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Lung transplantation in India: A possible treatment option

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Review Article

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ABSTRACT

The burden of chronic respiratory diseases in India is on the rise, accounting for nearly 1 in 10 deaths. Chronic obstructive pulmonary disease is highly prevalent in India and is projected to be the third leading cause of deaths worldwide by 2020. Improved access to healthcare and better imaging modalities have led to an increase in the diagnosis of pulmonary fibrosis and cystic fibrosis in India. For these end-stage lung diseases, lung transplantation is an effective and established treatment option in North America and Europe. The indications, techniques, outcomes and complications of lung transplantation are well documented. The criteria for recipient/donor selection are now better defined and the surgical technique has improved over the past 2 decades. Based on our experience of setting up a lung transplantation programme, we have outlined the resources required for the perioperative and postoperative management of such patients.

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INTRODUCTION

With improved methods of diagnosis and effective management of chronic respiratory diseases in India, the number of patients with end-stage respiratory disease who may require lung transplantation for survival and/or long term quality of life is likely to increase. We discuss the indications, management and outcome of lung transplantation patients in the USA and, based on our experience, give details of the requirements to start a successful lung transplantation programme.

BURDEN OF RESPIRATORY DISEASES IN INDIA

Chronic respiratory diseases are on the rise in India, accounting for approximately 9% of all deaths in 2005.[1] Chronic obstructive pulmonary disease (COPD) was the fourth leading cause of death worldwide in 2001 and is expected to be the third leading cause of death by 2020.[2,3] Recent reviews of the epidemiology of COPD in India report prevalence rates of 2%–22% (median 5%) in men and 1.2%–19% (median 2.7%) in women.[4,5] A large multicentric study sponsored by the Indian Council of Medical Research (ICMR) estimated the prevalence of COPD to be 5% in men and 3.2% in women. This extrapolates into a national burden of more than 8 million men and 5 million women.[4,6] This figure is probably an under-assessment as the true prevalence of these diseases in the Indian subcontinent remains unknown because many patients with COPD have never been diagnosed or have been misdiagnosed. A study at the Hinduja Hospital of 2065 adults undergoing spirometry as part of a routine health check revealed that a staggering 96% of those with forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) <70% had not been correctly labelled and diagnosed as COPD.

By 2020 India alone will account for 18% of the 8.4 million tobacco-related deaths globally.[7] Thanks to greater availability of computed tomography (CT) and fibreoptic bronchoscopy in India, idiopathic pulmonary fibrosis (IPF) is now being diagnosed more often.[8] While estimates of the incidence and prevalence of IPF in India are scarce, the clinical spectrum and presentation of this disease appear to be similar to the clinical characteristics observed in western countries.[9] However, it has been noted that Indian patients seem to develop the disease a decade earlier than their counterparts in the West.[10]

Cystic fibrosis (CF), once thought to be primarily a disease of western populations, is now being diagnosed in patients of Indian origin who have emigrated to the USA and UK, with an estimated frequency of 1:10 000 to 1:40 000.[11–13] Although this is lower than the estimated incidence of 1:2500 in Caucasians,[14] the clinical characteristics and disease progression of Indians diagnosed with CF are similar. CF has also been observed in children living in India. As the present prevalence rates remain unknown, paediatric pulmonologists strongly suspect that CF cases in India are often misdiagnosed and therefore underreported.[11] It is anticipated that as the quality of healthcare continues to improve in India, CF will be diagnosed more often and survival of patients will improve, as is the case in western countries. Consequently, an increasing number of patients could live long enough to develop end-stage lung disease.

LUNG TRANSPLANTATION: A TREATMENT OPTION?

