UNC ADULT LUNG TRANSPLANT PROTOCOL MANUAL

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Lung Recipient Referral, Evaluation and Selection process

I. Description

This policy outlines the referral, evaluation and selection processes for the lung transplant program.

II. Rationale

In adherence to CMS Conditions of Participation, this policy exists to ensure fair and nondiscriminatory distribution of organs.

III. Policy/Procedure

A. Policy

1. Patients are referred to the 4th floor transplant office (phone: 984-974-7589, fax: 984-974-6822) or one of the Pulmonary Physicians by the referring physician, another transplant center, or occasionally self-referred. Pertinent information is requested using a template sheet, with a cover letter summarizing the salient points of the patient's case. The referring physician information is requested, including e-mail, and direct phone number.

The referral is reviewed daily by the transplant Attending (supplemented, if necessary / time permitting, by direct contact with the referrers), and the Summary Sheet is completed prior to the team meeting. The summary sheet includes at a minimum, indications for transplant, any "red flags" and basic clinical information including PFTs, co-morbidities, BMI etc. Patients are categorized according to the data as for a rapid clinic visit, full evaluation, ESTEP with follow up, or rejection for major reasons.

2. All patient referrals will be reviewed using established program criteria. Patients may be referred through Pulmonary Clinic, the Lung Transplant Office, and/or through the inpatient consult service.

Criteria and/or Contraindications for Lung Transplantation include but are not limited to:

ABSOLUTE CONTRAINDICATIONS	RELATIVE CONTRAINDICATIONS
1. Irreversible chronic kidney dysfunction; Cr clearance <50 2. Significant hepatic dysfunction with evidence of portal hypertension 3. Severe Heart Disease (e.g. cardiomyopathy) and/or Severe Coronary Artery, Disease (LVEF<35%) 4. HIV infection 5. Active Hepatitis or chronic Hepatitis B or C infection with signs of cirrhosis or persistent viral loads 6. Active or recent cancer (within 5 years) except non melanoma skin cancer 7 Documented non-adherence to medical therapies and appointments. 8. Chronic, active use of narcotics or benzodiazepines. 9. Active substance abuse 10. Actively smoking or use of any nicotine containing products (1 year abstinence required) 11. Untreated or uncontrolled Psychosis 12. Untreated infection 13. Burkholderia Cenocepacia 14. BMI less than 16 15 BMI greater than 36	1. Greater than 75 years of age 2. BMI greater than 32 or less than 18 3. Inability to ambulate/rehabilitate 4. Inadequate social support system 5. Inability to meet the financial obligations projected for transplantation, immunosuppression, supportive therapies, and relocation. 6. Psychosocial instability 7. History of drug or alcohol dependency 8. Untreated significant mental illness 9. Coronary artery disease 10. Untreated atrial fibrillation or any unstable arrhythmia 11. Recent or unresolved pneumonia or pulmonary infection in patients without Cystic Fibrosis or Bronchiectasis 12. Previous Transplants 13. Ventilation, >50 years old 14. Systemic steroid therapy exceeding 20 mg per day 15. Other significant systemic disease 16. Severe esophageal dysmotility. 17. Allergy or intolerance to critical transplant medications 18. Previous sternotomy or thoracotomy with lobectomy/pneumonectomy for unrelated reasons 19. Elevated PRA (>80)

Note: Re-transplantation is considered on a case by case basis.

B. Procedure

1. If the patient meets the criteria for transplantation and this modality of treatment is possible for the patient (either at the present or at a future date) the patient should be referred to the Transplant Program for an in depth evaluation and discussion of transplantation which includes but is not limited to consults with a surgeon, pulmonologist, transplant coordinator, social worker, financial coordinator, dietician, and if indicated infectious disease and psychiatry.
2. To make an appointment for transplant evaluation and discussion, call the Transplant Program Office as above.
3. Prior to the appointment, the patient's medical summary should be sent to the Transplant office.
4. The patient is presented at selection conference on Tuesdays at 8:30AM and all testing is reviewed.

- Acceptance or refusal of the transplant candidate will be made in this multidisciplinary committee and the criteria used will be documented in the patient's medical record - document the specific criteria used such as medical diagnosis, contraindications (or lack of) and any exceptions to the criteria if applicable.

E.S.T.E.P. – Early Stage Transplant Education Program

- Since successful outcomes after transplantation require that patients (and those who support them) can comply with a complex regimen of care, and can meet a variety of medical and nonmedical fiscal expenses, we conceived an "Early Stage Transplant Education Program" (E.S.T.E.P) at our center, and piloted it for select patient groups.

- Components of ESTEP

- **Transplant physicians**: Physicians provide medical information, evaluate clinical status, evaluate and rate medical compliance / knowledge (Lung Transplant Adherence Record (LTAR)). Physicians will contact referring physicians to gain greater insight into the patient compliance and ability to cope with illness.
- **Financial coordinators**: Financial coordinators (in conjunction with social workers) will evaluate at-risk patient's fiscal "fitness" for transplant. This will include not only close scrutiny of insurance benefits, but also a detailed analysis of anticipated pharmacy, housing, rehabilitation, transportation and other costs. Critically, more frequent visits with financial coordinators will now be scheduled for at-risk individuals.
- **Social workers**: Our transplant social workers will meet with at-risk ESTEP patients earlier and more frequently. Follow-up will allow them to monitor / and assist with fund-raising activities. We have developed a package with more detailed information for patients with respect to fundraising, which can be reviewed at each encounter. Where deficiencies in the patient's care plans and social situation are identified, more frequent observation will facilitate tracking of improvement (or lack thereof). At risk patients can also interact with our social workers on a bi-monthly basis in our transplant support group. In addition, UNC has established an "in-house" transplant patient assistance fund.
- **Psychologists**: As part of our root cause analysis, and based on our suspicion that psychosocial challenges were affecting our outcomes, the team transplant psychologist, Eileen Burker PhD, has analyzed psychological factors that may predict success and failure after transplant. Patients completed the Multi-dimensional Health Locus of Control Scale (MHLCS) before and after transplant. After adjusting for age and medical diagnosis, participants with medium and high levels of internal health locus of control (IHLC) were shown to have lower hazard ratios than those with low IHLC. In essence, patients who feel empowered to control their own health have better outcomes, while those who feel that their health is externally controlled and feel "helpless" to affect it, have less satisfactory results. This is critical information. This scale will now be used routinely as part of the initial and follow-up evaluation process in at risk patients. It will influence listing decisions and guide counseling activities. More frequent follow up will facilitate tracking of issues of psychological concern (such as anxiety, depression).
- **Physical therapists**: Physical therapists (PT) will evaluate participation and performance in pulmonary rehabilitation and personally interact with PT staff from external rehabilitation programs. Participation in pulmonary rehabilitation is not only an important factor in optimizing patients' fitness for surgery, but also an important surrogate measure of compliance.
- **Nutritionist**: Weight loss / gain / maintenance as well as blood glucose control
- **Pharmacists**: Clinical transplant pharmacists will evaluate compliance with pretreatment medications (where necessary contacting pharmacies and insurers to confirm that prescriptions are being appropriately filled). They will also evaluate patients' understanding of their pre-transplant medicines, and educate patients about agents used after transplant.
- **Nurse Coordinators**: Coordinators will provide general education about transplant and coordinate the process.

- Patients enrolled in the ESTEP program will be discussed in the weekly multidisciplinary meeting. Often, a series of return visits will be necessary. Patients will also be offered the UNCH (NCMH) ALO Mitigating Factors Application 07/06/12 34 opportunity to attend our transplant support group. The intent was to provide early education for medically at-risk patients and give them an opportunity to react pro-actively, but also to increase the team's insight into their capability to cope after surgery.

The Full Evaluation Process:

- Takes place over 2 weeks in Chapel Hill, generally as an outpatient.

