Post Lung Transplantation Care

DM Seminar

Inderpaul singh

Lung transplantation

- Care of lung transplant recipient involves close surveillance
- The basic aim is to ensure proper functioning of graft & timely management of various complications
- Short of randomized trials in lung transplantations most data is from transplantation of other solid organs
- Even though outcomes have improved with time much needs to be improved

Management Post Transplantation

- Routine Management
  - Follow up
  - Pulmonary Function Tests
  - Bronchoscopy
  - Chemotherapy
- Complications
  - Primary Graft Dysfunction (PGD)
  - Airways complication
  - Infections
  - Rejection
  - Post transplantation lymph proliferative disorders
  - Lung cancer
  - Recurrence of primary disease
  - Re transplantation

Outcomes

- Conflicting literature on benefits of lung transplantation on survival
- No randomized trial comparing lung transplantation with expectant management
- 1,5 and 10 years survival rates(adjusted) are 83%, 54%, 29% respectively
- Overall median survival or half- life of 5.3 years
- Median survival after transplantation varies with the underlying disease
  - 7 yrs for cystic fibrosis
  - 6.1 yrs for alpha 1 ATD
  - 5.6 yrs for idiopathic PAH
  - 5.1 yrs for COPD
  - 4.3 yrs for IPF

Clin Chest Med 32 (2011) 253–264
Am J Transplant 2010;10(Part 2):1047–68
J Heart Lung Transplant 2010;29:1104–18

Routine management

- **Follow up**
  - **First year** after transplantation (PFT, bronchoscopy, chest X ray once a month)
    - Twice weekly for 1 st month; Once a week during 2 nd month; Once in two weeks during 3 rd month; Once a month during 4-6 months (CT thorax at 6 months)
    - Once a month during 7-12 months (PFT, chest X ray monthly; Bronchoscopy once in 2 months & CT thorax at 12 months)
  - **1 -2 years** after transplant
    - Once every 2 months (PFT, bronchoscopy at each visit; X ray every 4 months; CT thorax at 18 & 24 months)
  - **2-3 years** after transplant
    - Once in 3 months (PFT, X ray at each visit; CT thorax at 30 & 36 months)
  - **3-4 years** after transplant
    - Once in 4 months (PFT, X ray at each visit; CT thorax at 42 & 48 months)
  - **4 years and beyond**
    - Once in 6 months (PFT, X ray at each visit)
  - **At any time**
    - If hospitalized, at any time**,** seen twice weekly and back to the one month schedule until condition improves. Then regular schedules will start again

Wexner medical center

Bronchoscopy

- Is pivotal in managing patients with lung transplantation
- “Gold standard” for early recognition of rejection and graft dysfunction
- Ruling out infections as a cause of clinical worsening
- Allows distinguishing acute rejection from other causes of allograft dysfunction (airway stenosis or infection)
- TBLB done in lower lobes as the rejection process is worst in lower lobes as compared to the upper lobes

How frequent ?

Is there really a role of surveillance bronchoscopy?

Does early detection of rejection convert to survival benefit ?

Clin Chest Med 32 (2011) 295–310
Ann Thorac Surg 2000;69(5):1529–31

The debate is on !

For routine bronchoscopy

- Detects clinically silent acute rejections (18%-39% asymptomatics with grade 2 or higher acute rejection)[1-3]
- Differentiates acute rejection from other causes of allograft dysfunction (airway stenosis or infection)[1]
- Adverse events relatively low with no reported mortality[1-4]

1. Clin Chest Med 32 (2011) 295–310
2. Am J Respir Crit Care Med 1995;152:2037–43.
3. J Heart Lung Trans- plant 2008;27(11):1203–9.
4. J Heart Lung Transplant 2009;28(1):14–20.
5. J Heart Lung Transplant 2002;21(10):1062–7.

Against bronchoscopy

- Contains cost without compromising BOS or survival[1-3]
- No clinical benefit of routine surveillance bronchoscopy in a single center study[4]
- However the study and the intervention group had significant difference in induction regimen used and baseline CMV status[4]

1. Cleve Clin J Med 1993;60: 303–19.
2. Am J Respir Crit Care Med 1997;155:1705–10
3. J Heart Lung Transplant 2002;21:319–26.
4. J Heart Lung Transplant 2009;28(1):14–20.

What to do then ?

- The final word is yet to be out !
- A randomized trial to answer the question is the need of the hour
- Studies assessing non invasive serum markers to evaluate acute rejection need further validation
- The best approach till then conceivably is surveillance bronchoscopy
- The benefit to detect and treat acute allograft rejection and infections dwarfs the minimal risks associated with FOB
- The cost of bronchoscopy should be compared with the cost of re implantation

Pulmonary function tests

- PFT is the glucometer of lung transplant patients
- Patients need to maintain a spirometry dairy
- A sustained fall of > 10% in FEV1 or FVC corresponds to clinical worsening
  - Infections
  - Acute rejection
  - Airway stenosis
  - Chronic rejection

Clin Chest Med 32 (2011) 295–310

Immunosuppression

- What to use for induction and maintenance?
- How to monitor?
- Side effect profile?
- What are the conventional and novel approaches ?

Conventional approach

- Early treatment protocols were primarily based upon experiences from other solid organ transplantation
- However several large multicenter clinical trials have been performed since to improve current understanding in post lung transplant immunosuppression
- **Induction therapy**
  - Potent immunosuppression during perioperative or early post operative period
  - Reduces risk of acute rejection & allows for gradual initiation of maintenance therapy
  - Target T- lymphocytes
- **Maintenance therapy**
  - Involves calcineurin inhibitors (CNIs; eg, cyclosporine, tacrolimus), antiproliferative agents (eg, azathioprine, mycophenolate mofetil [MMF], sirolimus), and corticosteroids

