm

Normal white blood cell count (WBC) at BWH = 4-10 K/uL. For lung transplant patients an intervention for leukopenia is required when WBC < 2 K/uL.

Considerations:

- Time since transplant
- Infectious etiology- Viral infections (CMV, EBV, Influenza)
- Transplant Medications and overall immunosuppression
 - Thymoglobulin, CellCept (mycophenolate), Imuran (azathioprine), Rapamune (sirolimus), Valcyte (Valganciclovir), Bactrim (SMZ/TMP), Dapsone, etc.

Interventions:

IF WBC <2 K/uL

- Draw quantitative CMV PCR (viral load) if not drawn within the past week and consider checking ImmuKnow assay
 - ImmuKnow (If clinically indicated): One kelly green tube (with Na/hep) On the rec it needs to say: cell mediated immune function sent to ARUP lab, # 51273
- Assess that Valcyte and Bactrim are appropriately adjusted for renal function. If Valcyte will require constant adjustment for fluctuating renal function consider consulting ID to determine if it would be better to hold Valcyte to avoid creating resistance from inappropriate dosing.
- Check CMV Status:
 - If D+/R- continue Valcyte until CMV PCR results available. If results negative, consider holding.
 - If D+/R+ or D-/R+, hold Valcyte until WBC count normalizes.
 - If D-/R- hold valacyclovir until WBC normalizes
 - While Valcyte dose is held consider continued monitoring of CMV PCR approximately every 2 weeks until Valcyte can be dosed at goal.
 - Consider switching Valcyte to Prevymis (letermovir) 480mg once daily for CMV prophylaxis. Prevymis has a lower incidence of leukopenia/neutropenia than Valcyte and does not require renal adjustment. It is only approved for CMV prophylaxis, not for treatment. Letermovir has no coverage of HSV, so patients started on it should also be placed on valacyclovir 500mg BID (or renally adjusted) for HSV prophylaxis.
- Consider holding or dose reducing Cellcept
- Add diffs to CBC so that ANC can be followed
- If ANC < 1000, Hold CellCept, consider holding valcyte (discuss with attending/team/ID, particularly for CMV D+/R- cases), and administer Neupogen (filgrastim, GCSF) 5mcg/kg (available sizes 300mcg and 480mcg) and recheck ANC; Discontinue if ANC > 2000.
- Follow-up on ImmuKnow results (normal range 225 to ~500) and discuss lowering immunosuppression targets if appropriate.
 - Suggestions to decrease immunosuppression if results <225
 - First decrease Mycophenolate 50% and repeat ImmuKnow 4 weeks after change.

- If ImmuKnow remains low decrease tacrolimus trough goals (If patient <1 year post transplant adjust goal to 6-8 ng/ml; if patient >1 year post transplant adjust to 4-6ng/ml) and repeat test 4 weeks following.
- Follow-up on CMV PCR and continue sampling every 2 weeks while leukopenic
- If CMV PCR is positive start treatment (adjust for renal dysfunction)
 - Valganciclovir 900mg PO BID
 - IV Ganciclovir 5mg/kg BID
- If CMV PCR is negative hold Valcyte despite CMV status. (discuss with attending / team / ID, particularly for CMV D+/ R- cases)
- Assess immunosuppression levels and ImmuKnow results and review with team to see if adjustments should be made.
- Last Line- If nothing else is working consider stopping Bactrim and changing to an alternative agent, Atovaquone or Dapsone (be sure to check for G6PD deficiency before starting Dapsone prophylaxis).

U. ImmuKnow Protocol

The Cylex immune cell function assay (ImmuKnow) was approved by the FDA to monitor global immune response in solid organ transplant recipients on immunosuppression. The assay measures the amount of ATP produced in CD4 T-cells following stimulation by phytohemagglutinin-L (PHA), thus assessing overall CD4 T-cell function through the ability of T-helper lymphocytes to respond to this stimulation. Being a basic energy source of all cells, ATP is required for most functions of immune cells.

Immune Response Results

Strong >525
 Moderate 226-524
 Low <225

While a strong immune response indicates a very active immune system, these results have not been highly correlated with rejection episodes in transplant. However, on the other end of the spectrum low immune response results have been correlated with infectious complications potentially suggesting over-immunosuppression. Currently there are no recommendations on adjusting immunosuppression based on these results; they remain a guide to correlate with clinical picture.