One of the final treatment options in the algorithm for end-stage lung disease from these conditions is lung transplantation. The first human lung transplant was performed by Dr James Hardy at the University of Mississippi, USA, in 1963. The patient survived for 18 days before succumbing to complications.[15] Twenty years later, following improvements in immunosuppressive therapy and surgical techniques, Joel Cooper and Alexander Patterson (senior author of this article) from the University of Toronto

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reported the first long term survivor following lung transplantation.[16–18] Since then, lung transplantation has become an accepted and effective surgical treatment for a variety of end-stage lung diseases.[19] The International Society of Heart Lung Transplantation (ISHLT), which has a global registry of all lung transplants (*www.ishlt.org/registries*),[20] has accrued data on 23 716 lung recipients. Worldwide, more than 2000 lung transplants are performed annually. About 50% of these transplants take place at 23 centres with an average activity of >30 transplants per year.[21]

Dr K. Cherian was the first in the Indian subcontinent to perform a successful heart–lung transplant in Chennai in 1999. Since then, he has performed 2 more successful heart–lung transplants.[22]

WHO RECEIVES LUNG TRANSPLANTATION IN THE WEST?

According to internationally recognized, standard criteria, lung transplantation is offered to patients who have severe end-stage lung disease despite maximally aggressive medical therapy, or to patients for whom no effective medical therapies are available. Prospective transplant patients have a limited life expectancy (usually <2 years); it is anticipated that the transplant will provide both a survival benefit and an improvement in the quality of life. The patients should be capable of full rehabilitation post-transplantation and must demonstrate an adequate psychosocial profile. Absolute contraindications that preclude lung transplantation include extrapulmonary organ dysfunction, malignancy, hepatitis B and C virus infections, and HIV infection. In addition, current or recent history of smoking, alcoholism or drug abuse precludes eligibility for transplant. Relative contraindications include age >65 years, malnutrition, dependence on mechanical ventilation, infectious diseases, obesity and severe osteoporosis.

The indications for lung transplantation can be divided into 4 main categories:

1. Obstructive lung disease: COPD, alpha-1 antitrypsin deficiency emphysema, obliterative bronchiolitis
2. Suppurative lung disease: Cystic fibrosis, bronchiectasis
3. Interstitial lung disease: Idiopathic pulmonary fibrosis and other causes such as sarcoidosis, connective tissue diseases, etc.
4. Vascular: Pulmonary hypertension, Eisenmenger syndrome.

In the October 2007 ISHLT registry report, the main indications for lung transplantation were COPD (37%), idiopathic pulmonary fibrosis (19%), cystic fibrosis (16%), and alpha-1 antitrypsin deficiency emphysema (8%). Figure 1 shows the indications of adult lung transplantations over the time period 1990–2005 (Data reprinted with permission from ISHLT).

WHO IS AN IDEAL LUNG DONOR?

The ideal lung donor (Table I) is one who has been pronounced brain dead. From a medical standpoint, donors should be <55 years of age, have minimal to no smoking history, a clear chest X-ray, no evidence of pulmonary infection on bronchoscopy and sputum Gram stain, and a pO_2 >300 mmHg on 100% FiO_2 and minimal positive end-expiratory pressure (PEEP, 5 cm H_2O). However, since the demand for donor lungs currently exceeds the supply, these selection criteria are not rigidly followed. Favourable outcomes using 'extended donors' have been reported from several centres.[23,24] However, the debate is ongoing among health professionals and medical ethicists in many countries about the use of non-heart-beating donors, who do not meet the criteria for brain death but have irreversible brain injury.[25] Living lung donors have also been utilized in selected circumstances; this option continues to be closely scrutinized from both the medical and ethical standpoints.[26,27]