Pulmonary: PFTs, CXR, chest CT if not done previously, perfusion lung scan (helps plan recipient lung removal sequence – right versus left), sputum microbiology, sensitivity/synergy studies if pan-resistant organisms. If any issue with pneumothorax, old chest trauma, prior chest surgery, volume reduction Thoracic Surgery to review.

Diaphragm: review fluoroscopy with radiology and if indeterminate, we will request EMG of the diaphragm

Brachial Plexus Assessment: clinical maneuvers that can elicit signs/symptoms of thoracic outlet syndrome or other pathology with the brachial plexus as it exits the chest
- Elevated arm stress test (EAST) - arms are elevated with repetitive opening and closing of fists
- Brachial plexus tension test of Elvey - arms out, wrists dorsiflexed, tilting of the head produces symptoms on contralateral side
- Costoclavicular maneuver - shoulders drawn downward and backward- changes in radial pulse with production of symptoms
- Hyperabduction maneuver - arms hyperabducted to 180 degrees; if radial pulse decreased compression should be suspected

Cardiac: Echocardiogram, Holter/MRI (for sarcoid), right heart catheterization is mandatory for measurement of right heart and pulmonary pressures to calculate lung allocation score. (Left heart catheterization /coronary angiogram if age > 50 years old or CAD suspected).

Bone density /nutrition: Bone densitometry, and review of medications /strategies to address bone loss. Nutrition is also addressed in order to optimize BMI and other facets of nutrition, especially in the CF patients. Patients must get their BMI greater than 16 (ideally greater than 18) or less than 32 (ideally 30). They will be seen by nutrition who will guide diet and need for feeding tube placement. Bowel habits, digestive enzyme, and vitamin regimen should be reviewed.

Other Tests/Labs: HLA (repeat every 3 months on wait listed patients), Blood group x 2 (see specific regulations regarding blood group), creatinine clearance measurement (CrCl < 50 ml/min is a contraindication for lung transplant), six minute walk test, viral serologies and viral studies etc. Consider Barium swallow, upper GI endoscopy, and pH probe / manometry if clinically indicated for reflux/swallowing disorders.

Psychology: Transplant psychologist and team review the patient and family and send a full written report to the team leaders (including an assessment of the patients' capability to comply with the post-transplant complex medical regimen, and overall suitability for lung transplantation).

Social Work: Transplant social work reviews the patient social supports and other issues. At a later date the "contract" for lung transplant is reviewed and signed by specific team members.

Insurance: The financial coordinator reviews medical and prescription insurance and other financial issues

Infectious Diseases: A complete listing of all previous microbiologic data is obtained by the lung transplant coordinator. ID attending evaluates the patient prior to transplant for the following:
-assessment of risk of post-transplant infectious complications
-lifestyle counseling
-diagnosis and treatment of any active or latent infections
-vaccination review and update

Vaccine	Timing	Dose
Pneumococcal (23)	Within 5yrs of tx, repeat every 5 yrs	0.5mg IM X1
Prevnar (13)	Within 5yrs of tx, repeat every 5yrs	0.5ml IM X1
Varicella	Not given if within 3mo of tx	0.5ml subQ
Td/Tdap	Within 10yrs of Tx and repeat every 10yrs post transplant	0.5ml IM X1
Heb B	Rapid (within 4 weeks of tx)	Day 1: 40mcg IM Day 7: 40mcg IM Day 21: 40mcg IM Day 50: Check HBV sAb, if not detectable, do standard procedure X1
	Standard or if tx >6mos away	Day 1: 40mcg IM Month 1: 40mcg IM Month 2: 40mcg IM Month 6: Check HBV sAb, if not detectable, do standard procedure X1
Hep A, inactivated	Within lifetime	Day 1: 720units IM Month 6: 720units IM Month 7: Check Hep A Ab, if not detectable, repeat series
Influenza	Annually	0.5ml IM

Lung Allocation Score (LAS): The LAS can be calculated using a spreadsheet and entering the parameters: Diagnosis (etiology of lung disease e.g. CF, IPF etc.), pulmonary artery pressure (PAP), PCWP, FVC, presence of diabetes, venous PCO2, six minute walk distance, use of oxygen, use of assisted ventilation/ NIV, age, serum creatinine, NYHA functional class, and BMI. The LAS has to be updated every six months (unless the patient gets transplanted) although updated PAP and PCWP data is not absolutely required (echo estimated of changes in the data will be accepted). If no data is entered in a particular box, the lowest data point possible is entered for that patient, so it is in the patient's interest to obtain the data for the "best" (highest) possible overall LAS. Generally, 6MWT and PFTs are easiest to update.

Transplant meeting/decision to list/listing actions: Patient and data are presented (see exact presentation format in the meeting agenda and minutes) at the weekly meeting; When all members of the team are in agreement that there is no contraindication, including a careful review of the psychosocial situation (see checklist), the patient is listed and the LAS is simultaneously calculated, which dictates the patient's place on the waiting list for lung transplant. The transplant office fills out a candidate registration form for UNOS and the patient gets a listing letter from UNC (*and the referring physician receives a phone call from the coordinator*).

"Transplant Contract" is signed at this time. This document is intended to facilitate the patients and families understanding on what they are agreeing to in terms of their commitment to their own health and the health of their lung grafts. It includes, among other things, a commitment to undertake consistent exercise / rehabilitation, and participation at the Lung support group.

Miscellaneous Logistics: Depending on the patients physical location of his/her home base, the patient will either relocate to Chapel Hill, or if within three hour drive of Chapel Hill, will waits at home for a call when donor organs become available ("Angel" flights in special circumstances can be organized). The patient is required to attend/phone in to support group in Chapel Hill and enroll in a rehabilitation program. In some cases, UNC PT Department will engage in special programs of rehab for pre-transplant patients (see "contract" between listed patients and UNC Team).

Lung Transplant Pre-Transplant Check List

Item	Checked Date	Checked By	Comments
Referral Information Received (Coord/TPA)			
Referral Entered (TPA)			
Referral Information Screened by Attend/Coord			
To TFC for Benefits Verification			
1st Selection Conference			
Letter to RMD re: eval decision (Coord/TPA)			
Benefits Verified (TFC)			
1st Clinic Appointments Scheduled			
Clinic Appointment letter/Packet sent (TPA)			
Psychology/Psychiatry			
REALM-R			
SIPAT			
STSW Risk Score			
Social Work			
Support Group Attendance			
Pharmacy Consult			
Nutrition Consult			
Infectious Disease Consult			
Creatinine Clearance			
ABO Verified x2			
HLA Results (repeat Q3mo when listed)			
ABG			
Serology (EBV, CMV, HSV, HIV, Hep A, B, C)			
Serology (Toxo, Varicella, RPR)			
Vitamin ADEK			
Pre TX Surgeon and Brachial Plexus Eval			
Physical Therapy Evaluation			
6 minute walk			
Pulmonary Function Tests			
Chest X-Ray			
Chest CT			
RUQ Ultrasound			
QDR			
Echo			
VQ perfusion scan			
Diaphragm Fluoroscopy(Prior to CT) Doc. MD Review			
Bilateral. EMG(If indeterminate. Fluro.) Sch. Tu,Wed,Th			
Cardiac Cath(R or R/L if older than 50yo)			
Immunizations(Pneumonia,Influenza,HepA,B,TDAP)			
PPD or Interferon Gold			
Colonoscopy (if older than 50yo)			
Mammography			
PSA Screen			
Pelvic w/ Pap Smear			
Dental Evaluation			
Urine Tox			
Barium Swallow			
PH Probe			
Modified Barium Swallow Study/Speech			
Consent/Pt. Ed. Checklist			
Insurance info sent to insurance co. (TPA)			
Insurance auth received for listing (TPA)			
Activation/Decision Letter sent to patient (TPA)			
Letter to RMD re: listing decision (Coord/TPA)			

Allocation of Organs

Initial donor selection, role of Carolina Donor Services (CDS*)*: Once donor organs become available, LAS, blood group, donor size, CXR findings, blood gas data (on 100% FiO2), smoking history, and other clinical factors dictate events and the decision of the surgeon as to whether to accept or not (other clinical organ viability data). "Extended" criteria donors are those in whom the data fall outside the conventionally accepted range (e.g. smoking history, extended days on a ventilator, positive gram stain etc.). A recently approved UNC/Duke research program ("EVLP") offers opportunities to use previously unusable donor lungs (see NEJM April 2011, Toronto group report).