What to send:

One kelly green tube (with Na/hep)

On the rec it needs to say: cell mediated immune function sent to ARUP lab, # 51273

Timing of ImmuKnow Blood Draws:

Draw if clinically indicated – when concern arises for over-immune suppression (e.g. – recurrent infections) or under-immune suppression (e.g. - recurrent episodes of rejection) without clear clinical evidence of the patient’s immune status (e.g. – patient is not leukopenic).

Interpretation of Results:

Results of the ImmuKnow Assay should be used in conjunction with available clinical and laboratory information to assess the level of immune suppression.

- 1) ImmuKnow Assay < 225 in association with leukopenia (WBC count < 2,500 or ANC < 1000) – Supportive of excessive immune suppression – management per leukopenia algorithm.
- 2) ImmuKnow Assay < 225 in association with stable WBC count > 2,500 and ANC > 1,000)
 - a. Clinical Evidence of Infection: Consider lowering immune suppressive regimen:
 - i. Ensure steroids tapered per protocol
 - ii. Decrease or hold purine modulator
 - iii. Lower CNI goal therapeutic level
 - b. No Clinical Evidence of Infection: Repeat ImmuKnow Assay within 4 weeks, follow guidelines above.
- 3) ImmuKnow Assay 226 – 524: Alterations to immune suppressive regimen only as clinically indicated
- 4) ImmuKnow Assay >525:
 - a. With clinical evidence of rejection:
 - i. Discuss treatment decisions for rejection
 - ii. Ensure steroids are tapered per protocol
 - iii. Ensure 3 drug immune suppression protocol is implemented (consider GCSF to support WBC count in setting of leukopenia)
 - iv. Utilize Tacrolimus and Mycophenolate if possible (consider interventions to minimize side effects to allow utilization if possible)
 - v. Ensure goal therapeutic CNI level is maximized: Incorporate renal function, WBC count, and other clinical issues when setting goal level.
 - b. Without clinical evidence of rejection:
 - i. Consider WBC count trend – if rising, may support finding of under-immune suppression
 - ii. Repeat within 4 weeks to reassess

V. Calcineurin Inhibitor Management Protocol

This algorithm provides some guidance for CNI management, though the clinical status and complicating factors of each patient must be considered in determining the appropriate adjustment of CNI dosing.

CNI Dosing:

- 1) Calcineurin inhibitor (CNI) treatment should be initiated as soon as is safe to do so after transplant completion. The level of cytopenias and renal dysfunction, as well as the use of induction, should be considered in determining the optimal timing of CNI initiation.
- 2) The preferred route of CNI introduction is enteral or sublingual. Guidelines for dosing are provided in the Immune Suppression Management Guidelines.
- 3) Goal therapeutic levels for patients:
 - a. in the first 12 months post transplant and in the setting of normal renal function are:
 - i. Tacrolimus: 8-12 mg/dl
 - ii. CSA: 250-350 mg/dl

- b. more than 12 months post-transplant and in the setting of normal renal function are:
 - i. Tacrolimus: 6-8 mg/dl
 - ii. CSA: 150-250 mg/dl
- c. In the first 12 months post transplant and in the setting eGFR<45-50:
 - i. Tacrolimus: Approximately 8
 - ii. CSA: Approximately 250
- d. more than 12 months post-transplant and in the setting of eGFR<45-50 are:
 - i. Tacrolimus: Approximately 6
 - ii. CSA: Approximately 150
 - iii. Discuss with transplant physician, may need to consider lower goals dependent on severity of renal dysfunction

Management of Elevated CNI Levels:

Assess whether level drawn is true 12 hour trough level (trough drawn < 12 hours post prior dose may lead to false indications of supra-therapeutic level).

In the setting of clinical manifestations of toxicity, management should be discussed in detail with the physician. In the setting of asymptomatic elevated drug levels, the following provides a guideline for management:

Always consider whether new medications have been initiated which may be contributing to elevated drug levels (antibiotics, antifungals, other inhibitors of P450 system, etc.).

- 1) CNI level <= 25-50% above goal: Decrease dose by 25-50%, recheck level in 3 to 7 days.
- 2) CNI level 50-75% above goal: Decrease dose by 50%, recheck level in 3-7 days, consider holding one dose prior to institution of new dosing regimen.
- 3) CNI level > 75% above goal: Hold further CNI dosing, repeat level in 24 hours, once level <50% above goal, restart dosing at 50-75% decreased dose.

Management of Low CNI Levels:

Assess whether level drawn is true 12 hour trough level (trough drawn > 12 hours post prior dose may lead to false indications of sub-therapeutic level).

