Appendix 5: IPLTC Guidelines for Maintenance Immunosuppression and Treatment of Acute and Chronic Rejection

Based on the discussions through the IPLTC, at the external review meeting during the planning phase of the grant, and through the protocol development, we have compiled a list of areas of consensus in clinical evaluation and practice. This document summarizes these areas and highlights the areas in which consensus has been developed including the clinical evaluation of the pediatric lung transplant candidate, clinical practice for immunosuppression and rejection, viral prophylaxis and therapy, and procedural methods for bronchoscopy.

I. CLINICAL EVALUATION (STANDARD OF CARE PRE-TRANSPLANT EVALUATION)

Vaccine Record	Pre-transplant titers required as standard of care: • CMV IgG, IgM • EBV VCA IgG, IgM • VZV IgG • Hepatitis A (total) • Hepatitis B (Hep B surface Ab, Hep B surface Ag, Hep B core Ab) • Hepatitis C AB • HIV • Serum immunoglobulins (IgG, IgM, IgA, IgE)
Pre-transplant Titer (optional based on site-specific practice)	• Tetanus IgG • Pneumococcal (Types 1, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 12F, 14, 18C, 19F, 23F) • Measles IgG • Mumps IgG • Rubella IgG • Diphtheria IgG • Histoplasmosis complement fixation & immunodiffusion • Blastomycosis complement fixation & immunodiffusion • Aspergillus complement fixation & immunodiffusion • Coccidiodomycosis complement fixation & immunodiffusion • Toxoplasmosis
Pretransplant Colonization	Bacterial culture & susceptibilities • Staphylococcus aureus (MSSA, MRSA) • Pseudomonas aeruginosa • Burkholderia species • Acinetobacter • Others
Fungal Culture	• Candida species • Aspergillus species • Other molds
Other Cultures/Tests	• Mycobacteria (atypical) • PPD or Quantiferon-gold TB test
Donor Titers	• CMV • EBV

II. CLINICAL PRACTICE

A. Induction and Initial Immunosuppression

Site	Induction
Children's Hospital of Philadelphia Children's Hospital Boston	*RATG* 1.5 mg/kg IV on days 0(day of transplant), 1,2,3,4
Columbus Children's Hospital	None
Great Ormond Street Hospital for Children	*Basiliximab* (OR and POD 4) 10 mg (<30kg) 20 mg (> 30kg)
St. Louis Children's Hospital	*Daclizumab* 1mg/kg IV q2wks x 5 doses
Stanford	*RATG* 1.5mg/kg IV on days 0(day of transplant),1,2,4,5,6
Texas Children's Hospital	*Basiliximab* (OR and POD 4) 10 mg (<30kg) 20 mg (> 30kg)

B. IPLTC Guidelines for Maintenance Immunosuppression

1. Tacrolimus Dosing

Prior to going to the operating room	A single, oral dose of 0.1 mg/kg tacrolimus
Post-operatively	Start tacrolimus by 72 hrs post-op: 0.01-0.04 mg/kg/day IV continuous infusion OR 0.1-0.3 mg/kg/day via NG or G-tube divided into 2 equal doses OR 0.08 mg/kg/day sublingual divided into 2 equal doses
Once taking PO	0.1-0.3 mg/kg/day PO divided into 2 equal doses

* Every 8 hour dosing should be considered in infants and young children if therapeutic levels are hard to achieve (due to rapid metabolism of the drug in this age group).

2. Tacrolimus Monitoring
   Therapeutic drug monitoring should start on the second post-operative day.

	Frequency of Monitoring After Transplant	**Target Trough Level After Transplant**
First 2 Weeks	Daily	10-20 ng/ml
Weeks 2-4	Biweekly	10-15 ng/ml
1-3 Months	Weekly	
3-6 Months	Monthly	
After 6 Months	Every 3 to 6 months	
After 1 year		6-10 ng/ml

Dose adjustments are to be done according to patient's renal function. The above given recommendations for therapeutic drug monitoring of tacrolimus may not be suitable for infants secondary to the different pharmacokinetics in infants

