Trying to Manage the Unmanageable: The Lung Transplant Clinical “Protocol”
(Goal: decrease patient complications without increasing the clinician’s anxiety)

Underlying Theme: Lung Transplant Problems are Ubiquitous and Nonspecific

The pensive/worried pulmonary clinician talking to you about a lung transplant problem:
“*It could be anything!*”
“It all looks the same to me”,
“That’s why we got the biopsies!”
“We trust your judgment”
“The patient’s outcome is in your hands”

Surgeon’s response to discussion: “*$¥ٸ!!#!!! clinicians”

In patient Hospitalization in the Post Operative Period (usually ~2 weeks)

Possible Major Lung Complications
1. **Ischemia Reperfusion Injury (I/R; ARDS/DAD):** usually diagnosed on clinical grounds with hypoxemia (low PaO2/FiO2 ratio), diffuse symmetric “edema” pattern on chest xray, noncompliant lungs physiologically. In general this problem has decreased in magnitude due to better preservation solutions and surgical techniques. The majority of patients recover but nonetheless severe forms can lead to death or other complications.

2. **Infections:** Usually bacterial (nosocomial organisms). Present with pulmonary infiltrates of any nature, cough sometimes, fever, leukocytosis. Diagnosis usually made by culture of lung secretions. Most patients respond well to antibiotics. This problem too has declined somewhat due to intensive antimicrobial regimens used prophylactically.

3. **Acute Allograft Rejection:** Presentation not dissimilar to the above problems and potentially overlapping. Dx can be empiric but most prefer pathologic confirmation with Transbronchial biopsy (TBBx). Rx: High dose steroids which is effective in the vast majority.

4. **Airway Dehiscence:** Usually in the first few weeks. Less common (<5%) in the modern era. Dx: clinical. Most heal spontaneously but some require surgery.

5. **Hyperacute Rejection:** From preformed antibodies. Very rare in the modern era given recipient alloantibody evaluation by PRA and flow cytometric methods.

Medical Management: the First Year

Surveillance
1. Daily temperatures, BPs, spirometry (hand held) and symptom diary.
2. Thrice weekly: exercise tolerance and oxyhemoglobin saturation during rehabilitation
3. Weekly to monthly clinic visits for symptom review, exams, lab work (including CMV monitoring with viral load by PCR), chest xrays and formal spirometry.
4. Quarterly bronchoscopies (programs vary) looking mostly for silent AR or occult infection.
5. Preventative medications: immunosuppressants, PCP/CMV/fungi/herpes prophylaxis (varying protocols)

Possible Major Lung Complications
1. **Infections:**
(A) Usually bacterial or fungal (mix of nosocomial and community acquired organisms). Presentation usually patchy infiltrates, often bilateral accompanied by fever, leukocytosis and cough. Diagnosis by sputum/bronchoscopy culture.

(B) CMV also occurs in this period as preventative medications (valganciclovir) are withdrawn. Patients present most commonly with fatigue and leukopenia with or without respiratory symptoms. Infiltrates, if present, are diffuse and symmetric but most cases are diagnosed before infiltrates arise. Diagnosis: Gold standard is pathology but most centers initiate treatment with a positive PCR result (the sensitivity and specificity of this test is still be evaluated in clinical research studies).

(C) Fungal Infections: less common. Typically more nodular in appearance or cavitating. Diagnosis by culture of secretions, rarely by pathology.

(D) Other infections: rarely Legionella, Nocardia, NTM, more commonly community viruses. Diagnosis rests on stains, cultures and probes.

2. Acute Vascular Allograft Rejection: Often chest xray silent. Symptoms range from none to dyspnea and/or cough and/or fever. Often detected early with declines in spirometric indices or with surveillance bronchoscopy in a “well” patient. Dx can be empiric but most prefer pathologic confirmation with TBBx. The ISHLT severity scoring system is universally used. Rx: High dose steroids which is effective in the vast majority.

3. Humoral Allograft Rejection: May present subtly or fulminantly with hypoxia, diffuse infiltrates, respiratory failure. May mimic ARDS from sepsis but shock is usually not present. Dx clues: timing and presentation, bloody BAL fluid, HLA antibodies in serum (although certainly not critical). Pathology is gold standard with capillaritis and C4d staining (but much needs to be worked out regarding the sensitivity and specificity of the C4d stain). Rx: Plasma Exchange, steroids, Rituxan (anti-CD20), etc (in evolution).

4. ARDS: Garden variety. Diffuse pulmonary infiltrates and significant hypoxemia. DAD to the pathologist. Concerning clinical overlap with humoral rejection. Outcomes probably worse in lung transplant recipients but no good published studies.