Always consider whether new medications have been initiated which may be contributing to the low levels (nafcillin, P450 system potentiators, etc.).

- 1) CNI <= 25-50% below goal: Increase dose by 25-50%, recheck level in 3-7 days.
- 2) CNI level more than 50% below goal: Discuss with transplant physician, increase dosing by at least 50%, consider switching to sublingual administration to increase absorption, consider whether admission for frequent monitoring of level or IV infusion is indicated, recheck level in 24-72 hours.

W. Management of Desensitization and Antibody Mediated Rejection

The decision to perform desensitization and/or initiate treatment for antibody mediated rejection will be made on a case by case basis.

a. Desensitization

The following algorithm will be used to determine recipient antibodies to incorporate into the program for DSA assessment at the time of organ offer:

- Recipients without circulating antibody will be screened every 2-4 months.
- Recipients with circulating antibody will be screened monthly until three tests have been performed, and then every 2-4 months.
- All candidates should be assessed for sensitizing events at every clinic visit and when contacted regarding a change in clinical status. Sensitizing events are depicted below:

- An accurate patient history must be obtained and shared with the histocompatibility laboratory, on an on-going basis [1A]. Specifically, the clinical program needs to document:
 - I. HLA sensitizing events:
 - Pregnancies
 - Transfusions
 - Previous transplant
 - Implants (VADs, homografts, etc.)
 - II. Inflammatory events that may boost pre-existing alloimmune memory:
 - Major surgeries
 - Major infections
 - Recent vaccinations
- Only patients without HLA sensitizing events may be considered immunologically low risk for alloimmune memory [EO]. All other patients should be categorized as having latent potential or active potential for an alloimmune memory response.
- The patient's alloimmune status should be used for risk stratification and informing frequency of pre- and post-transplant testing [EO].
- The patient's immunization to alloantigens is dynamic. Re-evaluation of this status is required pre- and post-transplantation to assess whether management and monitoring protocols should be adjusted [EO].

Am J Transplant 2018; 18: 1604

Candidates noted to have sensitizing events should undergo repeat screening for circulating antibodies immediately after identifying the event and then monthly until three assessments have been completed.

- All current antibodies will be included for DSA assessment. In addition, all antibodies ever present on two or more samples will be incorporated for DSA assessment.
- Autoantibodies (i.e. antibodies to antigens common to both donor and recipient) will be excluded from DSA assessment.
- In the event of circulating antibodies, a cPRA will be calculated. Candidates with cPRA \geq 50% will have either a review of crossmatch history and/or cytotoxic quick screen assessment performed to better inform the team as to the recipient's true likelihood of obtaining a suitable donor. This information can be used to guide recipient understanding of their likelihood of transplant.

- The quick screen assessment will be performed at dilutions of 1:8 and 1:32. If a substantial decrease in cPRA is noted on dilutional assessment, consideration could be given to pre-transplant attempts at desensitization. If, however, a significant change in cPRA is not noted on dilutional assessment, this will argue against attempts at pre-transplant desensitization.
- Also consider c1q testing to determine the cytotoxicity of the circulating antibody as a trigger for pre-transplant desensitization.
- Regardless of whether or not pre-transplant desensitization is attempted, the presence or absence of circulating donor specific antibody as assessed at the time of the organ offer will dictate whether a prospective crossmatch is needed. ***In order for this approach to be successful, it is imperative that we assess the presence or absence of DSA immediately upon receiving the organ offer and notify the organ bank of the need for a crossmatch, if applicable. This will optimize the ability to obtain a crossmatch before the scheduled OR time.***
- Candidates with known circulating antibody should have blood samples obtained monthly and stored with the tissue typing lab for a total of three months. Screening will then occur every 2-4 months. Screening should be performed as noted above. The remaining samples will allow us to have a current sample to use for crossmatching.
- At the time of the organ offer: If class I DSA is present, a prospective CDC T and B cell crossmatch should be requested. If class II DSA is present, a prospective B cell CDC crossmatch should be requested. These requests should be made through the onsite donor coordinator.
- The candidate should be brought in for potential transplant as per usual procedure (i.e. do not wait for crossmatch results to bring them in) so as to make sure we do not have delays beyond those presented by the need for crossmatch.
- If a prospective crossmatch is positive, we will not proceed with transplantation for that recipient. As this will likely be determined very close to the OR time, it is important to consider bringing in a back-up recipient in these cases, so that the organs are not lost in the event of a positive crossmatch.
- If the crossmatch is negative, we should plan to institute plasmapheresis and proceed with transplant. Intraoperative pheresis catheter placement should be requested, with plan to initiate plasmapheresis as soon as possible after arrival in the ICU. The Bard catheter is the preferred pheresis line in this specific patient population
- The 11c and blood bank teams should also be notified of the need for initiation of plasmapheresis postoperatively.