3. Mycophenolate Mofetil
   a. MMF Dosing
      600 mg/M^2 BID in non-CF patients
      800 mg/M^2 BID in CF patients at puberty and above
      **Consider higher initial dosing in younger CF patients

   b. MMF Monitoring
      i. Trough levels should be monitored weekly during the first 3 months after transplant. Once a steady state is reached frequent monitoring is not necessary and the trough level can be checked during routine follow up visits.
      ii. Recommended target trough level is: greater than 1.0 mg/L and less than 3.5 mg/L.
      iii. Full pharmacokinetic studies and consultation with a Pharm-D are recommended if gastrointestinal or bone marrow side effects are problematic.

4. Steroids
   a. Steroid Dosing
      Intraoperatively: 10 mg/kg (max 1 g) IV at time of reperfusion of transplanted lungs.

      Methylprednisolone 0.5 to 1 mg/kg/day BID x 3 days then tapered down according to each center's protocol to a dose of 0.5 mg/kg/day by six weeks if no acute rejection is present, and to 0.2mg/kg/day by one year post-transplant if no acute rejection has occurred.

III. Treatment of Acute Cellular Rejection (Grade A2 or greater)

Initial Treatment	Methylprednisolone 10-20 mg/kg/day (max = 1 g/day) for 3 to 4 days AND increase maintenance back to previous ACR free doses. *Alternative for A2:* *Oral steroid therapy (3 mg/kg –100 mg) initial dose then wean over 14 days to previous dose.*
Repeat biopsy in 2-4 weeks depending on histology and/or clinical status (treatment success = ≤ A2).	
Persistent/Recurrent acute rejection	If same or lower ACR grade (i.e. A3 to A2), repeat high dose (IV) steroid protocol If worsening lung function and/or ACR grade, or severe ACR (A4): Antithymocyte globulin
Steroid resistant rejection	In cases of steroid resistant rejection, antibody-mediated rejection should be excluded with the appropriate methods (Immunohistochemistry)
Failed two courses of steroids	Antithymocyte globulin (dosing may be based on reduction CD3 <100/mm3) OR Rabbit (rATG): 1.5 mg/kg/day, maximum of 150 mg/day for 10-14 days OR Equine (ATGAM): 10-15 mg/kg/day for 10-14 days
Alternatives for refractory ACR	OKT3: 2.5 mg < 30 kg, 5.0 mg > 30 kg daily for 10-14 days Campath 1H (Alemtuzumab) Total lymphoid irradiation. Photophoresis Methotrexate. Rapamycin

IV. EVALUATION OF HUMORAL REJECTION

A. Stages per ISHLT guidelines

Putative stages of humoral response to an organ graft

I: Latent humoral response	Circulating antibody[1] alone (but without biopsy findings or graft dysfunction)
II: Silent humoral reaction (accommodation vs. prerejection state)	Circulating antibody[1] + C4d deposition (but without histologic changes or graft dysfunction)
III: Subclinical humoral rejection[2]	Circulating antibody[1] + C4d deposition + tissue pathology (but without graft dysfunction)
IV: Humoral rejection	Circulating antibody[1] + C4d deposition + tissue pathology + graft dysfunction

[1] Circulating antibody to HLA or other antigens expressed on donor endothelial cells.

[2] May differ among organs, as the ability to detect particularly mild degrees of graft dysfunction varies among organs.

From: Revision of the 1995 Working Formulation for the Standardization of Nomenclature

B. Evaluation
   1. Screening Serum
      i. PRA every three months for first 18 months then every 6 months.
      ii. If clinical history has evidence of rejection or loss of lung function can screen more frequently.
      iii. If PRA elevated depending on level consider monthly.
      iv. Results should be reported as mismatched HLA class I and class II.
   2. Screening Biopsy
      i. C4d staining to be performed at all biopsies.
         a. Immuno-fluorescence on fresh frozen section (1-2 biopsy samples)
         b. Standard immuno-perxidace stain for C4d on formalin fixed specimens.
      ii. If specimen positive repeat after therapeutic intervention.