Clin Chest Med 32 (2011) 295–310

Induction therapy

- Involves institution of potent immunosuppression in perioperative or early perioperative period
- To reduce risk of acute rejection & provide bridge till maintenance immunosuppression takes effect
- Target T-lymphocytes
  - Humanized or chimeric monoclonal antibodies to CD25 & the alpha subunit of the interleukin-2 receptor (IL-2R) (eg, daclizumab, basiliximab)
    - inhibit T-cell proliferation and differentiation, without inducing depletion
    - By inhibiting generation of $CD4^+$ $CD25^+$ $FoxP3^+$ T regulatory cells, may disrupt the delicate balance between alloreactivity and tolerance
  - Polyclonal antithymocyte globulins (ATG) such as Thymoglobulin or Atgam
    - result in profound depletion of T-cells, including alloreactive T-cells
    - May spare $CD4^+$ $CD25^+$ $FoxP3^+$ T regulatory cells promoting immunological tolerance
  - Alemtuzumab (Campath-1H) humanized monoclonal antibody to CD-52
    - results in profound and prolonged T-cell depletion with variable effects on B-lymphocyte, natural killer cells, and monocyte populations

Agent	Mechanism of action	Side effects	evidence
Daclizumab, Basiliximab Basiliximab; 20mg i.v on days 1 & 4 Daclizumab; 1mg/kg every 2 wks for 5 doses	monoclonal antibodies to CD25 & the alpha subunit of IL-2R inhibit T-cell proliferation and differentiation, without inducing depletion	Inhibition of $CD4^+$ $CD25^+$ $FoxP3^+$ T regulatory cells, may disrupt the delicate balance between alloreactivity and tolerance Hypersensitivity reactions (rare)	Retrospective study of 4000 lung transplants comparing IL-R antagonist or polyclonal ATG or no induction improved survival at 4 years (64%,60%,57% resp) BOS rates were higher in ATG group *Clin Transplant 2008;22(5):603-8*
Polyclonal antithymocyte globulins (ATG) such as Thymoglobulin or Atgam Thymoglobulin received 3–6 mg/kg, begun slowly with rate escalation every 30 minutes	profound depletion of T-cells, including alloreactive T-cells spares $CD4^+$ $CD25^+$ $FoxP3^+$ T regulatory cells promoting immunological tolerance	anaphylaxis, cytokine storm, serum sickness, leukopenia, anemia, thrombocytopenia increased risk of infection & malignancy	In a randomized single center study of 50 LT comparing ATG vs daclizumab no difference in survival, AR or CR However CMV infections higher in daclizumab group *J Heart Lung Transplant 2007;26(5):504–10*
Alemtuzumab (Campath-1H) 30 mg infused steadily over 2 hours	humanized monoclonal antibody to CD-52 Leads profound and prolonged T-cell depletion with variable effects on B-lymphocyte, natural killer cells, and monocyte populations	Infections, infusion-related anaphylaxis and profound cytopenias	Retrospective study of 48 transplants comparing either alemtuzumab or ATG with daclizumab favored alemtuzumab which had lowest rates of acute rejection. *J Heart Lung Transplant. 2011 July ; 30(7): 743–754* In a prospective trial of 20 patients comparing alemtuzumab with reduced maintenance therapy & standard high dose immunosuppression no difference was observed in survival or acute rejection rates *Interact Cardiovasc Thorac Surg 2010;10(2):190–4*

Final word

- The evidence to support use of induction is still weak
- There is no consensus regarding the best inducing agent and the use of induction
- However many centers prefer to use IL-2 receptor antagonists
- Larger randomized studies are needed to elucidate the best inducing agent

Maintenance immunosuppression

- At its outset the short term outcomes after lung transplantation were dismal
- Initial immunosuppression involved administration of high dose steroids which proved detrimental in various animal studies[1]
- Landmark paper by Dr Joel Cooper led to the birth of present era immunosuppression regimen[2]
- Involves a combination of CCI,antiproliferative agent and oral corticosteroids[3]

1. JAMA 1963;186:1065–74.
2. N Engl J Med 1986;314(18):1140–5.
3. Clin Chest Med 32 (2011) 265–277

Corticosteroids

- Almost all centers tend to use corticosteroids throughout the course of the transplant recipient's life
- Steroids inhibit the inflammatory response at various levels via cellular receptors and by direct action by binding DNA directly
- Typically initiated at a dose of 0.5 mg/kg/day for the first 3 months and is then tapered to 15 mg/day by month 3 and to 5 mg/day by the first year.
- Diabetes, hypertension, weight gain,osteoporosis,increased incidence of infections are the common side effects
- During acute rejection increasing doses of corticosteroids are used

Semin Respir Crit Care Med 2010;31:172–178
Clin Chest Med 32 (2011) 265–277

Calcineurin inhibitors (CNI)

- Includes cyclosporine A (CSA) & tacrolimus
- Narrow therapeutic window
- Most common side effect renal insufficiency, hemolytic uremic syndrome, hypertension, hyperkalemia, hypomagnesaemia, and hyperlipidemia

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Clin Chest Med 32 (2011) 265–277

CSA

- forming a complex with the cytoplasmic carrier protein cyclophilin and binding to calcineurin to inactivate it
- Can be given enterally or parenterally
- oil-based oral CSA characterized by erratic drug absorption and metabolism.
- K newer cyclosporine microemulsion formulation (Neoral) has better bioavailability.
- Levels are measured 2 hours after intake
- Trough levels 250-350 ng/ml 1st year then 200-300 ng/ml

Tacrolimus

- More potent than CSA (10-100 times)
- Binds to cytoplasmic protein FKBP-12 inactivating calcineurin
- Orally,i.v,or sublingually
- Oral significant pharmacokinetics similar to CSA
- Tacrolimus preferred over CSA
- Levels adjusted based on trough levels
- Trough levels 10-12 ng/ml 1st year then 6-8 ng/ml

Semin Respir Crit Care Med 2010;31:172–178
Clin Chest Med 32 (2011) 265–277

Which CNI to use?

- Comparative studies suggest that tacrolimus based immunosuppression has better efficacy
- Single center randomized trial of 133 LT favored tacrolimus over cyclosporine
  - significant reduction in BOS (21.7% vs 38%)
  - Reduced acute rejection rates
  - Improved survival

Ann Thorac Surg 1995;60(3):580–4 [discus- sion: 584–5].

- Another study of MMF & prednisolone & either of CNI also favored tacrolimus
  - fewer acute rejection episodes per 100 patient (0.225 vs 0.426; *P<.05)*
  - however no difference in BOS or survival

J Heart Lung Transplant 2001;20(5):511–7.