b. Antibody Mediated Rejection (AMR)

- AMR is suspected in the setting of a decline in PFT's, or other signs of allograft dysfunction, in the presence of circulating donor specific antibody (DSA), or pathologic manifestations consistent with AMR, such as capillaritis, or other manifestations as outlined in published literature (JHLT 2013; 32(1): 14) (see section 7 subsection AMR).
- In the setting of acute respiratory failure of unclear etiology, recurrent acute cellular rejection, or chronic lung allograft dysfunction, AMR should be considered in the differential diagnosis.

- Our program does not perform routine surveillance for de novo DSA in the absence of clinical symptoms. However, candidates with known sensitizing events occurring pre or post transplant should have DSA assessment performed monthly for 3-6 months after transplant for events that occurred pre transplant and for 3-6 months after the event for events that occur post transplant.
- In the setting of concern for AMR, assessment for DSA will be performed by prescreen and completing class I and II single antigen testing.
- If DSA is detected and a decision is made to initiate therapy, request a dilutional assessment (titers) to assess response to therapy. Consider dilutional assessment (titers) with the initial request for hospitalized patients, or patients with rapid decompensation in whom a determination to initiate therapy is needed urgently. In these circumstances, contact the tissue typing lab to request urgent completion of testing.
- Also consider c1q testing to determine cytotoxicity of the antibody.
- If tissue samples are obtained in the setting of suspected AMR, consider request for c4d staining. While c4d deposition in the lung is more difficult to interpret than in the kidney, this assessment can support the diagnosis if staining is positive in a peri-capillary distribution. C4d staining should also be considered in the setting of high grade (A3 or A4 , B2R) or recurrent acute cellular rejection.
- AMR can occasionally occur in the absence of circulating DSA, and strong consideration should be given to treatment in the presence of allograft dysfunction with supporting pathologic changes, even in the absence of DSA.
- After treatment, DSA should be repeated within one week, with dilutional assessment. A follow up schedule for DSA testing will be made on a case by case basis.

c. Therapy

- To initiate plasmapheresis at the time of transplant, page the Blood Bank MD on call at pager 35110. Treatment:
 - Plasmapheresis Every Other Day x 3 sessions
 - IVIG (Gammagard Liquid 10%) 2gm/kg x 1 dose (please use IBW to calculate dose and round to the nearest 5gm), should be given following the final plasmapheresis session. Premedication 30-60 minutes prior to each IVIG infusion is required:
 - Acetaminophen 650mg PO/PR x1
 - Diphenhydramine 50mg PO/IV x1
 - Methylprednisolone 40mg x1 if not receiving pulse mentioned above
 - Please see the IVIG Drug Administration Guideline for infusion instructions and adverse reactions to monitor for. http://www.bwhpikenotes.org/policies/Pharmacy/Drug_Administration/DAG/Igg02DAG.htm
 - Rituximab 375mg/m² x1 following completion of the second dose of IVIG. Please schedule a chemotherapy nurse to infuse the medication at least 24 hours in advance (Chemo in the Outfield RN Michaelle Renard [pg 13453]). The patient must have height & weight measured, verified & documented by two of the floor

nurses. This can be documented in the patients grey chart. These measurements are required for accurate calculation of the dose and must be done on the day the order is entered in the chemotherapy order entry system (COE).

Rituximab also requires pre-medication with Acetaminophen, diphenhydramine and methylprednisolone at the doses described above.

- Repeat serum screen for HLA 1 week after therapy and consider further therapy with weekly Rituximab, additional plasmapheresis or alternative therapies such as bortezomib if indicated.
- Should bortezomib (Velcade) be required, please follow protocol below which can be given with or without rituximab at the discretion of the transplant team. Bortezomib also requires a chemotherapy nurse to administer the medication. Please contact the Chemotherapy in the outfield coordinator in advance to arrange for a nurse, document height & weight, and consent the patient to receive bortezomib. There must be ≥72 hours between doses of bortezomib. The patient should be monitored for infusion reactions, GI symptoms (N/V/D) as well as peripheral neuropathy.