Organ evaluation*:* If the donor is at UNC, CDS will already have called the Pulmonary Transplant Team to perform a bronchoscopy to review the airways, and sample airway microbiology. CDS then collates these data with all other clinical data.

Donor Outside UNC: If the organs are provisionally accepted by the CT surgeon on-call, the Lung Transplant Coordinator on-call contacts the potential recipient and the Surgical Team sends a team member to review the organs first hand, which involves repeating the bronchoscopy, reviewing the chest radiograph, and most recent blood gas data (Pulmonary Physicians / Fellows may accompany the team member for accreditation and/or experience if so desired: request must be made to the surgeon on-call in advance). If still compatible with organ viability, the organs are removed, harvested, placed on ice ("hypothermic ischemic time"), and brought back to UNC ("cold ischemia time" is the time from cross clamping at the donor site, placement on ice, until thawing on the back table in the OR at UNC).

Organ Retrieval: The technical specifics of organ retrieval are beyond the scope of this document, the reader is referred to the surgical literature.

Donor Net Clinical Refusal Criteria

Basics
1. Donor Age > 75 years old
2. Donor distance >2000mi from Chapel Hill

Physical
1. Height of donor: >13 inches taller or 13 inches shorter

Recent / History
1. History of cancer or malignancy in the last 5 years excluding non-melanoma skin cancers
2. History of a CABG if we need both lungs

General Communication flow for lung donor offers at UNC
1. If screening criteria not met, offer is declined per UNOS donor net protocol
2. If Donor offer is acceptable the donor net coordinator on call will provisionally accept the organ offer in Donor Net
3. If the potential recipient is subsequently matched with the donor then the Donor Net Coordinator on Call will contact the UNC transplant surgeon
4. If the transplant surgeon agrees to proceed with the transplant, the surgeon will discuss with the UNC lung transplant coordinator on call who will contact CDS to notify and arrange for transport as well as call in potential recipient as well as activate the UNC transplant team per established guidelines.

Recipient Pre- and Peri- operative Protocol

Role of the UNC Lung Transplant Coordinators: The Coordinator on-call is responsible for the logistic organization of the recipient admission (in conjunction with the thoracic surgery intern and Pulmonary Fellow on-call). The Coordinator communicates with the recipient, the thoracic surgery intern, the ER, Admitting for a bed (on 4 Anderson, 6BT / MICU if the patient is an inpatient), the ICU supervisor, the Charge Nurse in the CT-ICU, Blood Bank, (the surgeon posts the case in the OR), pharmacy for issuing the pre-transplant orders for special medications (e.g. specific induction agent – see appendix) to ensure smooth passage of the patient through the admission and pre-op process. EPIC is under constant development – the Thoracic surgery intern enters the orders. A "Pathway" is now available to all team personnel.
As of 2014, the Tx physician and surgeon on call discuss the proposed transplant (donor / recipient issues) in all cases.

Admission to UNC: Recipient called in by the coordinator and is admitted via the ER at UNC, or sometimes directly to a bed on 4 Anderson (depending on the timing).

Peri-Operative Plan: The perioperative plan including appropriate antimicrobials and induction will be determined at time of listing and will be recorded in EPIC on their face sheet and documented in a Note

Pre-operative orders: Immediate Pre-op and Immediate Post-op orders in EPIC in order sets. The testing is:

__ Chem 14: Na, K, Cl, CO2, BUN, Cr, Glu, Ca, Mag, Phos, Tprotein, Alb, Uric Acid, LD
__ LFTs: AST, ALT, GGT, Alk phos, D Bili, T Bili, amylase, Lipase
__ Hgb A1c
__ CBC W/Diff
__ Coags: PT, PTT, INR
__ VBG
__ Type and Screen
__ HLA Recipient Work Up
__ HLA Antibody Screen
__ Quantitate IgG
__ CMV Antibody titers, IgG and IgM
__ EBV Serologies Antibodies
__ Toxoplasma antibodies, IgG and IgM
__ Parvovirus antibodies, IgG and IgM
__ Hepatitis A serologies (Total IgG and Viral antibody IgM)
__ Hepatitis B serologies (Core antibody IgM, Surface antigen and Surface antibody)
__ Hepatitis C Antibody
__ Rubella Serology
__ Varicella Serology
__ RPR
__ HIV AB/Ag Combo
__ HSV I & II Antibodies
__ Urinalysis and Culture
__ CF sputum culture and sensitivities (only if CF or PCD)
__ Lower Respiratory Culture
__ Respiratory Virus PCR (nasal swab)
__ Chest X-Ray
__ EKG 12 lead
__ Antibiotics per the predetermined Peri-Operative Plan

Immediate Post-op (hospitalized) Period

Cardiothoracic intensive care unit:
- Patient is under the direct care of the cardiothoracic surgeon
- Pulmonary supervises the immunosuppression regimen for all patients.

"Joint" care between surgical and medical transplant teams:
- The Pulmonary Medicine Transplant team consults daily on the patient in the CT ICU, communicates with the nurses, pharmacist, physical therapist, and makes recommendations which are then communicated directly to the surgical team.

Orders/communications:
- Pulmonary medicine may write direct orders while the patient is in the CT ICU or on 4 Anderson for medical management (ie antibiotics, immunosuppressives etc,) with communication to the surgery team

Ventilator management / Analgesics / Anxiolytics:
- The thoracic surgeons with the critical care team typically manage the ventilator settings; pulmonary may advise

Diaphragm Assessment:
- If patient is not extubatable within 3 days of transplant without an acceptable etiology, diaphragm EMG obtained
- fluoroscopy of the diaphragms will be obtained within 1 week of transplant

Hypertension:
- Common complication post transplantation, often related to use of tacrolimus.
- Calcium channel blockers (ie. amlodipine 5-10 mg po daily) and/or beta blockers (ie. metoprolol 100 to 400mg po daily in divided doses) are recommended. Monitor for edema and increasing CNI drug levels if diltiazem is used due to drug interaction. ACE-Inhibitors/ARBs are generally avoided in the immediate post-transplant period

Constipation/Bezoars:
- Common particularly in in CF patients, manifested as slow recovery of GI function post op, epigastric fullness, burping, erratic CNI levels, abdominal discomfort, and radiographic / endoscopic evidence of bezoar (may require endoscopic removal but then watch for aspiration into lung/ lung injury). Miralax, lactulose, GoLytely

Obliterative Bronchiolitis/Bronchiolitis Obliterans Syndrome (OB/BOS) Prophylaxis:
- Azithromycin 250 mg po daily as soon as patient tolerates PO
- Omeprazole 40 mg po daily to BID as soon as patient tolerates PO

Family communication:
- The medical team participates in all communications with the family members post-transplant. It is critical that the family understand the various roles of the team members, and specifically who is managing what (e.g. chest tubes, analgesia).

Discharge /Medication Education:
- Pulmonary Medicine Transplant Team is responsible for ordering all outpatient medications and assisting the coordinators with the prior authorizations.
- The Coordinator teaches about safe self-management of their post op recovery phase. This involves charts of the patient's medications, education about doses, side effects, and instructions on how to respond to phone calls to adjust at short notice.
- Transplant pharmacy is to aid coordinators in medication teaching to patient & their caregiver(s). Pharmacist may also aid coordinator in making or updating discharge medication regimen. Dietary / activities post discharge are also addressed, with follow up clinic / rehab / bronchoscopy schedule.