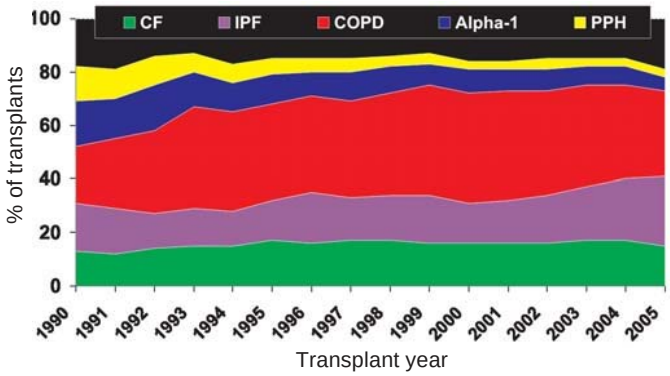

FIG 1. Indications for adult lung transplantation (%)
CF cystic fibrosis IPF idiopathic pulmonary fibrosis
COPD chronic obstructive pulmonary disease
Alpha-1 alpha-1 antitrypsin deficiency emphysema
PPH primary pulmonary hypertension
(Reproduced with permission from Elsevier Limited)

TABLE I. Criteria for an ideal lung donor

- Age <55 years
- Clear chest X-ray
- Smoking history <20 pack-year
- PaO_2:FiO_2 >300
- Sputum Gram stain free of organisms
- Bronchoscopy with clear secretions
- Absence of chest trauma
- ABO group compatability

LUNG TRANSPLANTATION SURGERY: A SAFE TECHNICAL PROCEDURE

Lung transplantation surgery has evolved into a safe technical procedure over the past 2 decades. Advances in lung preservation, immunosuppression and technical refinements have significantly improved the outcomes following lung transplantation. Surgery can be done with or without the use of cardiopulmonary bypass depending on the indication for the operation and the experience of the surgical team. The types of operations include:

1. Single lung transplant: This procedure can be done for most indications (COPD, IPF) except for patients with suppurative lung disease such as cystic fibrosis and bronchiectasis.
2. Bilateral lung transplant: This procedure is mandatory for suppurative lung diseases (cystic fibrosis and bronchiectasis) and can be done for all other indications.
3. Heart–lung transplant: This operation is reserved for patients with end-stage cardiac and pulmonary disease (Eisenmenger syndrome).[28]

Better overall survival rates in recipients of bilateral lung transplants compared with those in patients who underwent single lung transplants[21,29] are largely responsible for the popularity of bilateral lung transplants. The ISHLT registry data indicate that 63% of current transplants are bilateral.

In the largest single-centre experience from the Washington University School of Medicine, St Louis, USA, the operative mortality for adults undergoing lung transplantation was 7.1%

and the mortality for the paediatric population was 16.1%. The most significant perioperative morbidity is primary graft failure and the incidence was about 23% in their experience (Table II).

LUNG TRANSPLANT CERTIFICATION IN THE USA

Lung transplant surgeons are trained cardiothoracic surgeons who require additional dedicated training for lung transplant surgery during their cardiothoracic residency or an additional year of training in the USA. The United Network for Organ Sharing (UNOS), a central governing institution that regulates all transplant activity in the USA, requires a lung transplant surgeon to have experience with a minimum of 15 harvests and 15 implantations at a UNOS-certified institution, before being certified to do lung transplantation independently. UNOS requires a lung transplant physician to be a pulmonologist with additional training in taking care of at least 15 lung transplant patients. The pulmonologists have to be involved in the pre-transplant assessment, perioperative care and post-transplant management of these patients. They also need to be involved with at least 3 donor management, organ harvest and implantations. Medicare requirements for reimbursement of procedural costs for an institution are that they perform a minimum of 10 transplants with good outcomes on an annual basis for hospital certification.

