Introduction

- First attempt of lung transplantation in 1963 by Hardy & coworkers
- First successful transplantation by Toronto group in 1983
- 1400 transplantations are done worldwide per year
- International society of heart-lung transplantation has registered > 14500 lung transplant recipients
Introduction

- Advances in operative technique & immunosuppression led to reduction in mortality rates to <10%
- 1 year survival of > 80%
- Improvement in post-transplant quality of life is noted
- Greatest risk factor for mortality is found to be ventilator dependency. (O.R. of 2.4)
- These patients not considered for transplantation.

Introduction

- Recently various other issues have been raised -
  1) Effect of obesity - high BMI: adverse effect on short term as well as long term survival
  2) Effect of gender combination: significant risk of primary graft failure is associated with Female to Male but beneficial results with Female to Female
Types of transplantations

- **Unilateral / Single lung transplant**: good results in patients with
  1) pulmonary fibrosis
  2) emphysema (small size & older patients)
  3) acceptable option in pulmonary hypertension

- Experience over past two decades shows that **bilateral lung transplants** shows better results

Types of transplantations

- Superior late survival
- Simpler early postop management
- Preferred modality in pediatric patients
- **Absolute indications** for bilateral lung transplantation -
  1) cystic fibrosis
  2) bronchiectasis
Types of transplantations

- Indications of **heart-lung transplantation**
  1) advanced lung disease with poor LV function
  2) complex congenital cardiac abnormalities
  3) Eisenmengers syndrome

Donor supply

- Increasing gap between demand & supply
- Newer strategies
  A) **Marginal donors**:-
    - Do not fulfill these rigid criteria-
    1. Age < 55 years
    2. Clear CXR
    3. No smoking history
    4. Sputum Gm stain negative
    5. Normal gas exchange
Donor supply

- Donor sputum positivity do not predict post-op outcome
- Majority of the donors are trauma and brain dead patients
- Fluid overload is common in prospective donors; diuretics significantly improve gas exchange
- Atelectasis common in potential donors:
  1) FOB- Aspirate secretions
  2) Alterations in ventilator settings

Donor supply

- Trauma victims - chest wall contusion may mimic a shadow in CXR
- Minor pulmonary contusions should not preclude successful transplantation
- Precautions while using these marginal donors
  - Should not be used in complicated procedures
  - Usually are not used for single lung transplantations
**Donor supply**

B) **Living lobar transplantation**
- Harvesting left Lower lobe from one healthy donor & right lower lobe from another
- pioneered by university of southern California program.
- Impressive results in both adults & children
- associated with significant complications but no fatalities have been reported

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**Donor supply**

- **Non-heartbeating donor**
  - Warm ischemia time after cardiac arrest an important marker of primary graft dysfunction
  - BAL fluid macrophages & IL1 levels correlate with warm ischemia time

- **Split lung transplant technique**
  - Left donor lung is divided; upper lobe is inserted in right hemithorax & lower in the left hemithorax
  - Does not increase number of donors
Donor supply

- Xenotransplantation
  - Initial enthusiasm- unlimited donor supply
  - Hardening factors-
    - 1) Severe immune response
    - 2) Apparent incompatibilities between the coagulation systems of two species
  - Investigational modality

(European resp. journal 2003; suppl.47)

Selection criteria

Criteria to define end stage lung disease in various diagnosis are still under way

- Age limits- Relative
  - 55 years - heart-lung
  - 60 years - bilateral lung
  - 65 years - single lung
Contraindications

**Absolute-**
1) Significant nonpulmonary vital organ dysfunction
2) active malignancy within last 2 years
3) HBsAg +ve
4) HCV with abnormal liver biopsy
5) Substance abuse in last 6 months

**Relative -**
1) symptomatic osteoporosis
2) severe musculoskeletal disease
3) unresponsive psychosocial issues
4) suboptimally treated medical conditions
   a) malnutrition
   b) mechanical ventilation
   c) HIV status- can be considered if CD4 count >200 or no AIDS defining criteria present
Disease specific selection criteria