Bortezomib (Velcade) Protocol	Treatment Days			
	1	4	7	10
Plasmapheresis	x	x	x	x
Methylprednisolone 100mg IVP	x	x		
Methylprednisolone 50mg IVP			x	x
Bortezomib 1.3mg/m ²	x	x	x	x
(+/-) Rituximab 375mg/m ²	x			

¹Plasmapheresis performed first. At completion plasmapheresis, administer methylprednisolone 100 mg (intravenous push) prior to the bortezomib dose on treatment day 1 and 4, methylprednisolone 50 mg (intravenous push) prior to the bortezomib dose on treatment day 7 and 10. Thirty (30) minutes following methylprednisolone, administer bortezomib (intravenous push). Sixty (60) minutes following bortezomib, administer rituximab (intravenously) per institution policy. Consider as needed medications for nausea, vomiting and diarrhea during treatment days.

d. Pheresis Catheter Management

- When requesting pheresis line placement; notify IR that the Bard catheter is the preferred pheresis line in this specific patient population
- In-patient or outpatient pheresis done in the BWH blood donor center: the blood donor center will manage dressing and connector changes. Notify blood donor center that the clave connectors are the preferred connector in our lung transplant population.
- Should patient be discharged with pheresis catheter (determined by covering attending) services will need to be set up for flushes and clave connector changes. Notify specified services of BWH policy for pheresis line management
- Pheresis line management for lung transplant patients in accordance with BWH nursing policies
 - To access pheresis line
 - a. In addition to standard precautions, a pheresis line connector must be scrubbed for 10 seconds with alcohol prior to accessing

- b. After each use (pheresis, fluids, meds, blood administration, or blood draws):
 - i. Withdraw 5 ml from each lumen and discard in appropriate receptacle
 - ii. Flush with **5 ml of 10 units/ml** heparinized saline into the lumen
 - iii. Re-clamp catheter
 - iv. Document catheter care on appropriate forms
 - c. A new Clave connector must be used after each use
 - When catheter is NOT BEING USED for fluids, meds, blood administration, and/or blood drawing M-W-F
 - a. Clave Connector:
 - i. Must be changed a minimum every 4 days
 - ii. Withdraw 5ml from the lumen and discard in appropriate receptacle
 - iii. Flush 5ml 10units/ml heparinized saline into the lumen
 - iv. Reclamp catheter
 - Pheresis line dressing must be changed every 7 days or more frequently if it becomes soiled or non-occlusive
 - a. Observe site of insertion and document appropriately
 - b. Notify transplant team of an concerns of infection at insertion site
 - c. Do not use line if it has become dislodged or has migrated position
 - If there is a problem with pheresis catheter maintaining patency:
 - a. Withdraw 5ml from the lumen and discard in appropriate receptacle
 - b. Instill catheter volume of 1:1000units/ml heparin into catheter lumen (catheter volume is noted on the catheter)
 - c. Consider dwell with TPA
 - d. If unable to withdraw from lumen, pheresis line must be discontinued
- Points of emphasis: 5ml is removed from the catheter to ensure that any clots are removed from the catheter lumen and to ensure that, if heparin was used previously, that no 1:1000units/ml heparin is infused into the patient
 - Pheresis catheters placed in IR are to be removed by the IR team only as per the IR Physician Director
 - For additional information regarding line management, please refer to Nursing Clinical policies IVT – 00 and IVT – 21 in BWH Pike Notes

X. Campath (Alemtuzumab) Rejection Protocol

Mechanism: Campath binds to CD52, an antigen on T and B lymphocytes, majority of monocytes, macrophages, NK cells, and some granulocytes, leading to antibody-dependent cellular mediated lysis.

- Prior to administration make sure patient does not have active infection and check CBC. If patient is neutropenic and/or thrombocytopenic consider waiting until this has resolved before administering Campath.

- Ordering: As this medication is technically considered a chemotherapy agent, it can only be ordered through the chemotherapy template by an attending with chemotherapy writing privileges.

Campath should be arranged to be given outpatient in the infusion clinic unless patient not medically stable

- Dosing & Administration:
 - Dose: Alemtuzumab 30mg x 1
 - Route:
 - Given subcutaneously in the thigh or buttock as one 30 mg injection
 - *DO NOT* give as IV Bolus or IV Push
 - Premedication:
 - Acetaminophen 650mg PO/PR x1, 30 minutes prior to alemtuzumab infusion
 - Diphenhydramine 50mg PO/IV x 1, 30 minutes prior to alemtuzumab infusion
 - Corticosteroids are optional
 - Order PRN's for infusion reactions as per therapy plan. Consider:
 - Hydrocortisone sodium Succinate 200mg IV x1 PRN infusion reactions
 - Meperidine (Demerol) 12.5-25mg IV Q15-30 minutes PRN Rigors
- Preparation & Stability: Drug will be prepared by the pharmacy; dose can be mixed in 100mL 0.9% sodium chloride or dextrose 5% in water and should be used within 8 hours of dilution.