Post-transplant diet / Food Safety:
- Transplant dietitian will meet regularly with patient and caregivers to address nutrition concerns related to healing, blood glucose levels and dietary changes needed after discharge due to immune suppression

Post-op (after discharge) Period

Patient Location:
- Patients should stay locally for a minimum of at least three months post operatively or longer if not rehabbing well

Lung Transplant Coordinators:
- Education on the do's and dont's of post-transplant care for patients and family members. Specific education is given to all patients on physical activity post op, driving policies, sexual activity, dietary restrictions etc.

Outpatient Transplant Pharmacist:
- The outpatient transplant pharmacist (Pager 216-2729) will be informed of newly transplanted patients for medication management follow-up in the outpatient clinic. The outpatient pharmacist will aid in adjusting immunosuppression, monitor protocol adherence, assist in infectious disease treatment and prophylaxis, educate patients to reinforce medication regimen adherence, and assist in medication management and optimization of comorbid disease states.

pH probes and Manometry:
- Done within 8 weeks of transplant
- Organized through UNC GI lab. If pH probe "positive" (>3% time, pH recorded < 4 in distal esophagus with symptoms or > 6% of time without symptoms) refer for evaluation for Nissen Fundoplication.

Fundoplication:
- Based on the need for symptom control / pH & mano data / risk of GERD and OB. Fundoplication should be performed within three months of transplant to minimize problems with subsequent BOS.

Bronchoscopy schedule:
- Airway Clearance and airway inspection: immediately at time of operation (airway anastomosis inspection) and as needed for airway clearance
- Biopsy and BAL Surveillance:
    - Month 1, 3, 6, and 12. Other bronchoscopies are performed as needed or as emergency basis based on symptoms or prior rejection
    - 5-6 specimens should be obtained if possible under fluoroscopy to ensure good sampling. Try to get feedback, or personally review with pathology to confirm quality of specimens.
    - Specimens should always be placed on "rush" order. If placed before 12PM, results should be available that evening or the following morning. Histology reads are not possible on Saturdays /Sundays, so timing is critical for Friday bronchoscopy.
    - For high risk patients, high risk labs (HIV, Heb B, Hep C and vitamin levels) will be checked with each surveillance bronhcoscopy

Post Transplant Clinic Schedule and Clinical Considerations:

- Week 1, 2, 3, 4
- Week 6, 8, 10, 12
- Month 3, 4, 5, 6, 8, 10, 12
- Every 3 months
- In cases of > 5 year survivors, patients living in other states, annual visits are the minimum to keep prescriptions up to date. Emergency prescriptions will be issued for a maximum of one month, per good clinical practice.

- Transplant clinics are on Wednesday and Friday morning (Wednesday for new patients, follow up of pre-listed patients, and any emergencies; Fridays for all other appointment types). Patients can be seen any day of the week if needed for acute issues

Lab Schedule:
- Follow Lung Transplant Post-Op Clinic Worksheet, however, schedule may be tailored to clinical situation.
- Minimum labs ordered include CBC with differential (pancytopenia especially after induction therapy, consider GCSF if ANC < 500, , chem 14 (SCr and electrolyte disturbances with drug therapy), HLA, CMV PCR, EBV PCR, tacrolimus and cyclosporine troughs should be 12-hours from the previous dose. Sirolimus troughs should be 24 hours from the previous dose.
- regular checks of immunogluobiulin levels as well as DSA panels.

Fever:
- Always significant in this population. Differential diagnosis in immediate post-operative phase includes acute rejection, infection, intra-thoracic collections early post op, cholecystitis and bowel perforations.

Worsening PFTs:
- If immediately post-op or within first few years post-transplant, acute rejection and infection are likely. If worsening occurs later in course, chronic rejection (BOS) is more likely but acute reversible causes should be ruled out.

Elevated WBC :
- Possibly medication induced (steroids), rule out acute rejection and infection.

Reduced WBC:
- Possibly medication induced (alemtuzumab, MMF, valganciclovir, or mixture of immunsuppressives and other medications). If WBC < 2.0 or ANC < 500 consider G-CSF. Do not hold MMF for long periods of time unless absolutely necessary.

Elevated LFTs:
- Common to have mild elevations in LFTs in CF, typically cholestatic presentation. Consider medications (ie voriconazole or other azole anti-fungal) for possible adverse effect. Rule out CMV or other causes for acute elevation. Abdominal ultrasound is the best initial test, consider GI / biliary problems.

In F.O.C.U.S. – Increased Frequency of Observation in Clinic, with Up-Graded Supervision

- Based on a case-by-case evaluation, the team surmised that it was not always possible to predict which lower SES individuals would (or would not) thrive after transplant. However, in the early post-operative period we were able to identify a cohort of individuals whose ability to comprehend and comply with a complex regimen of care was lacking. For this reason, the team established an intensive intervention program, designed to improve outcomes in these patients, and piloted it in select individuals. This has evolved into The "Increased Frequency of Observation in Clinic, with Up-graded Supervision (or "In.F.O.C.U.S") program, which involves a multidisciplinary team seeing "at-risk" patients weekly or bi-monthly for prolonged periods (beyond 18 months in a fraction of cases). This allowed the team to intervene and correct deficiencies in patient compliance / comprehension.

- Specific measures include:
  - Intensive pharmacy intervention: A transplant pharmacist will perform pill box checking, pill box filling, as well as intensive medication education with patients and caregivers on each visit. Where necessary, they will contact pharmacies and insurers to confirm that prescriptions are being appropriately filled.
  - Follow up phone interactions will be used to ensure that health behaviors in the home environment are optimal.
  - Frequent evaluation and more precise management of chronic complex medical problems (e.g renal failure, volume status, drug intolerance / side-effects, diastolic or systolic left heart failure etc).
  - Educational sessions with transplant coordinators.
  - Frequent follow up with social work specialists.
  - Frequent follow up with psychologists.
  - Frequent follow up with financial counselors: UNCH (NCMH) ALO Mitigating Factors Application 07/06/12 35
  - In-house (vs local) involvement of other specialist consultants.
  - More intensive follow-up with physical therapy: to ensure that rehabilitation goals are being met (if patients are not in our in-house program).
  - Adherence: We will continue to rate adherence to medical interventions and document this in the Lung Transplant Adherence Record (LTAR) (Appendix V). This will be evaluated in a multidisciplinary format and used to guide future interventions. For some piloted individuals, we have continued this approach well beyond a year. Based on this experience, we are confident that this intervention has reversed outcomes which otherwise would have been negative. Specifically, we have identified a cohort of patients transplanted in the last 18 months whose survival would have been in doubt during the first year without this degree of intense intervention. The recent appointment of a nurse practitioner for the Lung Transplant program will greatly aid this program (see below – team structure and description).

Induction Protocol if Moving Forward with Transplant

A. Post-op Day 0 (intra-operatively):

- Methylprednisone
  - 250mg IV with each lung implant (reperfusion of allograft)

- Basiliximab (simulect) 20mg IV, given prior to first implant
  - Premedication: Methylprednisolone 125mg IV PB (with first dose), diphenhydramine 25mg IV, acetaminophen oral liquid 650mg.
    - Administer all pre-medications 30-60minutes before the dose

B. Post-Op Day 4:

- Basiliximab (simulect) 20mg IV
  - Premedication: Administer scheduled methylprednisone (use steroid dose per protocol below as pre-medication), diphenhydramine 25mg IV, acetaminophen oral liquid 650mg.