**COPD**-
- FEV1 < 25% predicted (without reversibility)
- PaCO2 >55 mm of Hg
- elevated pulmonary artery pressure (PAP)
- cor pulmonale

Other indices shown to correlate mortality-
1) subjective breathlessness
2) weight loss
3) exercise tolerance
4) hospitalization
5) lung morphology
Disease specific selection criteria

- all patients requiring hospitalization for exacerbation should be considered for surgery
- 1 year mortality after hospitalization -23%

B) IPF-
- Highest attrition rate with waiting list mortality 30%
- due to high mortality & poor prognosis - 3 months credit on waiting list
- initially, owing to unpredictable nature of course, view was to refer all patients for transplantation at diagnosis
- patients with exercise induced desaturation are ideal candidates

_Chest_ 2005;127:1006-1016
Disease specific selection criteria

Current consensus-
1) symptomatic progressive disease despite 3 months of medical therapy
2) rest or exercise induced desaturation
3) symptomatic with
   - VC < 60-70% predicted
   - DLCO < 50-60% pred.

Cystic fibrosis

- Prognostic criteria-
  1) age per year
  2) sex
  3) FEV1
  4) weight for age
  5) pancreatic insufficiency
  6) D.M.
  7) S. aureus
  8) B. cepacia
  9) No. of acute exacerbations
Patients divided into 5 prognostic groups
- only group 1 & 2 with 5-year survival rate < 30% benefited
- resistant B. cepacia infection is absolute contraindication

Advancement in medical management - reduced need for transplantation
- 1990 - 10.5% of all cases
- 2001 - 3.6% of all cases
Criterias for PPH

- Symptomatic progressive disease despite optimal medical treatment for 3 months
- Cardiac index < 2 lit/min/m²
- Right atrial pressure > 15 mm Hg
- PAP mean > 55 mm Hg

Sarcoidosis

- Most patients benign course
- 10-20% permanent sequel
- 2.5% of all transplants
- Only stage 4 disease is considered
- FVC < 50% & FEV1 < 40%

*Chest 2005; 127(3), 1006-1016*
Lymphangioleiomyomatosis

- FEV1/FVC < 45%
- TLC < 113%
- Average from diagnosis to transplant - 11yr

Eisenmengers syndrome

- Better prognosis than patients with PPH with similar PAP levels
- Epoprostenol therapy improved survival & reduced need for transplantation
- Heart-lung transplantation is preferred
**Immunosuppression**

A) *Induction phase-*
- ATG
- Selective IL2 receptor antagonists

B) *Maintenance phase-*
- Steroid + calcineurin inhibitor
- Steroids (low dose) life long
- Tacrolimus for 1-5 years

**Newer drugs**

1) Sirolimus

2) Everolimus- used in combination with cyclosporin & prednisolone shown to have freedom from biopsy proven acute rejection in 88% cases
Complications

*Causes of respiratory failure after LTx*

- **Early**
  - Ischemia reperfusion injury
  - Infection
  - Technical problems
  - Acute rejection

- **≥3months**
  - Infections
  - BOS

Ischemia reperfusion injury

- Most frequent cause of early mortality
- Presents as ALI / ARDS
- Reduced incidence since 1990-
  1) Low K- dextran solution
  2) Nitric oxide added to flush solution
  3) Prevention of hyperinflation during harvesting
  4) Controlled reperfusion with leucocyte depletion

*Curr.opin.Crit.care 2006 Feb;12, 19-24*
Ischaemia reperfusion injury contd.