- Similar results favor tacrolimus over cyclosporine

J Heart Lung Transplant 2007;26(10):1012–8.

Antiproliferative agents

- Maintenance immunosuppression regimens typically include at least one antiproliferative agent
- Azathioprine is the oldest drug in this category and is still used by one-third of all transplant centers
- Newer agents such as MMF and sirolimus have been incorporated into immunosuppression protocols at many programs

Agent	Mechanism of action	Common adverse effects	evidence
Azathioprine 2mg/kg/d	6MP inhibits DNA & RNA synthesis by interfering with purine synthesis Polymorphism in thiopurine S-methyltransferase (TPMT) increases risk of marrow toxicity	Myelosuppression, pancreatitis, cholestatic hepatitis, hypersensitivity like reaction characterized by sepsis like syndrome	
Mycophenolate (MMF) 1000-1500 mg bid	hydrolyzed to mycophenolic acid, a potent inhibitor of B- and T-lymphocyte proliferation that blocks inosine monophosphate dehydrogenase, a critical enzyme for the de novo synthesis of guanosine nucleotides	neutropenia, anemia, diarrhea, nausea, and abdominal pain.	two prospective, randomized studies have shown no difference in either short- term (6-month rates of acute rejection and survival) or long-term (rates of acute rejection, BOS, and survival) outcome When compared with azathioprine Transplantation 2006;81(7):998–1003 J Heart Lung Trans- plant 2005;24(5):517–25
Sirolimus Trough levels of 6-12 ng/ml	Structurally similar to tacrolimus binds to FKBP forming an immunosuppressive complex that inhibits the mammalian target of rapamycin (mTOR) that is critical for cell growth, proliferation & survival	diarrhea, nausea, edema, hyperlipidemia, and cytopenia as well as more serious complications such as impaired wound healing, bronchial anastomotic dehiscence, venous thromboembolism, and pneumonitis	In a head to head comparison of sirolimus with AZA, no differences in acute rejection, BOS, or survival rates at 1 or 3 years were noted. Higher discontinuation of sirolimus due to poor tolerance. However, patients with renal insufficiency associated with chronic administration of CNIs, and recurrent skin cancers substitution of the CNI with sirolimus may improve renal function & inhibit progression of skin malignancies Drugs 2007; 67(3):369–91 Am J Respir Crit Care Med 2011;183(3):379–87

Novel approaches

- Despite improvements in surgical techniques,ICU care & immunosuppression long term outcomes still remain poor
- Various novel approaches to treat graft rejection, maintenance & monitoring immunosuppression to optimize efficacy have been tried
  - Aerosolized Immunosuppression
  - Macrolides
  - Statins
  - Extracorporeal Photopheresis

Aerosolized immunosuppression

- Unlike other solid organs, lungs offer unique opportunity to administer drugs via inhaled route
- Aerosolization of Cyclosporine has been most extensively studied
  - inhaled cyclosporine initiated within 6 weeks after transplantation and given in conjunction with a standard systemic immunosuppression regimen
  - either 300 mg of aerosol cyclosporine or aerosol placebo 3 days a week for the first 2 years after transplantation
  - No differences were noted in the primary endpoint, rates of acute rejection (A2 or greater), between the two treatment groups
  - overall survival and BOS-free survival were significantly better in the treatment arm
  - no difference in rates of respiratory infections or other adverse events between the two groups

    N Engl J Med 2006;354(2):141-50
  - Aerosolized cyclosporine is currently under investigation in a much larger phase III multicenter clinical trial that recently achieved its target enrollment of approximately 300 patients (ClinicalTrials.gov identifier: NCT00633373)
  - Small case series suggests its role in treating established BOS or persistent acute rejection

    Am J Respir Crit Care Med 1997;155(5):1690–8

    Am J Respir Crit Care Med 1996; 153(4 Pt 1):1451–5.
- Inhaled corticosteroids
  - Study including 30 patients did not show significant difference in survival,incidence of acute rejection or subsequent BOS

    Transplantation 2002; 73(11):1793–9

Macrolides

- The interest in macrolides stems from their immunomodulatory role in diffuse panbronchiolitis
- Mechanism of action
  - downregulate production of a number of proinflammatory cytokines (eg, IL-8, IL-6) and increase levels of anti- inflammatory cytokines (eg, IL-10)
  - may also reduce neutrophil adhesion and chemo- taxis, decrease production of reactive oxygen species, and promote apoptosis of activated neutrophils
  - effects on bacterial adherence to airways, composition of airway biofilm may protect from infection & subsequent inflammation
  - Possible role in decreasing GERD by increasing gastric motility
- Evidence
  - Pilot study of 6 LT patients with BOS stage 1 or more were treated with 250 mg of azithromycin thrice weekly demonstrated significant improvement in FeV1 of 630 ml

    Am J Respir Crit Care Med 2003;168(1):121–5
  - In a retrospective single-center analysis of 179 consecutive lung transplant recipients who developed at least stage 1 BOS, treatment with azithromycin before the development of BOS stage 2 was independently associated with a reduced risk for death

    J Heart Lung Transplant 2010;29(5):531–7
  - In a prospective study of 14 patients with varying degree of BOS 12 weeks treatment with azithromycin, 6 patients showed significant improvement in FeV1 (> 10%)
  - Those who responded had increased BAL neutrophilia (>15%)

    Am J Respir Crit Care Med 2006; 174(5):566–70

Statins

- Clinical evidence supporting a potential benefit of statins in transplantation was first reported in cardiac transplantation

  N Engl J Med 1995;333(10):621–7

- Mechanism of action
  - in vitro studies have shown that statins reduce γ-interferon-induced expression of major histocompatibility complex (MHC) class II molecules on human endothelial cells and macrophages
  - statins modulate T-cell activation and differentiation, increase numbers of $CD4^{+}CD25^{+}$ regulatory T cells, reduce lymphocyte adhesion and pulmonary neutrophil influx, and inhibit expression of proinflammatory cytokines

    Atherosclerosis 2008;197(2):829–39
    Nat Med 2008;14(11): 1155–6

- Evidence in lung transplantation
  - one single-center retrospective study of 39 lung transplant recipients who were prescribed statins for treatment of hyperlipidemia and compared with a control group of 161
  - Six-year survival was significantly better in the statin group (91%) compared with the control group (54%)
  - treatment group had lower rates of acute rejection (15.1 vs 25.6% of biopsies, $p< 0.01$) and BOS. (0 vs 37%)

    Am J Respir Crit Care Med 2003; 167(9):1271–8

Extracorporeal Photopheresis

- Initially developed for the treatment of cutaneous T-cell lymphoma

  J Am Acad Dermatol 2009;61(4):652–65

- Clinical application in solid organ transplantation was first seen in kidney transplant patients

  Urol Res 1987;15(4): 211–3.