POST-LUNG TRANSPLANT IMMUNOSUPPRESSION

About half the patients receiving lung transplants receive perioperative induction therapy. Use of polyclonal antilymphocyte/antithymocyte globulins to prevent immune rejection of the graft has declined in recent years, whereas the use of a monoclonal interleukin-2 receptor antagonist had risen until 2005 but then sustained a modest decrease. Maintenance immunosuppression usually involves a 3-drug regimen: prednisone, a calcineurin inhibitor (cyclosporin/tacrolimus) and cell cycle inhibitor (azathioprine/mycophenolic acid). A patient for whom maintenance immunosuppression is initiated will remain on therapy for the rest of his/

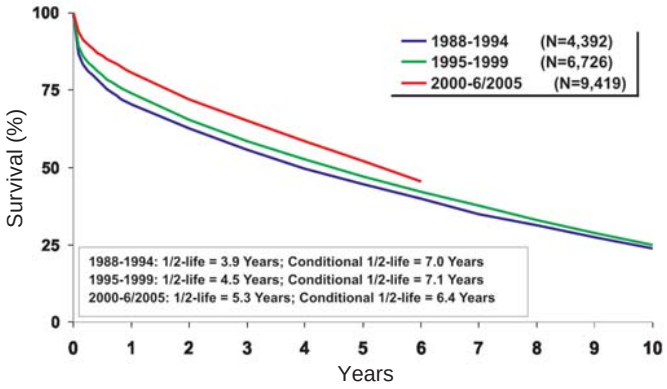

FIG 2. Kaplan–Meier survival by era for adult lung transplantation (1988–2005) (Reproduced with permission from Elsevier Limited)

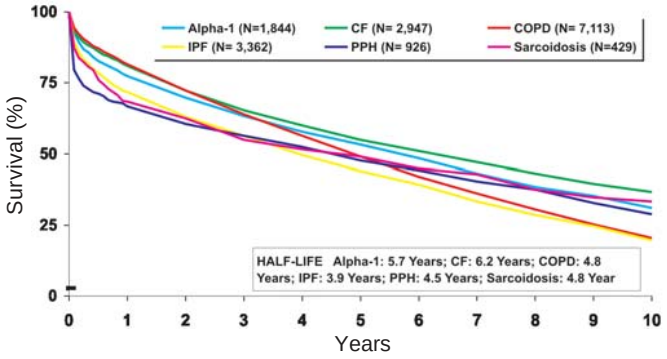

FIG 3. Kaplan–Meier survival by diagnosis for adult lung transplantation (1994–2004) (Reproduced with permission from Elsevier Limited)

TABLE II. Data of recipients transplanted at the Washington University, St Louis, USA programme

Item	Paediatric (*n*=277)	Adult (*n*=706)
Age (years)		
Mean	10.7 (SD 6.4)	47.6 (SD 12.2)
Median	12.1 (IQR 5.4–15.8)	50.5 (IQR 38.9–57.6)
Gender (female)	156 (56.3)	357 (50.6)
Diagnosis		
Emphysema	0	399 (56.5)
Cystic fibrosis	138 (49.8)	118 (16.7)
Pulmonary vascular disease	71 (25.6)	63 (8.9)
Other pulmonary disease	68 (24.6)	126 (17.8)
Type of transplantation		
Bilateral	204 (73.6)	526 (74.5)
Single	8 (2.9)	176 (24.9)
Heart–lung	16 (5.8)	4 (0.6)
Bilateral lobar (living)	39 (14.1)	0
Bilateral lobar (cadaveric)	4 (1.4)	0
Single lobe	1 (0.4)	0
Bilateral–liver	5 (1.8)	0
Mean duration of mechanical ventilation (days)	5 (IQR 2–14)	2 (IQR 1–4)
Stay in ICU (days)	7 (IQR 4–17)	3 (IQR 2–5)
ECMO support after transplantation	27 (9.7)	20 (2.8)
Primary graft dysfunction	62 (22.4)	160 (22.7)
Hospital mortality	46 (16.6)	50 (7.1)

Values in parentheses are percentages unless specified IQR interquartile range ICU intensive care unit
ECMO extracorporeal membrane oxygenation

her life. The cost of immunosuppression, depending upon the regimen used, is about US$ 1500–2000 per month (*see* Table III). In the USA, Medicare Part B covers 80% of the cost after an annual deductible charge of US$ 100 and the remaining 20% of the cost is either out-of-pocket or patients can have supplemental insurance for the same.