Post-Transplant Immunosuppression

A. Mycophenolate mofetil (Cellcept):

- 1000mg IV Q12 hours until able to tolerate enteral medication, then 1000mg PO/NG Q12 hours
- If patient >65yo, dose reduction to 750mg Q12 hours
- Azathioprine can be used if Mycophenolate mofetil intolerance (GI toxicity, leukopenia)
  - Initial dose id 1-2mg/kg PO daily
  - TMPT level should be checked

B. Tacrolimus (Prograf):

- Initial dose: 0.5mg Sublingual Q12hours on POD 1 (sublingual is 2X more potent than oral)
- Generally takes 3-5 doses to equilibrate after last dose change so frequent dose changes should be avoided
- Target Trough Goal

Time post-transplant	Goal
0-12 months	8-12 ng/ml – if >65yo of if elevation in Cr, will aim for 8-10 mg/ml
12-18 months	8-10 ng/ml
18-24 months	6-8 ng/ml
>24 months	5-7 ng/ml

- Cyclosporine can be used if Prograf intolerance
  - Initial dose of 2mg/kg/day divided every 12 hours
  - Target Trough Goal

Time post-transplant	Goal
0-6 months	250-300 ng/ml
6-12 months	200-250 ng/ml
12-24 months	150-200 ng/ml
>24 months	100-150 ng/ml

C. Corticosteroids

- Methylprednisolone (IV)/Prednisone (PO) Taper:
  - POD #1: Methylprednisolone 125mg IV q12hr x 2 doses
  - POD #2: Methylprednisolone 80mg IV q12hr x 2 doses
  - POD #3: Prednisone 40mg PO q12hr x 2 doses
  - POD #4: Prednisone 20mg PO q12hr x 2 doses
  - POD #5: Prednisone 20mg PO daily until 3 month bronch (No rejection/DSA, continue taper)
  - POD #90: Prednisone 15mg PO daily until 6 month bronch (No rejection/DSA, continue taper)
  - POD #180: Prednisone 10mg PO daily until 9 month bronch (No rejection/DSA, continue taper)
  - POD #270: Prednisone 7.5mg PO daily indefinitely

Peri-Transplant Antibiotics

A. Each patient will have an individualized peri-transplant antibiotic regimen based on pre-transplant microbiology. Infectious Diseases in conjunction with the pulmonary transplant service will determine this regimen at the time of listing, and update as needed if new microbiology results become available.

B. The antimicrobial plan will be listed in EPIC under snap shot and will be in a transplant note

C. If no prior microbiology is available, standard anti-bacterial therapy includes cefepime and linezolid. If concern for aspiration in the donor, meropenem and linezolid will be used. If recipient has issues with leukopenia / thrombocytopenia, meropenem and cefteroline will be used.

Post-Transplant Infectious Disease Prophylaxis

A. CMV

- High Risk (CMV D+/R-) and Moderate Risk (CMV D+/R+ or D-/R+): Ganciclovir 5mg/kg IV Q24H until able to tolerate enteral medication, then valganciclovir 900mg PO daily for at least 12 months
  - Dose adjust valganciclovir based on renal function
  - Monitor with CMV PCR Q2 weeks for 3 months than monthly

- Low risk (CMV D-/R-): Acyclovir 400mg PO BID for 1 month

- Renal Dosing for valganciclovir:

CrCl (ml/min)	Dose (mg)	Interval
≥60	900	Daily
40-59	450	Daily
25-39	450	Every other day
10-24	450	Twice weekly

- Comments:
  - No CMV monitoring is needed for asymptomatic patients while on prophylactic therapy after the above specified time frame
  - CMV monitoring is appropriate for patients on prophylactic therapy if there is concern for sub-therapeutic valganciclovir

B. EBV monitoring

- EBV D+/R- : Obtain EBV PCR every other week for 3 months, then monthly for the next 9 months
- EBV D+/R+, D-/R+, D-/R- : No monitoring needed for asymptomatic patients

C. PJP

- First line: TMB/SMX 1 SS (400/80) daily life long starting on POD 7
  - Use alternative agents if hyperkalemia and if sulfa allergic
  - If stopped for hyperkalemia, a re-challenge should be attempted once the adverse effect is resolved

- Alternatives:
  - Dapsone 100mg daily for 12 months
    - Check G6PD prior to starting
    - Use alternative agent if G6PD deficient or develops hemolysis
  - Inhaled pentamidine 300mg once monthly for 12 months
    - Outpatient pentamidine is administered in the ID clinic
  - Atovaquone 1500mg daily for 12 months

D. Fungal

- All patients will receive Inhaled liposomal amphotericin B 25mg Monday/Wednesday/Friday while hospitalized.
- Systemic fungal prophylaxis will be used for lung diseases associated with chronic infections (ie Cystic fibrosis, bronchiectasis) or for patient with known history of fungal disease.
    - In patients not receiving systemic fungal prophylaxis, they will receive a HRCT scan at 2 months post transplant to see if they have any signs of fungal disease between their bronchoscopies done at 1 and 3 months post transplant. If HRCT scan is worrisome, a bronchoscopy with BAL and washes will be done to evaluate for fungal infection. Treatment will start if positive culture or galactomannan.
- First Line: Inhaled liposomal amphotericin B 25mg Monday/Wednesday/Friday + Itraconazole 300mg PO BID x 6 doses (loading dose), then Itraconazole 200mg PO BID until level is therapeutic
    - First trough level should be drawn within 5-7 days of initiation to achieve a prophylaxis goal trough of 0.5-1.0 mcg/ml
    - The active metabolite, hydroxyl-itraconazole level should not be used to drive dose adjustments
    - Subsequent trough levels should be checked within 5-7 days of dose change or as clinically indicated
    - Itraconazole should be administered with an acidic beverage such as cola, to increase absorption
    - Duration: Discontinued inhaled amphotericin once Itraconazole is therapeutic. Discontinue Itraconazole monotherapy at 3 months if no mold or fungus is found on the screening bronchoscopies
- Second Line: Try different azoles such as Voriconazole or Posaconazole
- Third Line: If unable to tolerate azoles, continue Inhaled liposomal amphotericin B 25mg Monday/Wednesday/Friday for 6 days, then once weekly for days 60-180, then Q2 weeks for the completion of 360 days
- If known pre-transplant Mold/Fungus: A targeted antifungal will be chosen such as Posaconazole (goal trough 750-1500) or voriconazole (goal trought 0.5-1.5) to optimize coverage and minimize recurrence post transplant and tissue invasive disease.
- Comments:
    - Prophylactic inhaled liposomal amphotericin B may be continued longer than the time needed to reach therapeutic azole levels if clinically indicated (eg. Slow anastomotic healing, recurrent fungal airway infection)
    - Patients colonized/infected with fungus pre-transplant should have individualized post-transplant fungal prophylactic regimens

Infectious disease prophylaxis during treatment of rejection (after the first year post transplant)

- CMV
    - If treated with steroids or B-cell agent (IVIG or Rituximab), no additional prophylaxis is recommended
    - If treated with T-cell depleting agent (thymoglobulin or alemtuzumab) or AMR protocol:
        - High Risk or Moderate risk (prior CMV viremia, D+/R-, D+/R+, D-/R+): valganciclovir 900mg PO daily for 3 months
        - Low Risk (no CMV viremia and D-/R-): acyclovir 400mg PO Daily for 3 months
- PJP (if not currently on PJP prophylaxis)
    - If treated with steroids or B-cell agent (IgG or Rituximab): Restart prophylaxis x 1 month
    - If treated with thymoglobulin: Restart prophylaxis for 3 month
    - If treated with alemtuzumab or AMR: restart prophylaxis for 12 months
- Fungal
    - If treated with steroids or B-cell agent (IgG or Rituximab): No prophylaxis is needed
    - If treated with thymoglobulin: Restart prophylaxis for 3 months
    - If treated with alemtuzumab or AMR protocol: Restart prophylaxis for 12 month