- ECP involves three steps:
  - Leukapheresis
  - ex vivo incubation of collected peripheral blood mononuclear cells with 8-methoxypsoralen (8-MOP)
  - photoactivation of 8-MOP with ultraviolet A (UVA) radiation

- Mechanism of action
  - Upon activation 8-MOP, covalently binds and crosslinks DNA, ultimately triggering leukocyte apoptosis
  - may modulate the alloimmune response by increasing the frequency of T-regulatory cells
  - May increase production of anti-inflammatory cytokines

  J Immunol 2005;174(10):5968–76

  J Heart Lung Transplant 2008;27(6):616–22

- Evidence in lung transplantation
  - First used in 1995 its use led to stabilization or mild improvement in PFT in 3 patients with refractory BOS

    N Engl J Med 1995;332(14):962

  - Retrospective single center review of 60 patients with progressive BOS despite enhanced immunosuppression, showed a significant reduction in the rate of decline in FEV1 in the 6 months preceding ECP initiation compared with the 6 months after ECP
  - Complications included CRBSI

    J Heart Lung Transplant 2010;29(4):424–31

Conclusion

- Induction therapy remains controversial in lung transplantation
- Data supporting superiority of one agent over the another remains limited
- Conventional agents including calcineurin inhibitors (CNIs; eg, cyclosporine, tacrolimus), antiproliferative agents (eg, azathioprine, mycophenolate mofetil [MMF], sirolimus), and corticosteroids remain the drugs of choice for immunosuppression
- Combination of tacrolimus azathioprine and oral corticosteroids constitutes the preferred initial regimen
- Novel approaches hold promise but need to be confirmed further with randomized trial

Acute Allograft rejection

- A common problem : Incidence of 36% during the first year[1]
- Is a major risk factor for bronchiolitis obliterans syndrome (BOS)
- Constitutes acute cellular perivascular (A-grade) rejection and acute cellular airway/ lymphocytic bronchiolitis (B- grade)[2] rejection
- Also includes acute humoral rejection (anti HLA antibody)[2]

1. J Heart Lung Transplant 2010;29(10): 1104–18
2. Clin Chest Med 32 (2011) 295–310

Risk factors for rejection

- **Allorecognition-related risk factors**
  - HLA mismatch increases the risk factor of acute rejection

    Am J Respir Crit Care Med 1998; 157:1833–7
    J Heart Lung Trans- plant 2000;19(5):473–9.
    J Heart Lung Transplant 1996;15(12):1209–16.

- **Immunosuppression-related risk factors**
  - Optimal regimen yet to be defined
  - Calcineurin inhibitor, cell cycle inhibitor and corticosteroid form the usual regimen
  - Adequate immunosuppression associated with lower incidence of rejection

    Clin Chest Med 32 (2011) 295–310

- **Recipient-related risk factors**
  - Genetic polymorphisms
  - Genotype leading to increased IL-10 production may protect against acute rejection, while a multidrug resistance genotype (MDR1 C3435T) appears to predispose to treatment- resistant acute rejection

    Clin Lab Med 2008;28(3):423–40.
    J Heart Lung Transplant 2004;23(5):541–6.
    Transpl Immunol 2005;14(1):37–42.

- **Infectious risk factors**
  - Community acquired infections like rhinovirus,parainfluenza virus coronavirus & RSV are associated with higher incidence of rejection
  - Studies directly linking cytomegalovirus (CMV) infection or CMV prophylaxis strategies with acute rejection have been inconsistent
  - CMV prophylaxis did not identify a correlation between CMV incidence and acute rejection rates

    Transplantation 2010;89(8):1028–33.
    Am J Transplant 2005;5(8):2031–6
    Chest 2001;119(4): 1277–80.
    Ann Intern Med 2010;152(12):761–9