Table III. Monthly expenditure on immunosuppressive drugs

Drug	Number	Cost (US$)
Neoral, gengraf, 25 mg	180 caps	295
Neoral, gengraf, 100 mg	180 caps	1160
or		
Tacrolimus, 1 mg	200 caps	295
Tacrolimus, 5 mg	60 caps	1061
or		
Sirolimus, 1 mg (not used frequently)	30 tabs	243
	150 tabs	1188
and		
Mycophenolate mofetil, 500 mg	120 caps	746
	180 caps	1115
and		
Prednisone, 5 mg	120 tabs	10

LONG TERM RESULTS

The benchmark survival rates for lung transplants are 87% at 3 months, 78% at 1 year, 62% at 3 years, 50% at 5 years and 26% at 10 years. Mortality is highest in the first year following transplantation. In the first 30 days following transplant, primary graft dysfunction is the most important cause of morbidity and accounts for the majority of deaths. Beyond that, infectious complications continue to be a cause of morbidity and mortality for up to a year. Chronic rejection, also known as bronchiolitis obliterans syndrome (BOS), remains the Achilles' heel of lung transplant survivors and is the foremost long term cause of death. Almost 50% of patients will have some degree of BOS by 5 years.[21] However, long term survival is improving over the past 2 decades among various working groups (Fig. 4).

Despite potential post-transplant complications, the procedure significantly improves the quality of life of recipients. More than 80% of post-transplant patients have no activity limitations; this benefit in survivors is seen even beyond 10 years. About 50% of 3-year survivors report that they have returned to either part-time or full-time work (Fig. 5).[21]

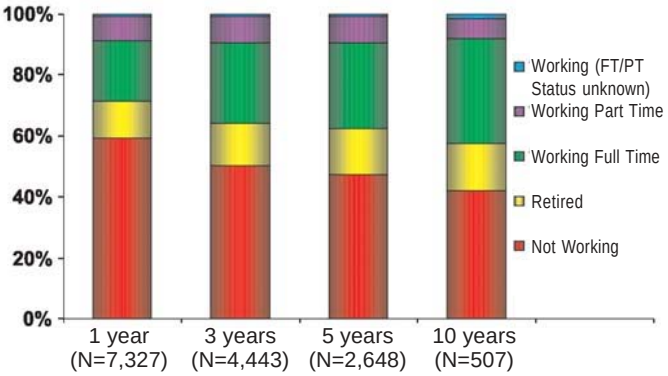

Fig 4. Employment status of survivors following lung transplantation (Reproduced with permission from Elsevier Limited)

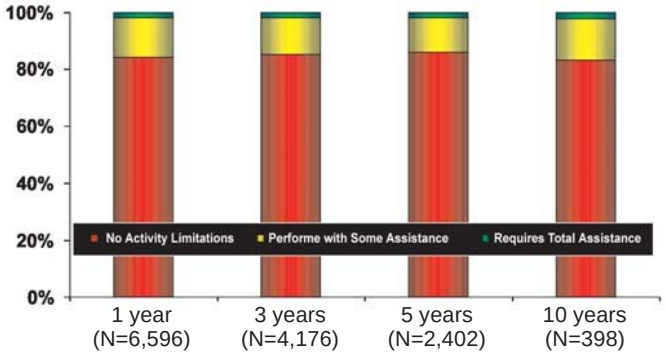

Fig 5. Functional status of survivors following lung transplantation (Reproduced with permission from Elsevier Limited)

EARLY COMPLICATIONS

Acute rejection

Acute allograft rejection is one of the most common complications following lung transplantation. Data from several large series document that only 8%–24% of recipients escape rejection in the first year following transplantation.[30,31] The importance of acute rejection lies in the fact that it is an important predictor of development of chronic rejection. The Lung Rejection Study Group (LRSG) has classified acute rejection into 2 components based on histological findings:

1. Perivascular inflammation, which is graded as follows: A0 (no rejection), A1 (minimal), A2 (mild), A3 (moderate) and A4 (severe).
2. Airway inflammation, which is graded as follows: BX (unknown), B0 (none), B1 (minimal), B2 (mild), B3 (moderate) and B4 (severe).