Rejection Diagnosis and Management

- Acute cellular rejection (ACR) – diagnosed with biopsy
  - Consider etiology for rejection
    - Optimized CNI drug levels and anti-proliferative agent dose, w/u GERD, evaluate for DSAs
  - Minimal or mild rejection (A1-A3):
    - Methylprednisone 10mg/kg IV infused over 30 minutes daily for 3 days
    - Prednisone tapper starting at 60mg PO and decreasing by 5mg daily until back to baseline
  - Moderate, severe or steroids resistant rejection: Thymoglobulin Protocol
  - Refractory rejection: Alemtuzumab

- Chronic Allograft Rejection (Bronchiolitis obliterans syndrome or Restrictive allograft dysfunction)
  - Consider etiology for rejection
    - Optimized CNI drug levels and anti-proliferative agent dose, w/u GERD, evaluate for DSAs
  - Consider thymoglobulin protocol
  - Consider Alemtuzumab protocol
  - Consider Photopheresis
  - Consider re-transplant

- Thymoglobulin Protocol
  - rATG 1.5mg/kg daily (rounded to the nearest 25mg) for a total of 6-7.5mg/kg
    - specify whether central or peripheral access
    - Pre-medicate with methylprednisolone 125mg IV, acetaminophen 650mg PO and diphenhydramine 50mg IV
    - Infectious prophylaxis as per the ID section
    - Consider decreasing the antiproliferative agent dose by 50% for 3 week
    - Hold Parameters for hematologic toxicity (should be assessed daily)

WBC	Platelets	rATG Dose
> 3000	> 75,000	100% (2 mg/kg¥)
2000 – 3000	50,000 – 75,000	Consider reduction by 50%
< 2000	< 50,000	HOLD rATG x 24 hours

  - For ATGAM, dose is 15mg/kg daily (rounded to nearest 250mg) for a total of 75-100mg/kg

- Alemtuzumab Protocol
  - Absolute contraindications: patients with active malignancy, history of malignancy (excluding skin cancer), active infection and non-adherence to prescribed medical therapies
  - 30mg IV once
    - Through a peripheral IV
    - Pre-medicate with methylprednisolone 125mg IV, acetaminophen 650mg PO and diphenhydramine 50mg IV
    - Infectious prophylaxis as per the ID section
    - Consider decreasing the antiproliferative agent dose by 50%

- IVIG Protocol
  - For Hypogammaglobulinemia (IgG <400 or <500 with active infection)
    - 0.5gm/Kg IV, can repeat every 4 weeks pending levels

  - For Antibody Mediated Rejection, please refer to the AMR protocol

- Donor Specific Antibody (DSA) and Antibody Mediated Rejection (AMR) Protocol

  - If new DSA and <u>No evidence of graft dysfunction</u>:
    - DSA MFI < 5000
      - Optimize immunosuppression
        - Tacrolimus trough 10-15
        - Cellcept 1000mg- 1500 mg BID
        - Prednisone 10-20mg/day
      - IVIG 0.5gm/kg Qmonth for 3months and then every 3 months until gone
      - Recheck DSA panel prior to each dose of IVIG

    - DSA MFI >5000
      - Optimize immunosuppression
        - Tacrolimus trough 10-15
        - Cellcept 1000mg- 1500 mg BID
        - Prednisone 10-20mg/day
      - IVIG 2gm/kg divided in one or two (weekly) doses.
        - Patients with CrCl <40ml/min get 2gm/kg divided in 4 weekly doses
      - Recheck DSA 3 weeks post last IVIG dose IVIG
      - If MFI >5000, continue IVIG 0.5gm/kg Qmonth for 3months and then every 3 months until gone. Recheck DSA panel prior to each dose of IVIG
      - Strongly consider Rituximab for 4 weekly doses

  - If new DSA and <u>evidence of graft dysfunction</u>:
    - Optimize immunosuppression
      - Tacrolimus trough 10-15
      - Cellcept 1000mg- 1500 mg BID
    - Methylprednisolone IV 500mg Daily for 3 days followed by Prednisone PO 60mg and tapper by 10mg daily until at 20mg QD and continue 20mg QD,
    - Plex on day 1, 4, 8, 11 followed by bortezomib & LD IVIG
    - Rituximab on day 1 after Plex and day 11
    - HD IVIG on day 11 then IVIG 500mg/kg weekly x 4 doses starting on day 20
    - Obtain DSA on day 60. If DSA > 5000 or if DSA > 1000 with persistent graft dysfunction continue IVIG 500mg/kg monthly x 3 month and re-evaluate

  - Med Doses
    - Rituximab 375 mg/m2
    - Bortezomib = 1.3 mg/m2
    - IVIG = Flebogamma or Gamunex 10% (Low dose[LD] = 100mg/kg) (High dose [HD] = 1500mg/kg)

Miscellaneous other medical complications

CMVDisease/Viremia:

- Manifested as fatigue, fever, lung symptoms, CXR changes, or indeed asymptomatic but with PCR positivity.
- Detectable CMV PCR implies viremia.
    - Depending on clinical status and presence of symptoms, treatment should be initiated or repeat PCR should be ordered. Persistent positivity or rising PCR despite adequate treatment doses may mean viral resistance, warrants sending out resistance genotyping. CMV syndrome is defined by viremia plus positive symptoms (fever, diarrhea, vomiting) Organ Invasive CMV Disease occurs in the presence of biopsy proven CMV. Depending on the severity of disease and symptoms, IV therapy may be necessary
- Treatment
    - Ganciclovir if pneumonitis, enteritis, other end organ invovlvment or concerns about oral absorption
    - Valganciclovir
    - Alternative Therapy: Foscarnet or Cidofovir. These agents are severely nephrotoxic and require hydration prior to administration.
    - Monitor CMV PCR weekly. Treatment clearance is defined by two undetectable PCRs one week apart. Induction treatment duration should continue for 14-21 days (or when two undetectable PCRs are obtained), consolidation therapy may continue for typically 1-3 months thereafter, however, longer duration may be necessary.

Renal Function (CrCl, ml/min)	Ganciclovir Induction	Ganciclovir Maintenance
>70	5mg/kg Q12hrs	5mg/kg QD
50-69	2.5mg/kg Q12hrs	2.5mg/kg QD
25-49	2.5mg/kg QD	1.25mg/kg QD
10-24	1.25mg/kg QD	0.625mg/kg QD
Hemodialysis	1.25mg/kg 3x per week	0.625mg/kg 3x per week
Renal Function (CrCl, ml/min)	Valcyte Treatment	Valcyte Maintenance
>60	900mg BID	900mg QD
40-59	450mg BID	450mg QD
25-39	450mg QD	450mg QOD
10-24	450mg QOD	450mg 2x/week
Hemodialysis	450mg QOD	450mg 2x/week

Post-transplant lymphoproliferative disease (PTLD).

- Consider PTLD workup in accordance with rising EBV PCR.
- Treatment
    - Varies significantly according to the type of lymphoproliferative disease present

Nutrition:
- Optimal nutrition to allow maximal rehabilitation and recover is essential. Beware placement of G tubes if patient very ill, better to place before the patient gets to a very low functional and nutritional status. Usually post op the patients recover weight and nutritional status quickly. Jodi Mettel, the CF nutritionist, sees all CF patient pre and post-transplant.

Diabetes:
- 5-15% of CF patients develop CF-related DM. The median age at diagnosis is 20 years. 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. Goal HbA1c < 7%, monitored every monthly through Month 3, then quarterly until target HbA1c is reached. DM patients should undergo yearly dilated eye examinations, foot examinations and have their blood pressure, lipids, and renal function monitored.

Bone Health:
- 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%). Recommendations include treatment starting immediately after transplantation with re-evaluation in one year. QDR ordered annually. Calcium and Vitamin D replacement should be resumed or initiated immediately post-transplant. Consider oral or IV bisphosphonate therapy. Encourage weight bearing exercise.