Mechanism of allograft rejection

Direct pathway
T cells of donor act as APC

Indirect pathway
T cells of host act as APC

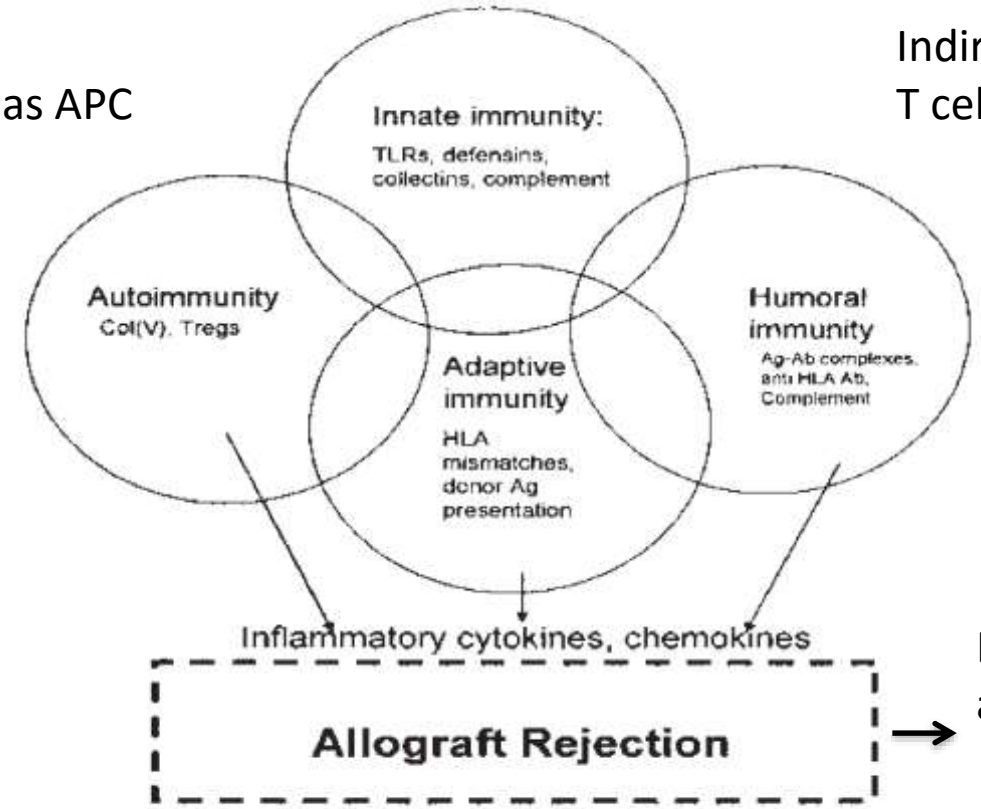

Figure 1 Immunological mechanisms of lung allograft rejection.

Recruitment & activation of recipient lymphocytes against allograft

Semin Respir Crit Care Med 2006;27(5):534–43.

Classification of rejection

Table 1
Pathologic grading of lung rejection

Category of Rejection	Grade	Severity	Histologic Appearance
Grade A: acute rejection	0	None	Normal lung
	1	Minimal	Inconspicuous small mononuclear perivascular infiltrates
	2	Mild	More frequent, more obvious, perivascular infiltrates; eosinophils may be present
	3	Moderate	Dense perivascular infiltrates, extension into interstitial space, can involve endothelialitis, eosinophils, and neutrophils
	4	Severe	Diffuse perivascular, interstitial, & air-space infiltrates with lung injury. Neutrophils may be present.
Grade B: airway inflammation	0	None	No evidence of bronchiolar inflammation
	1R	Low grade	Infrequent, scattered, or single-layer mononuclear cells in bronchiolar submucosa
	2R	High grade	Larger infiltrates of larger and activated lymphocytes in bronchiolar submucosa; can involve eosinophils and plasmacytoid cells
	X	Ungradable	No bronchiolar tissue available
Grade C: chronic airway rejection—obliterative bronchiolitis	0	Absent	If present describes intraluminal airway obliteration with fibrous connective tissue
	1	Present	
Grade D: chronic vascular rejection—accelerated graft vascular sclerosis		No grading	Fibrointimal thickening of arteries and poorly cellular hyaline sclerosis of veins; usually requires open lung biopsy for diagnosis

Abbreviation: R, revised.

Data from Stewart S, Fishbein MC, Snell GI, et al. Revision of the 1996 working formulation for the standardization of nomenclature in the diagnosis of lung rejection. J Heart Lung Transplant 2007;26(12):1229–42.

Acute cellular rejection[1]

Clinical	Laboratory
• Dyspnea • Cough (dry or expectoration) • ARDS • Fever • Hypoxia • Adventitious sounds	• Spirometry[2] – 60% sensitivity in detecting infection or grade A2 & higher – Does not differentiate b/w two – cities, septal ening, volume loss, and pleural effusions HRCT suggest acute rejection – Low sensitivity(35%) & no discriminatory value b/w rejection & other processes

TBLB remains the GOLD standard for diagnosis

1. Clin Chest Med 32 (2011) 295–310
2. Thorax 1997;52(7):643–7.
3. Radiology 2001;221(1):207–12.
4. Am J Roentgenol 2009;192(Suppl 3):S1–13

Clinical significance of rejection

- A single episode of acute rejection increases the risk of BOS[1,2]
- A1 rejection or a solitary perivascular infiltrate ?
  - Usually discounted & not treated
  - Enough evidence to suggest that A1 may increase risk of severe A2 or BOS[3,4]
  - Perivascular infiltrate worsens acute rejection[5]
- Grade B lymphocytic bronchiolitis is a risk factor BOS related deaths[6]

1. J Heart Lung Transplant 2002;21(2):271–81.
2. Transplantation 2008;85(4):547–53.
3. Am J Crit Care 2003;12(6): 497–507.
4. Transplantation 2005;80(10):1406–13.
5. J Heart Lung Transplant 2005;24(2): 152–5.
6. Am J Respir Crit Care Med 2008;177(9):1033–40.

Treatment

- Consists of increasing immunosuppression
- Grade A2 & higher should be treated
- Grade A1 & lymphocytic bronchiolitis may be treated
- Pulse steroids mainstay of treatment
  - 500 mg of methylprednisolone for atleast 3 days followed by oral prednisolone taper
  - But dose 0f 125-1000mg for 3-5 days also used
- Response to steroids variable early post transplant rejection responds better than late rejection
- Persistent rejection
  - A repeat course of steroids
  - Switching from cyclosporine to tacrolimus
  - Polyclonal antithymocyte globulin (ATG), anti-IL-2 receptor (IL2R) antagonists, or muromonab-CD3 (OKT3) are other alternatives
  - Inhaled cyclosporine, extracorporeal photopheresis,and total lymphoid irradiation may also be used

Clin Transpl 1998;327–40.
Respir Med 2009;103(8):1114–21.
J Thorac Cardiovasc Surg 2004;127(4):1126–32
Transfus Apher Sci 2002;26(3): 197–204.
Clin Chest Med 32 (2011) 295–310

Humoral rejection

- Antibody mediated allograft rejection are an important cause of graft dysfunction
- Antibody binding to allo-MHC or other endothelial or epithelial targets in the lung could lead to activation of the complement cascade & hence inflammatory cascade
- Compliment dependent cytotoxicity (CDC) assay has been used for HLA serotyping
  - Based on specific reactivity b/w serum antibody and cell surface antigen that activate compliment
- Solid phase technology is now used for HLA serotyping
  - More sensitive & specific
  - use a solid matrix coated with purified HLA antigens obtained from either cell lines or recombinant technology
  - detect both complement- fixing antibodies and non complement-fixing antibodies