Administration: This medication is technically considered a chemotherapy agent and will have to be administered by a chemotherapy infusion nurse. Please arrange for this to happen 24 hours in advance of administration of medication. To arrange for inpatient chemotherapy trained nurse please contact Chemotherapy in the Outfield, currently managed by Michaelle Renard.

- Adverse Reactions:
 - Infusion Reactions- pyrexia, chills/rigors, hypotension, urticaria, dyspnea, rash, emesis and bronchospasm
 - Post-marketing reports of serious and fatal infusion reactions including ARDS, syncope, pulmonary infiltrates, respiratory arrest, cardiac arrhythmias, cardiac arrest, angioedema, and anaphylactic shock.
 - Cytopenias- neutropenia, lymphopenia, thrombocytopenia, anemia
 - Infections: CMV and other infections
 - Neurological- insomnia, anxiety
 - GI- nausea, emesis, abdominal pain
- Monitoring:
 - At least Weekly CBC to assess neutropenia, thrombocytopenia and anemia.
 - Consider assessing CD4 counts until recovery to ≥ 200 cells/ μ L, as this is when patient will be at highest risk of opportunistic infections.
 - Consider monitoring CMV viral loads until CD4 ≥ 200 cells/ μ L.

- Prophylaxis:
 - Consider consulting ID for patient specific prophylactic recommendations following campath.
 - PCP-Verify that patient is receiving appropriate PCP prophylaxis with Bactrim or Mepron.
 - CMV-Restart CMV prophylaxis and consider monitoring serial CMV viral loads at least until CD4 \geq 200cells/ μ L.
 - Anti-fungal- Start voriconazole.
- Patient Counseling:
 - Advise patient of potential infusion reactions; increased risk of infections following infusion and for 6-12 months post; to monitor for signs and symptoms of cytopenias (easy bruising, pallor, weakness, fatigue); and that the effects of this medication on fertility in men and women has not been studied; patients should use effective contraception for at least 6 months following infusion.

Y. ECP (Photopheresis) Protocol

- ECP should be considered in the following clinical situations;
 - histopathologic or clinical evidence of acute rejection for whom augmented immune suppression is contraindicated
 - recurrent acute rejection refractory to augmented immune suppression
 - chronic rejection as evidenced by obliterative bronchiolitis on biopsy
 - decline in lung function consistent with Bronchiolitis Obliterans Syndrome in the absence of another reversible cause.
- Candidates for ECP should be HIV, hepatitis B and C negative.
- Patients should be hemodynamically stable and assessed for their ability to tolerate the extracorporeal blood volume shifts known to occur during this treatment. This assessment should occur at the time of initiation of ECP and preceding each ECP treatment.
- The patient should not have signs or symptoms of multi-organ failure (reassess prior to each ECP procedure).
- A minimum CD3 count of 500 cells/mm³ should be observed.
- Patient should not have a significant active infection which is uncontrolled by antibiotic, antiviral, or antifungal therapy at the time of initiation of ECP or at subsequent ECP procedures.
- Patient should have a minimum HCT 26-27 (per blood donor center), WBC count of 2,000 cells/mm³ and platelet count of 20,000/cmm.
- All cellular blood products administered during the course of photopheresis therapy must be leukocyte reduced by filtration and irradiated.
- ECP will be performed in accordance with standard practice under the guidance of the Blood Bank/Blood Donor Center staff.
- Treatment will begin on two consecutive days (two treatments) at weekly intervals for 4 weeks, followed by two consecutive days (two treatments) every other week, followed by treatment on two consecutive days (two treatments) monthly for four months.
- The treatment course may be interrupted at any time for evidence of improvement or disease progression, or for interval development of concurrent illness limiting the ability to administer treatment.