Hyperlipidemia:
- A common problem post-transplantation and thought to be related to effects of CNI and prednisone. Fasting lipid panel will be measured every 3 months until target goal is met. 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. Medical therapy may involve a HMG-CoA reductase inhibitor or fenofibrate therapy. 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 daily is a reasonable starting dose.

Anemia*:*
- Common, and almost always multi-factorial, drug induced anemia is most common reason, particularly due to immunosuppression. Treat each as individual circumstance allows / demands.

Leukopenia:
- Common and almost multifactorial with multiple drug causes
- Check CMV, EBV and parvovirus
- Consider reducing the dose of the antiproliferative agent
- Consider reducing the dose or stopping the antiviral agent if safe to do so
- Consider changing the Bactrim to another agent

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. Dermatology appointment should be made annually and patient should utilize sunscreen with a minimum of SPF 30.

Lung Transplant Post-Transplant clinic worksheet

LUNG TRANSPLANT POST-OP CLINIC WORKSHEET

Name:	MRN:	DOB:	Phone:	Coord:
Transplant Date:	Bil/Single:	Referring MD:	CMV: D/R, /	EBV: R:
Med Intolerance:		Meds on Hold:		Target Tac or Cya Level:
IV Meds:	Bos: Y/ N Stage:		Pharmacy #:	Pharmacy Fax:
Bacteria:		Fungi:		Virus:

	W1	W2	W3	W4	W6	W8	W10	W12	M3	M4	M5	M6	M8	M9	M10	M12	M15	M18	M21	M24	M27	M30	M33	M36
Clinic Visit Date																								
LAB WORK																								
Labs																								
CMV																								
EBV																								
HGBA1C																								
INR																								
HLA																								
IGG Total																								
Lipid Profile																								
Annual PSA																								
PROCEDURES																								
Chest X-Ray																								
PFT's																								
Bronchoscopy																								
QDR																								
REVIEW & EDUCATION																								
Home BP Check																								
Home Spirometry																								
Med Check/Refill																								
Infection Control																								
Sup Gr/Pulm Reh																								
DIOS Education																								
Sexual Function																								
HEALTH MAINTENANCE																								
Pap Smear																								
Mammography																								
Dermatology																								
Colonoscopy																								
Dental Care																								
Dietician Consult																								
Psych Consult																								
VACCINES																								
Pneumoccocal																								
[illegible]																								
Hep A																								
Hep B Titers																								
Influenza																								

PEDIATRIC LUNG TRANSPLANT: REVISED REFERRAL AND MANAGEMENT PROTOCOLS

Pediatric lung transplant cases are defined by UNOS as < 18th birthday at time of transplant. This document outlines revised management of adolescent patients years old to take advantage of current program strengths, optimize outcomes and reflect changes in pediatric referral patterns.

UNC's lung transplant program accepts pediatric patients 12 years and older for evaluation and management using the adult program's protocols and treatment principles, but with a defined "Pediatric path" for younger patients. Cases younger than age 12 years (i.e., not subject to LAS) will be considered on a case by case basis, especially if there are mitigating circumstances preventing care at a higher-volume pediatric lung transplant center.

UNC cannot accept pediatric referrals with out of state Medicaid.

PRE-TRANSPLANT MANAGEMENT

Initial assessment. Referrals to UNC for lung transplant evaluation who are < 16 years old at initial referral will go to the pediatric attendings (Dr. Noah or Dr. Dellon) for initial assessment. Referrals age 16 yrs and older will usually go to the adult team for initial assessment; exceptions may be made in individual cases based on size or developmental factors.

Listing. Patients accepted for listing will be categorized at the time of listing as "Pediatric" or "Adult" path for purposes of post-transplant management, based on age, weight and developmental factors. Patients in Pediatric path will be evaluated by Pediatric subspecialists (e.g., ID, Psychology) rather than adult.

Transition. Actively listed Pediatric patients who reach their 16th birthday while awaiting transplant will usually be transitioned to the Adult path pre-transplant. Such transitions will include a clinic visit in which they meet their adult transplant physician. Care coordination will continue with the pediatric coordinator (Kelly Watson) for continuity.

Bridging to transplant using ambulatory vv-ECMO and/or trach and vent for listed patients who progress to respiratory failure, will be considered on an individual basis (see Appendix 3). For patients in Pediatric path who are under age 15, bridging will be done in PICU, but patients over 15 yr (and > 30 kg) will usually be bridged in TICU. In either case, CTS will place tracheostomy and cannulate for ECMO. For patients on Adult path, bridging strategies and location (PICU/MICU/TICU) will be discussed by the team on individual basis.

DONOR MANAGEMENT

Management/optimization of donor organs (pediatric and adult) will continue to be done by the adult Transplant Medicine attending on call (Dr. Coakley or Dr. Lobo), in collaboration with CTS, but input on specific pediatric issues affecting donor suitability can be provided by the Pediatric Transplant attending on call (Dr Noah or Dr Dellon).

MANAGEMENT IMMEDIATELY POST TRANSPLANT

1. "Pediatric path" (< 16 yr)

Pediatric patients < 15 years (any weight) of age at time of transplant will go to PICU post-operatively where they will be co-managed by CTS and PICU staff, with close consultation from Ped Pulm Transplant and additional support as needed from adult Transplant Medicine. [1]

Patients 15-16 yrs old (and > 30 kg) at time of transplant will go to TICU for immediate post transplant management by adult surgical and medical teams (consultation when needed from Ped Pulm Transplant), then transferred to PICU for ongoing management requiring more than floor level care.

In either case, transfer from PICU to 5CH/CICC (Peds Blue Team) for post-Txp discharge planning.

Communications: Transplant coordinators will meet with PICU nursing staff pre-op to go over order sets and care pathways. Coordinators have a role in organizing pre-op preparation of transplant recipients, but no longer play a central daily role in the transplant admission post-op, until discharge planning. Due to OR schedules, CT Surgery cannot usually round with the PICU team, and will often need to instead provide direct input to the overnight PICU call team during early morning hours. Daily communications from PICU team or CICC/Blue Team to Transplant team will route through the Ped Pulm Transplant attending (Dr. Noah or Dr. Dellon), who will arrange to round each day with the primary (PICU or Blue) care team.

Follow up in Lung Transplant Clinic (4th floor Main Hospital) and for post-transplant surveillance bronchoscopies with Dr. Noah or Dr. Dellon. Transplant coordinator will set up lab orders and other services needing to see pt (e.g., CTS, SW, Nutrition, Pharm)

2. "Adult path" (≥ 16 yr)

Pediatric patients ≥ 16 years old at time of transplant will go to TICU post op and be managed by the adult surgical and medical teams as per their existing protocols.

Follow up in Lung Transplant Clinic (4th floor Main Hospital) with Dr. Lobo or Dr. Coakley. Transplant coordinator will set up lab orders and other services needing to see pt (CTS, SW, Nutrition, Pharm)

[1] See Appendix 1 for care principles and Appendix 2 for medication dosing; overall pediatric care pathway including daily medications, labs and consults is available from the Lung Transplant Coordinators.

APPENDIX 1: IMMEDIATE POST-TRANSPLANT CARE PRINCIPLES:

Perioperative Mechanical Ventilation:

- Tidal volumes 10mL/kg based on donor weight
- Goal to extubate early (i.e. post-operative day #1)
- Avoid atelectasis (importance relates to theory of disruption of hypoxic vasoconstriction in transplanted lungs, should be temporary)
- For primary graft failure extra-corporeal life support would be utilized to support the patient until the graft recovers. In this case, CT surgery would perform cannulation.

Post-operative cardiovascular support:

- Patients may come from the OR with Swan-Ganz catheter to aid in management of pulmonary edema, PVR, etc… (Will not be routine, however).