Clin Chest Med 32 (2011) 295–310

Pre-transplant Considerations for Sensitized Patients

- Circumventing donor HLA antigen against which recipient has potential antibodies is the primary goal of donor selection
- About 10 to 15% of lung transplant recipients are presensitized to HLA antigens
- If detected interventions to remove or decrease production of these antibodies may be considered before transplantation

Hum Immunol 2005;66(4):378–86

Post-transplant Considerations in Sensitized Recipients

- Presence of anti HLA antibodies leads to increased incidence of acute rejection, persistent rejection, increased BOS, and worse overall survival
- Both pre-transplant HLA sensitization & de novo donor-specific anti-HLA antibodies after transplantation have same implications
- Non donor-specific antibodies might cross-react with the donor HLA, or get rapidly absorbed in the lung allograft precluding their detection in the sera.
- The extent & frequency of humoral rejection in transplant recipient is still unclear

Semin Respir Crit Care Med 2010;31:179–188
Clin Chest Med 32 (2011) 295–310

Clinical patterns

Hyper acute rejection	Acute rejection
• Caused by pre existing recipient antibodies against donor HLA antigens • Occur within hours of transplantation – Profound hypoxemia – Diffuse pulmonary edema – Alveolar hemorrhage – High mortality • Responds to aggressive antihumoral therapy	• Occurs weeks to years later • Vascular injury with pulmonary capillaritis – Dyspnea – Hypoxemia – Pulmonary infiltrates on radiography – Poor response to steroids may be a clue • May respond to plasmapheresis

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Clin Chest Med 32 (2011) 295–310

Treatment

- Plasmapheresis is the mainstay of treatment especially in severe cases
- IVIG is used more commonly
  - Causes B cell apoptosis
  - Blocks binding of donor reactive antibodies
  - Inhibits compliment activation
- Rituximab when used in conjunction with IVIG may also be used
- Bortezomib has also been used
- Survival and subsequent freedom from BOS is higher in patients who clear donor specific antibodies

J Heart Lung Transplant 2005;24(12):2091–7.
N Engl J Med 2008; 359(3):242–51.
J Heart Lung Transplant 2010;29(9):973–80
Transplantation 2010;89(1): 125–6.

Clinical spectrum of chronic graft dysfunction

- Classical BOS
- Neutrophilic reversible allograft/airways dysfunction
- Upper lobe fibrosis
- Exudative/follicular bronchiolitis
- Large airway stenosis/malacia

Chronic Allograft Dysfunction (BOS)

- First described in 1984
- Is an entity diagnosed clinically
- Initially coined to identify patients with a progressive and irreversible decline in forced expiratory volume in one second (FEV1)
  - the functional loss had to be present for at least 3 weeks to exclude an acute, reversible process
  - the loss had to include a decrease in both FEV1 and FEV1/vital capacity ratio (ie, patients with a loss in FEV1 in the context of a restrictive ventilatory defect are not considered as having BOS)
  - confounding conditions that may produce a decrease in FEV1 (eg, infection, acute rejection, anastomotic complications, disease recurrence, and progression of native lung hyperinflation in patients with single-lung transplantation [SLT] for emphysema) needed to be excluded
- However subsequently several other phenotypes have been identified (reversible, restrictive ventilatory impairment, exudative or follicular bronchiolitis, large airway stenosis/malacia)

Classical BOS

- The incidence of BOS is decreasing but still remains most common long term complication & leading cause of death
- It accounts for 20-30% deaths after third post operative year
- Clinical presentation is heterogeneous presenting as an acute illness or a gradually progressive decline in functions
- Diagnosis is clinical by demonstrating fall in FeV1 over baseline
- HRCT may be helpful & demonstrates air trapping on expiratory cuts
- With disease progression there is permanent colonization with aspergillus and/or pseudomonas

Bronchiolitis obliterans syndrome classification system

	1993 Classification	2002 Classification	
	FEV_1 80% or more of baseline	FEV_1 >90% of baseline *and* FEF_{25-75} >75% of baseline	BOS 0
		FEV_1 81% to 90% of baseline *and/or* FEF_{25-75} = or <75% of baseline	BOS 0-p
BOS 1	FEV_1 66% to 80% of baseline	FEV_1 66% to 80% of baseline	BOS 1
BOS 2	FEV_1 51% to 65% of baseline	FEV_1 51% to 65% of baseline	BOS 2
BOS 3	FEV_1 50% or less of baseline	FEV_1 50% or less of baseline	BOS 3

J Heart Lung Transplant 2002;21:297–310.
Clin Chest Med 32 (2011) 311–326

Neutrophilic reversible allograft/airways dysfunction[NRAD]

- First described by Gerhardt et al who demonstrated improvement in FeV1 in 5 out of 6 patients treated with azithromycin
- Approximately 1/3 of BOS patients in different stages may respond to macrolides
- BAL fluid demonstrates neutrophilia
- NRAD may start earlier & progress slower than classical BOS
- Increased sputum production, mucous plugging & bronchiectasis are a more prominent feature

Other forms of chronic graft dysfunction

- Upper lobe fibrosis
  - first identified in 13 of 686 LT recipients who developed upper lobe fibrosis
  - present as non specific interstitial opacities progressing slowly to honeycombing traction bronchiectasis and volume loss
  - restrictive ventilatory defect
  - Poor prognosis
- Exudative/follicular bronchiolitis
  - 13 of 99 transplant recipients with exudative bronchiolitis, which appearing as a tree-in-bud pattern on CT
  - May respond to azithromycin

Clin Chest Med 32 (2011) 311–326

Treatment

- Optimization of immunosuppression
- increasing the net level of immunosuppression (eg, by using high-dose methylprednisolone, cytolytic therapy, or methotrexate)
- changing the maintenance regimen (eg, by shifting from cyclosporine A to tacrolimus or from azathioprine to mycophenolate mofetil, or by adding inhaled cyclosporine A) in patients with established BOS
- Macrolides especially if BAL neutrophilia is present
- Statins may prevent BOS if started early after LT
- Use of photopheresis in cases not responding to conventional treatment may prove beneficial
- Retransplantation