Z. Nissen Protocol

- **POD #0-1: NPO- Change tacrolimus to sublingual, all others to IV all meds to IV**
 - Tacrolimus PO:SL 1:1, adjustment of dose at discretion of transplant team based on serum level
 - CellCept IV:PO= 1:1 conversion
 - Prednisone can be changed to methylprednisolone IV at a 5:4 conversion
 - Bactrim DS tablet = 800mg Sulfamethoxazole/ 160mg Trimethoprim; frequency to be determined by toxoplasma status
 - Nystatin suspension can be changed to swish and spit 5cc four times daily
 - Valcyte must be changed to IV ganciclovir, Generally 900mg daily= IV ganciclovir 5mg/kg/day

 - , however doses must be adjusted based on renal function
 - Valtrex must be changed to IV Acyclovir. Generally 1000mg TID Valtrex = Acyclovir 10mg/kg IV Q8hours, adjusted for renal function
 - Change PPI to famotidine IV
 - BP meds to IV
 - SSRI's- no IV options, hold until can take crushed meds
 - Change Magnesium to IV scale
 - OK to HOLD- Calcium/Vitamin D/ Iron

- **POD #2-15: Full Liquid Diet x 2 weeks- Meds must be crushed**
 - Tacrolimus- Change back to PO dose on admission if trough levels had been stable. Prograf is available as capsules which can be opened and the powder can be sprinkled on to food.
 - CellCept is available as suspension 200mg/ml. This is preferred over tablets which can be crushed, however the powder is carcinogenic/teratogenic and should be handled with gloves by caregivers.
 - Methylprednisolone can be changed back to prednisone tablets which can be crushed
 - Bactrim can be switched back to tablets and crushed
 - Nystatin can be switched back to swish and swallow
 - Ganciclovir can be switched back to Valcyte, available as suspension 50mg/ml. Tablets can be crushed but powder is carcinogenic/teratogenic and should be handled with gloves.
 - Acyclovir can be switched back to Valtrex and tablets can be crushed
 - Switch H2 Blocker back to PO (PPI's can not be crushed)
 - BP meds to short acting tablets and crushed
 - Restart SSRI and crush tablet
 - Restart Magnesium and crush tablet
 - Calcium/Vitamin D/ Iron can be crushed

- **POD #16-29: Soft Solid Diet x 2 weeks- small/regular pills ok, nothing large**
 - Tacrolimus- OK to swallow capsules
 - CellCept- continue suspension, or cut in half and swallow
 - Prednisone- OK to swallow
 - Bactrim- continue to crush, or cut in half and swallow
 - Nystatin- swish and swallow
 - Valcyte- OK to swallow
 - Valtrex- continue to crush or cut in half and swallow
 - H2 Blocker or PPI- OK to swallow
 - BP meds- switch back to long acting tablets and swallow
 - SSRI- OK to swallow
 - Magnesium- continue to crush tablet
 - Calcium/Vitamin D/ Iron - continue crushed

- **POD#30+: Regular Diet- all meds PO**
 - Change all meds back to pre-Nissen formulation, OK to swallow.

AA. BWH Bone Health Protocol

This protocol should be activated for patients undergoing full evaluation for lung transplantation.

- Check vitamin D level with first evaluation blood draw.
- Begin Calcium and vitamin D supplementation for all patients undergoing evaluation.
- Review vitamin D level and increase vitamin D supplementation as appropriate:
 - 25 (OH) Vitamin D < 20 use high dose therapy : 50,000 units qweek
 - 25 (OH) Vitamin D > 20 use Calcium + Vitamin D daily preparation
- Review bone densitometry during patient presentation at formal listing meeting.
- For all recipients, obtain prior authorization for Reclast infusion
- Plan for Reclast infusion in Infusion Center on date of first post-transplant clinic visit.
- Obtain serial bone densitometry every 2 years for lung transplant recipients.
- Continue yearly Reclast replacement for all patients with osteopenia/osteoporosis.
- Consider 1-2 year drug holiday after 5 years in intermediate risk patients and after 10 years in high risk patients.

AB. IVIG Replacement Therapy

Hypogammaglobulinemia can be seen after lung transplantation, and can contribute to the development and impact of infection. This guideline provides an approach to the detection and management of hypogammaglobulinemia in lung transplant recipients at BWH.

IVIG Replacement Therapy:

1. Level to be checked with first infection post-transplant.
2. Low level defined as < 600 mg/dl for outpatients, BWH will approve replacement for levels < 400 mg/dl for inpatients
Treatment: Gammagard Liquid 10% 0.4gm/kg ideal body weight every 4-6 weeks for six doses.
3. Pre-medicate with acetaminophen (Tylenol) 650 mg PO x 1 (30 minutes prior to infusion)
4. Pre-medicate with diphenhydramine (Benadryl) 50 mg PO x 1 (30 minutes prior to infusion)
5. Hydrocortisone 100 mg IV prn: chills, fever, or history of reaction
6. Draw IgG level 2 months after 6th dose.
If levels still low at 6 months, increase dose (consider 500 mg/kg.)