C. Therapy options used by individual institutions (outside scope of protocol)
   1. IVIG infusion (1-2 grams/kg)
   2. Plasmapheresis
   3. Rituximab (monoclonal anti-CD20)
   4. Concomitant steroid bolus if suspicious for concurrent cellular rejection per site protocol

D. Repeat monitoring scheme after intervention
   Consider repeat PRA for donor-specific antibodies 1, 4, & 8 weeks post intervention

V. EVALUATION AND TREATMENT OF BRONCHIOLITIS OBLITERANS

A. Evaluation/treatment for BOS 0p or greater:
   1. Reassess for contribution of reflux and/or infection and treat as appropriate.
   2. Perform bronchoscopy and transbronchial biopsy:
      a. If no BO on transbronchial biopsy:
         i. Consider open lung biopsy if rapidly progressive
         ii. Add azithromycin *(Under 40kg dose: 250 mg q M, W, F, Above 40 kg dose: 500 mg q M, W, F)*
         iii. Switch MMF to Sirolimus (Sirolimus target trough level: 10-15 ng/ml)
         iv. Monitor patient closely.
      b. If patient progresses to BOS 1 in spite of the above interventions:
         i. Reassess for ongoing contribution of reflux and/or infection and treat as appropriate.
         ii. Re-biopsy (transbronchial or open lung biopsy)
         iii. Pulse with steroids (Methylprednisolone 10 mg/kg/day x 3 days) and use cytolytic therapy (Atgam 15 mg/kg/day x 10 days) in patients with lymphocytic inflammation in active BO lesions.
      c. If BO on transbronchial biopsy:
         i. Add azithromycin
         ii. Switch MMF to sirolimus
         iii. Pulse with steroids and use cytolytic therapy (Atgam) in patients with lymphocytic inflammation in active BO lesions.
   3. Reevaluate q 3 months. If progression of BOS grade consider:
      a. Changing sirolimus to methotrexate (5-15 mg/M^2 PO/IM weekly)
      b. Total lymphoid irradiation or photopheresis.
      c. Re-transplant evaluation if consistent with program guidelines.

VI. VIRAL PROPHYLAXIS AND THERAPY

Virus	Viral Prophylaxis	Viral Therapy
Respiratory Syncytial Virus (RSV)	Palivizumab below 2 years of age	1. Ribavirin: dose, route and schedule determined by site protocols 2. Increased steroid dosing 3. Consideration for palivizumab 4. Consideration for IVIG

Virus	Viral Prophylaxis	Viral Therapy
Influenza A/B	Per CDC Guidelines	Per CDC Guidelines
Cytomegalovirus (CMV)	1. Prophylactic dosing for 6 months with ganciclovir or valganciclovir a. Ganciclovir to start within 3 days of transplantation b. 10 mg/kg/day divided every 12 hours until oral intake adequate c. Adjustments for renal dysfunction as follows: i. Cl_{cr} 50-69 mL/minute: 2.5 mg/kg/dose every 24 hours ii. Cl_{cr} 25-49 mL/minute: 1.25 mg/kg/dose every 24 hours iii. Cl_{cr} 10-24 mL/minute: 0.625 mg/kg/dose every 24 hours iv. Cl_{cr} <10 mL/minute: 0.625 mg/kg/dose 3 times/week following hemodialysis d. Transition to valganciclovir with adequate oral intake e. Dosing based on BSA and creatinine clearance from Roche documents f. Dosing for both based on creatinine clearance	Intravenous ganciclovir 10 mg/kg/day divided every 12 hours for 14-21 days

Virus	Viral Therapy
Adenovirus	Cidofovir (+ probenecid, +/- IVIG)
Hypogammaglobulinemia	Evaluate every 3-6 months IVIG – 400 mg/kg Repeat levels at 2-3 weeks Dosing based on maintaining trough IgG >400 mg/dL

Procedural practice

A. Viral recovery (upper tract): Nasopharyngeal swab
B. Bronchoalveolar lavage
C. Transbronchial biopsy
D. Blood specimen collection and processing