Primary graft dysfunction

- Occurs within first 72 hours after LT
- Leading cause of early morbidity & mortality
- Affects 25 % of LT & No PREVENTIVE therapy
- Is a risk factor for Bronchiolitis obliterans syndrome
- Presents as ARDS

Table 1
ISHLT PGD grading schema

Grade	Pao_2/Fio_2	Radiographic Infiltrates Consistent with Pulmonary Edema
0	>300	Absent
1	>300	Present
2	200–300	Present
3	<200	Present

N Engl J Med 1999;340(14):1081–91.
Chest 2003;124(4):1232–41
Clin Chest Med 32 (2011) 279–293

Definition

Table 2
Proposed refinements to the ISHLT PGD Grading system

	ISHLT PGD Guidelines	Proposed Refinement
Definition of T0	<6 hours after final reperfusion (at the time of ICU admission)	At the time of ICU admission
Time points	T0, T24, T48, T72: use worse P/F (when multiple readings are available)	T0, T6, T12, T24, T48, T72: use P/F closest to these time points
CXR: unilateral infiltrates in BLT	No suggestions	Consider infiltrates only if bilateral
Type of transplant	Apply same criteria	Apply SLT and BLT separately

Abbreviations: BLT, bilateral lung transplant; CXR, chest radiograph; SLT, single lung transplant.
Data from Oto T, Levvey BJ, Snell GI. Potential refinements of the International Society for Heart and Lung Transplantation primary graft dysfunction grading system. J Heart Lung Transplant 2007;26:435.

Clin Chest Med 32 (2011) 279–293

Outcome

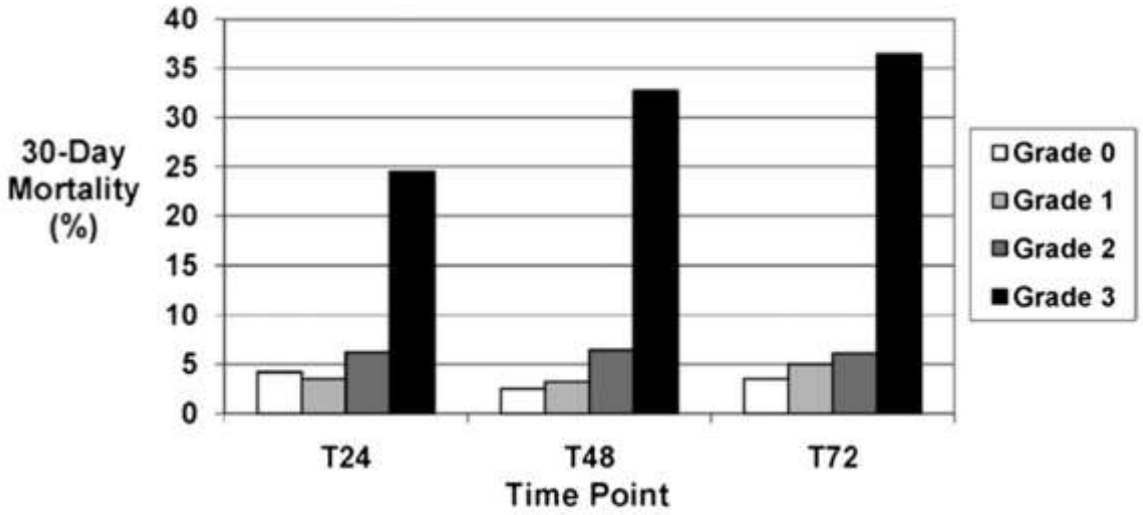

Fig. 2. Impact of primary graft dysfunction on 30-day mortality at different time points. (*Reproduced from* Christie JD, Bellamy S, Ware LB, et al. Construct validity of the definition of primary graft dysfunction after lung transplantation. J Heart Lung Transplant 2010;29:1236; with permission.)

Increased risk of BOS?

- Grade 3 PGD has the highest risk of BOS (RR of 3.31)
- Grade 1 & 2 have intermediate risk
- Grade of PGD at T0 can also predict the risk of future risk of BOS
- Pathogenesis
  - Initial
  - Multifa ation procedure
    - Pathophysiological changes in donor after brain death
    - Cold ischemia during organ preservation
    - Reperfusion in the recipient

Reactive oxygen species (ROS)

Am J Transplant 2008;8(11):2454–62.
J Heart Lung Transplant 2010;29:1231–9
Clin Chest Med 32 (2011) 279–293.

Prevention PGD

- Centers around lung preserving techniques
- Use of inhaled NO with equivocal results some studies showing benefit while others showing no benefit
- Use of iNO from the start of procedure till 48 hrs after transplant showed benefit
- Use of N-acetyl cysteine and activated protein C still experimental

Transplant Proc 2009;41(6):2210–2.
J Heart Lung Transplant 2009;28(11):1180–4
J Heart Lung Transplant 2010;29:1293–301.

Treatment

- Supportive
- Includes strategies applied to manage ARDS
  - Lung protective strategy
  - Avoidance of excessive fluid administration
  - iNO administration in severe PGD is beneficial
  - ECMO as a salvage therapy if started early (< 7days)

Heart Lung Trans- plant 2005;24(10):1489–500
J Thorac Cardiovasc Surg 2010;139(1): 154–61.
Am J Respir Crit Care Med 1997;155(6):1957–64.
J Thorac Cardiovasc Surg 2001; 122(1):92–102.
Ann Thorac Surg 2009;87(3):854–60.