To date, no predictors for the development of acute rejection have been delineated. Induction therapy in the form of interleukin-2 receptor blocker or antithymocyte globulin has been shown to reduce the incidence of acute rejection.[32,33]

Clinically, rejection presents as an upper respiratory tract infection with symptoms of cough, dyspnoea, low grade fever and fatigue. The diagnosis is usually made on transbronchial surveillance bronchoscopy and biopsy. Currently, all rejection graded A2 and above are treated with a pulse of steroids and an alteration in the maintenance therapy. Confirmation of resolution of the acute rejection with a follow up biopsy after 4–6 weeks is important due to its significant contribution to the pathogenesis of chronic rejection.

Primary graft dysfunction

Primary graft dysfunction is a form of acute lung injury that complicates lung transplantation. It remains the most important cause of morbidity and mortality in the early postoperative period following transplantation. Poor oxygenation, decreased lung compliance, interstitial oedema, elevated pulmonary vascular resistance and pulmonary infiltrates on chest X-ray are the characteristic clinical features of this condition. Patients remain ventilated for a prolonged period of time and in severe cases require extracorporeal membrane oxygenation (ECMO) support.[34] Treatment options include ventilatory support, diuresis, pulmonary vasodilatation, ECMO and urgent re-transplantation in severe cases.

Airway anastomotic complications

Before the era of cyclosporin, airway complications were a major cause of mortality following lung transplantation. The bronchial arteries are not re-constituted during implantation and the donor

bronchus has to rely on the pulmonary circulation in the early days following surgery. Post-transplantation pulmonary parenchymal pathology decreases this collateral flow and renders the donor bronchus ischaemic which leads to anastomotic complications. The incidence of airway complications that require intervention is about 10% in the modern era. Airway complications increase the cost associated with transplant and decrease the quality of life but do not appear to affect survival.

LATE COMPLICATIONS

Chronic rejection/bronchiolitis obliterans syndrome (BOS)

BOS is the major cause of late morbidity and mortality following lung transplantation. It is characterized by a progressive decline in graft function with an obstructive physiology. Clinically, it presents as a decline in FEV_1 from the baseline. It is a diagnosis of exclusion after all other causes of decreased lung function have been eliminated. Histologically, BOS is characterized by fibrous obliteration of the respiratory bronchioles. It affects almost 50% of lung transplant recipients by 3 years and remains the leading cause of late death following transplantation. The median time to diagnosis for BOS is 4.3 years in adult recipients. The pathogenesis of BOS is believed to be multifactorial and treatment usually involves alteration of immunosuppression or re-transplantation in selected cases. Table IV shows the classification of BOS.

IS IT WORTH IT?

While there is no doubt that lung transplantation improves the quality of life among its recipients, questions about the procedure's cost-effectiveness remain unanswered. It is estimated that, on an average, lung transplantation would cost approximately US$ 200 000–250 000, not including preoperative evaluation and follow up care.[35] The cost varies widely, both from centre to centre and with the diagnosis of the recipient. Liver transplants in India are about 20% as expensive as in western countries,[36] and we would anticipate that lung transplants in India would also entail reduced cost. Cost-effectiveness research to date has attempted to balance financial data with findings regarding both quality of life and costs of care for patients who do not undergo transplant for chronic end-stage lung diseases and, while the jury is still out, there is evidence of cost-effectiveness for certain subsets of patients who undergo lung transplantation.[37–39]