AC. Pneumococcal Protection Strategy

- Bactrim has been demonstrated to be protective against Pneumococcal Pneumonia. Therefore, whenever possible, Bactrim should be used as the prophylactic agent of choice for Pneumocystis prophylaxis.
- Pneumovax (polysaccharide) vaccine stimulates a B cell response, whereas the prevnar 13 conjugated vaccine is more immunogenic, and stimulates both a T and B cell response. It may be more effective than pneumovax in immunocompromised patients.
- Patients who are immune suppressed before transplant should receive the Prevnar 13 vaccine as their pre-transplant vaccine if no documentation of prior administration is available followed by Pneumovax at least 8 weeks after.
- For pre-transplant patients who are not considered otherwise immunosuppressed Pneumovax should be given.
- Any patient who was vaccinated before against *Pneumococcus* with Pneumovax should receive vaccination with Prevnar 13 at least a year later. Patients who received Prevnar 7 before should receive Prevnar 13 followed by Pneumovax as in the recommendation above (II).
- Prevnar 13 administration should be considered for patients who are receiving Pheresis or Rituximab.
- A single booster with Pneumovax is indicated for all patients under the age of 65 who have received Pneumovax more than 5 years prior.

AD. Antiplatelet/Anticoagulants

How early to stop meds before invasive procedures?

Class	Generic Name	Brand Name	When to stop	When to resume (If no post-op bleeding)	
Anticoagulant Agents	Warfarin	Coumadin	5 days prior & normal INR	Day of procedure	
		Enoxaparin	Lovenox	Treatment: 24 hrs	Treatment: 24 hrs
				Propohylaxis: 12 hrs	Prophylaxis: 6-8 hrs
		Dalteparin	Fragmin	Treatment: 24 hrs	Treatment: 24 hrs
				Prophylaxis: 12 hrs	Prophylaxis: 6-8 hrs
		Fondaparinux	Arixtra	4 days	6 hrs
		Dabigatran	Pradaxa	3 days if CrCl>50	24 hrs
				4 days if CRCL=30-50	
				>5 days if CRCL<30	
		Rivaroxaban	Xarelto	2-3 days	24 hrs
	Apixiban	Eliquis	No information: Half-life=8-15 hrs		
Anti-Platelet Agents	Dipyridamole/ Asprin	Aggrenox	7 days	Day of procedure	
	Asprin		7 days	Day of procedure	
	Clopidogrel	Plavix	5-7 days	Day of procedure	
	Prasugrel	Effient	7 days	6 hrs	
	Ticlopidine	Ticlid	14 days	Day of procedure	
	Ticagrelor	Brilinta	5 days	6 hrs	
	Cilostazole	Pletal	4 days	6 hrs	

When do you need bridging?

Please discuss with attending on service if bridging should be considered

Indication of bridging

High risk of thromboembolism:

- A. Active malignancy
- B. Antiphospholipid antibody syndrome
- C. Any high risk of thrombophilia
- D. Any thrombotic stroke TIA
- E. Atrial fibrillation with history of stroke or TIA
- F. History of VTE or stroke while holding warfarin for any period
- G. Prosthetic mitral valve or any mitral valve disease requiring anticoagulation
- H. VTE in last 3 months
- I. Recurrent VTE
- J. Ventricular Assist Device

AE. Gabapentin for Chronic Refractory Cough Dose Titration and Renal Adjustments

Patient instructions: Please stop upward titration at the lowest effective dose

Dose Titration	CrCl > 60 (Max: 1800mg/day to be divided 3 x daily)	CrCl 30-59 (Max 1400mg/day to be divided 2 x daily)	CrCl 15-29 (Max 700mg/day- to be given once daily)
Day #1	300mg at Bedtime	300mg at Bedtime	300mg at Bedtime
Day #2	300mg Twice Daily	300mg Twice Daily	600mg at Bedtime
Day #3	300mg Three times Daily	300mg AM & 600mg PM	Re-evaluate cough & renal function, dose can be increased to 700mg at Bedtime with an additional prescription for 100mg capsules
Day #4	300mg AM 300mg afternoon 600mg bedtime	600mg Twice Daily	
Day #5	300mg AM 600mg afternoon 600mg bedtime	Re-evaluate cough & renal function, dose can be increased to 700mg Twice Daily with an additional prescription for 100mg capsules	
Day #6	600mg Three times Daily		