Infections

- Important cause of early and late morbidity & mortality in transplant recipients
- Intensive immunosuppression increases the risk of acquiring infections
- Increase the risk of BOS subsequently
- Donor & recipient colonization, ineffective cough, post operative mechanical ventilation, mucociliary dysfunction, denervation all contribute to increased risks of infections
- Includes bacterial,viral,fungal & other opportunistic infections

Viral infections

Includes CMV,EBV, and others like RSV, influenza, parainfluenza, rhinovirus and adenovirus

- CMV is the most common opportunistic infection among LT recipients
- D^-/R^- low risk; D^+/R^- high risk
- Occurs 3-6 months after LT
- CMV prophylaxis
  - High risk : Valganciclovir or i.v ganciclovir for 6-12 month
  - Medium risk : controversial
    - Pre-emptive – monitor PCR every once or twice weekly
    - Universal- prophylaxis for all
- CMV infection : Viral replication
- CMV disease : Infection with symptoms
- Viral load cut off no uniformity Varies from 600 to 6000
- Treatment involves i.v ganciclovir (5mg/kg) till 1 week after no replication
- CMV sp IvIg can be used as an add on

- EBV mcc of post transplant lymphoproliferative disorder (PTLD)
- PTLD
  - Occurs in the setting of immunosuppression
  - Usually occur during first year after transplant
  - Polymorphic : B cells in various stages of maturation & reactive T cells
  - Monomorphic : transformed monoclonal B cells with cytogenetic abnormality, is a subtype of NHL
  - Presents as single, multiple nodules or masses, mediastinal LAD or pleural effusion
  - Beyond first year extra thoracic presentation more common
  - Treatment
    - De escalation of immunosuppression
    - Rituximab
    - CHOP
    - Surgery for local disease
    - Radiotherapy for local disease control

Bacterial infections

- Higher risk of colonization & infection with drug resistant organisms as compared to other solid organ transplantation
- Gram negative mc organisms
  - *P.aeroginosa* commonest organism
  - *ACB,E.coli, K.pneumoniae,Stenotrophomonas,B.cepacia* are other organisms
- *S.aureus* mc gram positive organism and second most common cause of bacterial pneumonia in LT recipients
- Due to immunosuppression LT recipients should receive prophylactic antibiotics covering *MRSA, P.aeruginosa* & atypical organisms as *listeria*,*mycoplasma*,*chlamydia*
- Sputum cultures of both recipient and donor are sent pre operatively & prophylactic antibiotics are planned accordingly and given for 7 days
- Antibiotics should be narrowed down as per cultures and need to given for atleast 14 days or longer if recovery is slow or cultures stay positive

Thorac Surg Clin 22 (2012) 403–412

Fungal infections

- Candida & aspergillus are mcc of colonization and infection in perioperative period
- Ischemic airway injury and previous colonization are the major risk factors for infection

Aspergillus species

- Commonest fungal infection in LT recipients
- Infection ranges from being localized to invasive
- Tracheobronchitis
  - Involvement of anastomotic sites & distal airways
  - Necrosis, ulceration, & pseudomembrane formation are characteristic
  - Risk highest in first 3 months
- Invasive
  - Non specific findings
  - Typical reverse halo is not usually seen
  - Galactomannan has a sensitivity of 30%
  - Diagnosis based upon clinico radiological & pathological findings
- Treatment
  - Azoles , AMP & echinocandins
  - Drug interactions with cyclosporine or tacrolimus needs to be monitored

Candida species

- C. albicans mc species
- Can cause muco-cutaneous to invasive disease with candidemia & multi organ involvement
- Echinocandins DOC for severe candida infections
- Copious secretions or ischemic airways and candida species in cultures need to be treated with either fluconazole or echinocandins

P.Jiroveci

- Universal prophylaxis has reduced the incidence
- Presentation as hypoxemic respiratory failure non specific findings on radiological
- Treated with trimethoprim/sulfamethoxazole along with corticosteroids

Other fungi

- Cryptococcus,mucormycosis are the other species
- Diagnosis primarily based upon histology

Prophylaxis

Universal : all patients with LT are given itraconazole or voriconazole with or without inhaled amphotericin

Targeted : patients with colonization with aspergillus

Nystatin or fluconazole for patients with oropharyngeal thrush

Thorac Surg Clin 22 (2012) 403–412

Mycobacterium

- Transplant recipients should be evaluated for latent tuberculosis
- Guidelines recommend treating latent infection
- NTM is common amongst patients with CF & bronchiectasis
- The risk of developing infections with NTM is highest with *M.abscessus*
- Treatment for both *M.tb*& NTM is similar to patients without LT

Thorax 2006;61:507–13
J Heart Lung Transplant 2006;25:1447–55.
Am J Respir Crit Care Med 2007;

Airways complication

- Complications at or around anastomotic site is a major cause of morbidity after LT
- Incidence of 7-15 %; mortality of 2-5 %
- Categorized as early (< months) or late (> 3 months)
- Risk of complication increases with a prior episode (35-70 % episodes recurring after 2 nd episode)
- No consensus exists regarding categorization of airway healing

Risk factors for airway complications

- Donor lung quality
  - Age< 50 years;< 20 pack years smoking history; PaO_2 > 300mmHg @ FiO_2 1.0
- Ischemia
  - allograft cold ischemic times should be limited to a maximum of 6 hours to minimize the risk of injury
  - Because bronchial artery is not anastomosed the circulation to the large airways is dependent upon pulmonary arteries
- Rejection & immunosuppression
  - Acute cellular rejection has been identified as an independent risk factor for bronchial complications
  - Use of sirolimus hampers bronchial anastomotic healing
- Surgical technique
  - end-to-end anastomosis ; interrupted suture or figure-of-eight suture ; short donor bronchus, within 1 to 2 cartilaginous rings of the upper lobe take-off,
- Infections
  - Colonization with aspergillus or Pseudomonas increases the risk

Malignancies

- Skin malignancy
  - Cutaneous squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) account for most cancers after SOT
  - predominantly affects sun-exposed areas
  - Prevention with protective clothing & sunscreen is the best measure
  - Switch from cyclosporine to sirolimus reduces the risk
  - Treatment is primarily surgical (Excision)
- Post transplant lymphoproliferative disorder
  - Caused by EBV
  - Monomorphic/polymorphic
  - Responds to chemotherapy
- Lung cancer
  - The risk of lung cancer after LT is between 0.25% to 4.0%
  - Higher risk in smokers, elderly, diagnosis of IPF or COPD

Clin Chest Med 32 (2011) 343–355

Conclusion

- Lung transplantation is the need of the hour
- Much evidence has been extrapolated from other solid organ transplantation
- Lung is unique in the sense that drugs can be administered via inhalational route
- Novel approaches of immunosuppression may improve outcomes in lung transplant recipients
- Much research is needed to further improvise the outcomes
- **Most importantly we need surgeons to do this for us**