- **Treatment**-
  - diuretics
  - maximal ventilatory support
- **newer modalities**
  - inhaled nitric oxide
  - inhaled prostacyclin
- **Course**-
  - resolves in 48-72 hrs

Infections

- **Bacterial**-
  - pseudomonas predominate in early post op (75%)
  - nocardia-2.1%
  - legionella, mycobacteria rare

- routine antibiotic prophylaxis reduced the incidence
- sputum cultures & antibiotic sensitivity done every 3 months
Viral infections

- CMV predominates
  - within 30-100 days after transplant
  - occurs as reactivation or prim. Infection (donor)
  - incidence varies between 13-75% in various studies
  - routine prophylaxis replaced by close monitoring
  - Treatment-gancyclovir 5mg/kg for 2-3 weeks

- HSV&VZV can cause pneumonia
- Acyclovir prophylaxis effective in patients not on gancyclovir
- EBV related post-transplant lymphoproliferative disease
- 4-10% cases
- usually fatal outcome
- recently Rituximab (anti CD20 Ab) found effective
Fungal infections

- Aspergillus most common
  1) ulcerative trachitis
  2) bronchitis
  3) pneumonia
  4) disseminated disease
  5) ABPA- reported
- I.V. or aerosolised amphi-B used for prophylaxis

Other rarer organisms

- Histoplasma
- Sedosporium
- Pneumocystis jiroveci
Rejection

- Acute rejection-
- < 7 days onset
- low grade fever, dyspnoea
- CXR- 1) Clear
  2) illdefined infiltrates
  3) pleural effusion
- reduced FEV1

Acute rejection

- **TBLB** - gold standard in diagnosis
- Noninvasive means-area of active research
  1) Cytokine milieu in BAL fluid
  2) gene upregulation as a biomarker
- Treatment- bolus I.V. steroids + increase in maintenance immunosuppression
- role of surveillance bronchoscopy to detect rejection early is controversial
BOS (chronic rejection)

- Predominantly a small airway disease
- Occurs in 50% patients surviving for 5 years
- Onset > 6 months
- Major cause of mortality
- CXR - can be normal
  - Late cases - bronchiectasis
- HRCT - mottled appearance with peripheral lucency

BOS

- **TBLB - gold standard**
- Role of induced sputum & BAL -
  1) Induced sputum - RANTES levels & eosinophils correlate with BOS development
  2) BAL - IL8 & neutrophil levels have negative correlation

(J. of heart-lung transplantation; June 2006)
BOS

- Treatment - variable course even without treatment
- various immunosuppressive regimens tried
- macrolides under evaluation

BOS

- **Factors associated** -
  1) CMV pneumonia - no. of episodes
  2) HLA mismatch
  3) GERD - laproscopic fundoplication reduces incidence
Bridge to transplantation

- **Novalung** - lung assist device (low resistance)
- indicated in ventilation refractory hypercapnoea patients
- to overcome need supply mismatch
- to reduce waiting list mortality
- other indications - 1) severe chest trauma
  2) severe pneumonia
  3) ARDS
  4) weaning

*(J. of thoracic & cardiovascular surgery; 131; March 2006)*

Recent advances in prevention & management of prim. graft failure

- **TP 10** - short term complement inhibition
- soluble complement receptor inhibitor
- use led to early extubation & reduced duration of mechanical ventilation
- improved overall outcome

*(J. of thoracic & cardiovascular surgery; Feb. 2005)*
Recent advances in prevention & management of prim. graft failure

- **Perfinidone** - inhibitor of TNFα
- reduced post-transplant lung injury in rat lung transplant models
- presently in phase 2 trial for end stage IPF
- Also effective in bleomycin induced lung injury

*(jr. of thoracic & cardiovascular surgery; 130; Sept. 2005)*

Novel therapies for prevention of ischemia reperfusion injury

1) High dose steroids
2) NAC
3) P-selectin inhibitors
   They are under trial
Survival statistics

- **TORONTO GROUP**
  - 5 year survival - 44%
  - 6 year survival - 34%
  - 7 year survival – 29%
- **ISHLT**
  - 1 year survival – 76%
  - 3 year survival – 57%
  - 5 year survival – 43%
- Pulmonary fibrosis has worst outcome

Current issues

- To fulfil ever increasing gap between demand & supply
- Suitable & cost effective bridge to transplant
- Early recognition & prevention of rejection & ischemia -reperfusion injury by noninvasive means
- to reduce long term morbidity due to transplant & immunosuppressive medications
Indian perspective

- First heart-lung transplant in India in 1999 in Madras medical mission
- 2 more patients underwent transplant after that
- Initial experience is encouraging