THE BARE ESSENTIALS TO START A LUNG TRANSPLANT PROGRAMME

In this age of outcomes-driven and cost-effective medicine, starting a lung transplant programme can be a challenging and daunting task. Besides the need for adequately trained and dedicated personnel experienced in lung transplantation, the key to success is the need for administrative and financial support from the respective institution/government in the early phases of development of the programme. The personnel absolutely necessary to start up a programme include at least 2 trained surgeons capable of performing all aspects of lung transplantation, a team of trained cardiothoracic anaesthesiologists and one (preferably 2) transplant pulmonologist(s). Other important members of the team include a transplant nurse coordinator(s), social worker, clinical psychologist, transplant pharmacist and a financial manager. The institution should have a dedicated perfusion team capable of providing not only cardiopulmonary bypass support in the operating room but also ECMO, if necessary in the postoperative period. The education of the nursing staff and physicians who will be involved in the care of these patients in the intensive care unit and wards cannot be overemphasized. Finally, the institution must have the basic infrastructure and support in terms of blood bank, histocompatibility leukocyte antigen (HLA) laboratory, clinical laboratory capable of monitoring immunosuppressive drug levels, endoscopy suites, pulmonary function laboratory and physical therapy.

TABLE IV. Classification of the bronchiolitis obliterans syndrome (BOS)

Class	Criteria
0	FEV_1 >90% of baseline and $FEF_{25\%–75\%}$ >75% of baseline
0–P	FEV_1 81%–90% of baseline and $FEF_{25\%–75\%}$ <75% of baseline
1	FEV_1 66%–80% of baseline
2	FEV_1 52%–65% of baseline
3	FEV_1 <50% of baseline

THE FUTURE

The founding of the Indian Society of Organ Transplantation in the 1980s (*www.isot2007.org*), and the subsequent passing of the Transplantation of Human Organs Act (Act No. 42 of 1994) by the Indian Government, were important steps in the implementation of a countrywide solid organ transplantation programme. This has translated into the development of some successful liver, kidney and other organ transplant/organ-sharing networks across India.[36,40] Other developments have included the initiation of the Multi Organ Harvesting Aid Network (*www.MOHANfoundation.org*) in 1997, Organ Retrival and Banking Organization (*www.aiims.edu/aims/orbo*) and the Indian Transplant Registry (*www.transplantindia.com*) in 2005. These physician/patient partnerships have made progress in their goal (according to MOHAN's mission statement) to 'popularize the cause of organ donation' by distributing donor cards and educational materials about organ donation, and by providing patients with transplant programme information and support.

Despite diligent efforts of activists in the transplant community, there remains a need for a central regulatory organization similar to the non-profit scientific and educational United Network of Organ Sharing (*www.unos.org*), which administers the organ procurement and transplantation network in the USA. Such an organization would enhance infrastructure to increase organ donation and procurement. Another important aspect of successfully developing organ transplantation in India lies in the education of its masses about the importance of donating organs.

There is passionate debate in India about spending money on newer procedures and technology compared with spending money on preventive healthcare. Experience in the USA has shown that the costs of lung transplantation are outweighed by the long term benefits. In India, in the field of transplantation, healthcare policy leaders have shown foresight in future planning. The central Ministry of Health and Family Welfare has already sanctioned Rs 600 crore to start 6 tertiary healthcare centres with transplant facilities in India by 2013. These facilities will be similar to the one at the All India Institute of Medical Sciences (AIIMS). The goal is to have at least one transplant centre in every state by the year 2020. Even private institutions such as the Global Hospitals Group are investing Rs 700 crore to set up transplant facilities in cities such as Chennai, Delhi, Kolkata and Mumbai. Organ transplantation in India is heading in a positive direction although it may not be at the pace that patients and physicians would like but the time may be right to consider lung transplant as a treatment option for end-stage lung diseases in India.

CONTRIBUTIONS

GAP leads one of the most successful and pioneering lung transplant programmes in the world at the Barnes-Jewish Hospital in St Louis, MO, USA while KP has successfully started a Lung Transplant program at the University of Iowa, Iowa, USA.

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