5. Post Transplantation Lymphoproliferative Disease (PTLD): Related to primary EBV infection. Present with lung nodule(s). Dx: EBV viral load by PCR but pathology (FNA, core or VATS biopsy) is the gold standard. Studies do not demonstrate that prognosis is dependent on Frizzera categorization or tumor clonality. Vast majority respond to reduced immunosuppression (+/- antiviral therapy). Chemotherapy is not indicated for early PTLD. EBV viral load starts dropping before tumor regression by scans.

Medical Management: Beyond the First Year (generally listed from most to least common)

1. Infections:
   (A) Usually bacterial from community acquired organisms.
   (B) CMV, fungal and other infections are less common as time goes by.
   (C) Community viruses more common: Dx: clinical usually although viral cultures/probes may help. Pathology is nonspecific (DAD).

2. Acute Vascular Allograft Rejection: Less common as time goes by but not unheard of.

3. Humoral Allograft Rejection: Less common as well.

4. Chronic Rejection (CR; aka Obliterative Bronchiolitis or Bronchiolitis Obliterans Syndrome): Affects >50% of all lung transplant survivors and is the leading cause of death. Mean time to presentation is 1.5-2 yrs. CR is usually a clinical diagnosis of exclusion after all disorders that decrease lung function have been excluded. Patients often suffer larger declines in FEF25-75 than FEV1 early on. Lung function decline is variable but usually much faster than most described lung diseases (COPD, asthma, IPF). CXR is usually normal since it is an airway disorder. The BOS severity scoring system is based on FEV1 decline relative to highest post-transplant FEV1.
Dx is confirmed with transbronchial biopsy (TBBx) pathology in a minority of patients (15%). While the ISHLT has promulgated a “B” scoring system for airway inflammation, it does not correlate well with CR diagnosed by the BOS scoring system and thus the FEV1 trumps the “B” scores when it comes to CR. Thus, when the biopsy receives a “B” score, the clinician needs to decide what is causing the airway inflammation (I/R injury, infection, CR, other). Rx: augmented immunosuppression, azithromycin, photophoresis, retransplantation, other. There is no convincing evidence that any of these therapies fundamentally alters the disease course, which is highly variable in natural history. The 5 yr survival of CR/BOS is ~30%. Less than 10% of lung transplant patients achieve operational tolerance (do not develop BOS) possibly due to reduced innate-adaptive cross talk, reduced allograft signaling for immune cell recruitment or enhanced regulatory T cell activities.

5. ARDS: as above.
6. Hyperinflation of native COPD lung: Clinically the patient presents with slowly declining lung function confounding the diagnosis of BOS. Nothing for a pathologist to be concerned with per se but it can ramify into the discussion of histological diagnosis of OB/BO.
7. Post Transplantation Lymphoproliferative Disease (PTLD): Related to reactivation EBV infection now with presentation described above. Considerably more difficult to treat. Reduced immunosuppression is the first step unless tumor is of the Burkitt’s type. Chemotherapy is indicated for nonresponsive late PTLD. Mortality is in the range of 50%.
8. Bronchogenic Cancer: presents as nodules or rapidly growing masses in the native or donor lung. It is in the DDx for PTLD, fungal infection or “round” pneumonia. Pathology is diagnostic.
9. Recurrence of Original Disease: Best described for sarcoidosis and most reports suggest histologic recurrence without overt disease progression.
10. Sirolimus-induced Lung Disease: Incidence unknown but felt to be uncommon. However it may be more frequent in the late (beyond 1 yr) use of sirolimus (recent study in Heart Transplant recipients reported a 24% incidence). Probably easier to diagnose in heart, kidney, liver and other non-lung Tx patients. Broad range of presentations from insidious to fulminant with dry cough and dyspnea usually within the first 6 months after drug initiation. Diffuse interstitial or alveolar infiltrates can mimic CHF, ARDS, other ILDs, or infection. Diagnosis: BOOP, NSIP, or non-necrotizing granuloma on lung biopsy. The pathology of BOOP may share similarities with BO (CR) especially on TBBx where the tissue sample size is small. Clinical Dx mandates a rule out of other causes and disease regression (usually) when the drug is withheld or high dose steroids are given (reminder: most patients are on low dose steroids already). Also note several cases of diffuse alveolar hemorrhage (DAH) have also been reported (pathology: vasculitis).
11. Aspiration: Micro-aspiration is common but it is not clear if this causes pulmonary infiltrates or aspiration pathology. The main concern is that this process may augment BOS.