LUNG TRANSPLANTATION

: CURRENT STATUS & INDIAN PERSPECTIVE

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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
- atelectesis 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

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

Criterias 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

Contraindications

- **Relative** -

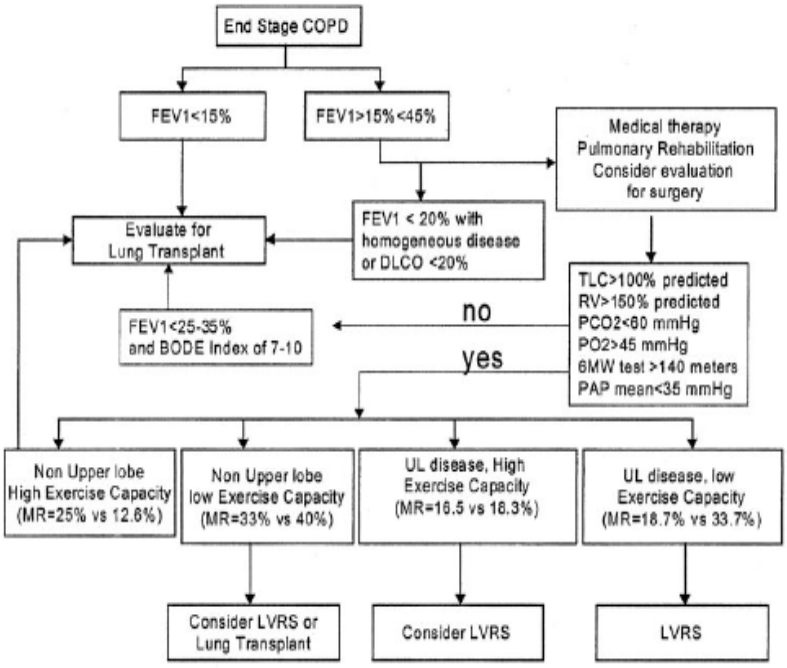
1)symptomatic osteoporosis
2)severe musculoskeletal disease
3)unresponsive psychosocial issues
4)suboptimally treated medical conditions
a)malnutrition
b)mechanical ventilation
c)HIV status- can be considered if CD4 count >200 or no AIDS defining criteria present

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 exacerberation should be considered for surgery
- 1 year mortality after hospitalization -23%

Chest. 2005;127:1006-1016

Disease specific selection criteria

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

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 exacerberations

Cystic fibrosis (contd.)

- Patients divided into 5 prognostic groups
- only group 1&2 with 5 year survival rate <30% benefited
- resistant B. cepacia infection is absolute contraindication

PPH

- 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/m^2
- right atrial pessure>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-**

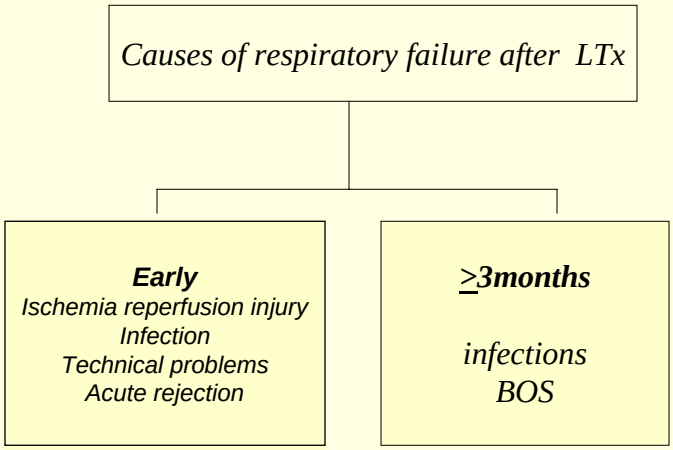
- Steroid + calceneurin inhibitor
- Steroids (low dose) life long
- Tacrolimus for 1-5 years

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



Curr.opin.Crit.care 2006 Feb;12, 19-24

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

Ischaemia reperfusion injury contd.

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

Infections

- **Bacterial-**
  - psuedomonas 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

Viral infections

- HSV&VZV can cause pnuemonia
- 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) pnuemonitis
4) disseminated diesase
5) ABPA- reported

- I.V. or aerolised ampho-B used for prophylaxis

Other rarer organisms

- Histoplasma
- Sedosporium
- Pnuemocystis jivorecti

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 > 6months
- major cause of mortality
- CXR- can be normal
  late cases- bronchiectesis
- 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 pnuemonitis -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 pnuemonia
  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 f eb.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