Analgesia:

- Judicious use of pain and sedating medications because of the goal of early extubation and ambulation
- No NSAID's (can cause renal failure in presence of calcineurin inhibitors)
- Possible that anesthesiology will place an epidural
- For older patients PCA's would be an ideal form of pain management

Immunosuppressant therapy:

- PICU Pharmacy will review all tacrolimus levels and dosing changes with Transplant Pharmacy. Goal is therapeutic tacrolimus within 2 weeks.
- Post-transplant immune suppression plan (typically tacrolimus, steroids, MMF, and induction with basiliximab) will be posted in Epic under Specialty comments.

Nutrition:

- Post-transplant, nutritional followup will be via Transplant team Nutritionist (Jodi Mettel)
- TPN is acceptable if needed but will not “routinely” be used due to risk of sepsis.
- Enteral feeds should be instituted as early as tolerated, but assessment of adequate swallowing is usually done prior to starting oral feeds post transplant.

Antibiotic management:

- For patients in PICU, Peds ID should be consulted to review antibiotic plans and prophylaxis
- Largely tailored to their pre-operative antibiotic management; there will be a post-op antibiotic plan posted in Epic under Specialty comments

Hematology:

- Keep hemoglobin > 8 mg/dL

Lines and Tubes:

- All patients will have 4 chest tubes (2 for each thoracic cavity) immediately post-op.
- If patients do have a Swan-Ganz, they will have an IJ cortis (this can be re-wired to a triple lumen catheter post-operative day #1)

APPENDIX 2: PEDIATRIC LUNG TRANSPLANT MEDICATIONS AND DOSING (REVISED 2017)

INDUCTION:

1. Basiliximab
   a. < 35kg: 10mg IV on days 0 and 4
   b. 35kg: 20mg IV on days 0 and 4
2. Methylprednisolone 10mg/kg IV x 1 prior to each lung reperfusion (maximum 1 gm)

PRE-OP ANTIBIOTICS

1. For CF patients already on IV antibiotics: continue pre-op regimen, and add MRSA coverage as needed (until donor cultures are negative for MRSA). For CF patients not on IVs:, use the regimen indicated the specialty comments pre-op plan..
2. For non-CF patients:
   a. Ceftazidime 75 mg/kg IV Q8h (maximum 2 gm)
   b. If history of MRSA: add vancomycin 15-20 mg/kg IV Q6-8h. [The adult program administers MRSA coverage to all recipients until the donor cultures are negative for this organism. The standard is vanc, unless the patient is considered at elevated risk for post-op renal dysfunction]

IMMUNOSUPPRESSION

1. Tacrolimus (Single Response) – initiate on POD 1; goal trough = 10-15 ng/mL [adults use 10-12]
   a. Patients not on azole:
      i. PO dosing: 0.1mg/kg BID
      ii. SL dosing: 0.05mg/kg BID
   b. Patients on azole:
      i. PO dosing: 0.05mg/kg BID
      ii. SL dosing: 0.025mg/kg BID
2. Mycophenolate mofetil (Cellcept)

   600mg/m2/dose IV BID (maximum dose: 1 gm)
3. Steroids

a. POD 1-3: methylprednisolone 0.5 mg/kg IV BID
b. POD 4-90: prednisone tablet/prednisolone liquid 0.5 mg/kg PO daily
c. POD 91-180: 0.4 mg/kg PO daily
d. POD 181-270: 0.3 mg/kg PO daily
e. POD 271-365: 0.2mg/kg PO daily

ANTI-INFECTIVE PROPHYLAXIS

Bacterial

1. Septra/Bactrim: 2.5mg/kg PO BID MWF [start when taking p.o. meds]
2. Dapsone – check G6PD prior to giving: 2mg/kg PO daily
3. Atovaquone: >24mo: 30mg/kg PO daily

Antifungal (Single Response)

1. Voriconazole [the adult program is using itraconazole for low risk patients (no prior H/O fungal infection) as seems to be better tolerated than vori (hepatitis, photosensitivity, periostitis). We use an azole in other patients (mainly CF), and like to start it pre-op and the CYP3A effects are not variable in the immediate post-op period.]
    a. <12 years old:
    b. 8 mg/kg Q12 x 2 doses (Maximum 400mg/dose)
    c. 7 mg/kg Q12 (Maximum 200mg/dose
2. >12 years old:
    a. 6 mg/kg Q12 x 2 doses (Maximum 200 mg/dose)
    b. 4 mg/kg Q12 (max 200mg)
    c. Obtain trough after 7 days; goal >700 mcg/mL
3. Posaconazole
    a. IV: 4 mg/kg IV BID on Day 1, then 4mg/kg daily (Maximum 300mg/dose)
    b. Obtain trough level by day 7 or sooner if clinically warranted
    c. Suspension: 4 mg/kg PO TID (Maximum 200mg/dose)
    d. Tablet (if tolerating PO): 300mg PO daily (assuming IV load)
    e. Obtain trough after 7 days; Goal > 700 mcg/mL
    f. If intolerant to azoles, then consider micafungin

Antiviral

1. Valcyte – for CMV intermediate and high risk (D+/R+, D-/R+, D+/R-)
        a. CrCl (mL/minute/1.73 m2) = [k x Height (cm)] divided by serum creatinine (mg/dL)
        b. Dose (mg) = 7 x body surface area x creatinine clearance

c. K constant:
d. Infants with low birth weight for gestational age: k = 0.33
e. Infants with birth weight appropriate for gestational age: k = 0.45
f. Children 1 to <2 years: k = 0.45
g. Girls 2 to 16 years: k = 0.55
h. Boys 2 to <13 years: k = 0.55
i. Boys 13 to 16 years: k = 0.7
j. Maximum: 900mg once daily

2. Ganciclovir – if patient is NPO
    a. 5 mg/kg IV Q24h
    b. Transition to once daily after 1-2 weeks if still on IV

3. Cytogam – for CMV high risk (D+/R-)
    a. 150 mg/kg IV on POD 1 and 14

4. Acyclovir – for CMV low risk (D-/R-)
    a. < 40 kg: 60-90 mg/kg/day PO divided BID-TID
    b. 40 kg: 800mg PO BID

PROPHYLAXIS

1. DVT:
    a. Heparin 5000 units SQ Q8h – only for patients > 16 years old and > 50 kg
2. Esomeprazole 1 mg/kg IV daily (maximum 40mg) – convert to PO when able
3. Bowel regimen
    a. Docusate:
        i. < 3 years old: 10-40 PO mg/day
        ii. 3-6 years old: 20-60 PO mg/day
        iii. 6-12 years old: 40-150 PO mg/day
    b. Senna
        i. 2-5 years old: 4.4-6.6mg PO QHS
        ii. 6 years old: 8.8mg PO QHS
    c. Miralax – add for CF patients
        i. 17g PO BID
4. Azithromycin

a. < 40kg: 250mg PO MWF

b. > 40kg: 500mg PO MWF

APPENDIX 3: APPROACH TO INFORMED CONSENT, ETHICAL DECISION MAKING, AND TEAM COMMUNICATIONS FOR PEDIATRIC PATIENTS IN RESPIRATORY FAILURE BEING BRIDGED TO LUNG TRANSPLANT

1. At time of active listing: Include general discussion of bridging methods including ECMO with Ped Pulm attending and transplant coordinator
2. At time of respiratory deterioration requiring PICU admission:
    a. Ped Pulm/CF attending, CT Surg, and PICU ECMO dir/attending, PICU nursing and Ethicist meet to discuss candidacy
    b. Ped Pulm/CF attending, CT Surg, and PICU ECMO dir/attending, PICU nursing review potential bridging methods with patient and parents at care conference
3. At time intervention is felt to be imminently required: Care conference with parents and Ped Pulm, PICU attending, CT Surg, ECMO team, PICU nursing, including rehab goals for re-activation of listing (if pt needs to be de-activated temporarily)
4. Check-in at weekly intervals after bridge support is initiated to reassess goals, anticipate and/or address complications

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