Lung Transplantation for Pulmonary Sarcoidosis

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1. Introduction

Sarcoidosis, a multisystem disorder, results in the production of multiple non-caseating granulomas capable of affecting all organs of the body. It usually occurs in patients between the ages of 10 and 40 years of age in 90% of cases. The prevalence has been reported to be 10-20 per 100,000 in the general population however the annual incidence is 107 per 100,000 (Rybicki, Major et al. 1997). There also appears to be a variation in the racial prevalence of the disease with Caucasians having a 0.85% lifetime risk for the disease while the lifetime risk for Black Americans is 2.5% (Rybicki, Major et al. 1997). The racial implications of the disease are not just confined to prevalence, evidence suggests that along with the increased prevalence of Sarcoidosis Black American patients also have a more acute and severe process in contrast to the usually slow insidious symptoms commonly seen in Caucasian patients (Newman, Rose et al. 1997). Familial clustering has also been identified in linkage studies and this has identified the short arm of chromosome 6 as the area of most interest (Baughman, Lower et al. 2003).

Despite intense study an exact etiology for Sarcoidosis has remained elusive for investigators, leaving many to speculate as to the pathogenesis of the disease. Most commonly the respiratory system is the primary target of the disease, in addition to this the skin and eyes are regularly affected leading researchers to believe that an environmental cause was the most likely cause. Many associations have been suggested ranging from wood burning stoves to inorganic particles, insecticides and moulds (Bresnitz and Strom 1983; Newman, Rose et al. 2004; Rybicki, Amend et al. 2004). The recent advancement in technology and the use of polymerase chain reaction to amplify the genetic products of sampled tissue resulted in the discovery of mycobacterial antigens in serum samples taken from patients with Sarcoidosis (Song, Marzilli et al. 2005). Most investigators however favour an immune response abnormality and that the antigen in question is of lesser significance. Evidence for this was seen with the association between human leukocyte antigen variants and Sarcoidosis, especially the good correlation between HLA-DQB1*0201 and acute disease with a good prognosis (Sato, Grutters et al. 2002).

The majority of Sarcoidosis affected individuals do not develop progressive fibrotic disease; indeed, two thirds of patients will have a remission with half achieving this within three years. The response once achieved is also favourable with less than 5% of patients achieving remission in one year subsequently having a relapse. In essence this results in one third of

patients developing progressive disease in addition to the 5% of patients who have a relapse. While the numbers with significant disease are less than the potential that might be affected, with 90% of patients presenting with respiratory impairment, the implications for surgery could be significant.

In Mississippi, over 47years ago, the first human lung transplant was performed on a patient with emphysema and lung carcinoma of the left main bronchus (Hardy, Webb et al. 1963). The patient survived for 18 days; 20 years later surgeons in Toronto performed another procedure with the use of coronary bypass technology and since then it has developed into a significant part of the clinical armamentarium used to treat a number of end stage lung diseases including Sarcoidosis. Improved outcome from lung transplantation has been attributed to better use of immunosuppression, surgical techniques and better donor selection. Recipients have also been scrutinised for acceptability with some believing that a multisystem disease such as Sarcoidosis might result in increased deaths postoperatively. This turned out to be unfounded as long as the individual patients fulfilled the routine testing requirements outlined below.

In order to assist in making the process of transplantation more transparent and equitable the method by which lungs are distributed in the United States has recently been updated. Diseases are given a number calculated from clinical parameters which is weighted based on the likelihood of surviving one year before transplantation and one year after transplantation. The calculated number, referred to as the LAS (lung allocation score), is based on historical data and is to be reviewed on a regular basis to maintain its accuracy(Egan, Murray et al. 2006). Sarcoidosis figures are therefore based on previous outcomes and survival data, and due to the low numbers of transplants performed historically for Sarcoidosis, patients may benefit when the reviews are performed. Outside the United States many units rely on clinical parameters and regular outpatient reviews to decide on urgency both for listing and organ allocation. This review will detail when patients should be referred and listed for lung transplantation and the complications that can be encountered during the process.

2. Diagnosis

To accurately diagnose Sarcoidosis three criteria are required. These include consistent clinical and radiographical features, supporting histology classically described as non-caseating epithelioid cell granulomas, and the exclusion of other causes of granulomatous disorders. Unless patients present with a characteristic Lofgren's syndrome a biopsy of the affected organ is usually necessary, however, considering the multisystem nature of the disease the area easiest to access can be used, for example a cervical or axillary lymph node.

2.1 Clinical presentation

Up to 50% of patients with Sarcoidosis may be asymptomatic at the time of diagnosis. Many patients will in fact be suspected of having the disease based on findings during incidental radiological testing. If present the respiratory system is most commonly involved with symptoms reported in 40% of patients. These symptoms usually manifest as dyspnoea, cough which can be productive or non-productive of sputum, chest pain, or haemoptysis in decreasing order of frequency. Constitutional symptoms are also reported in up to 40%with patients reporting fatigue, malaise, weight loss, night sweats, chills and fever. These features

are also more frequently reported in Black patients and patients from the Indian subcontinent.

Acute presentation with Lofgren's syndrome has been reported in 9-34% of cases comprising arthritis, erythema nodosum and bilateral hilar adenopathy (Siltzbach, James et al. 1974). Women may present differently with this syndrome affected predominantly with erythema nodosum, while men usually develop ankle periarticular inflammation and no erythema nodosum. The frequency of other organ involvement including liver, spleen, cardiac, ocular, central and peripheral nerve involvement is listed in Table 1.

Clinical Symptoms	Rate (%)
Asymptomatic	12-50%
Constitutional Symptoms	15-40%
Respiratory Symptoms	15-40%
Skin	10-35%
Eyes	10-25%
Joints	5-17%
Neurological	5%
Cardiac	5%

Table 1. Frequency of Clinical symptoms

2.2 Radiological features

As only 50% of patients have symptoms at diagnosis radiological features have become central to diagnosing and staging Sarcoidosis. Although there is a pantheon of modalities now available for radiological investigation not all have been assessed in Sarcoidosis. Chest X-Ray (CXR) remains the commonest first investigation to raise the suspicion of Sarcoidosis. As CXR has long been available the common abnormalities associated with Sarcoidosis are well described. These include bilateral hilar lymphadenopathy, with or without interstitial infiltration, nodular changes or fibrosis. This has resulted in the classification of Sarcoidosis into four stages based on the array of findings that might be present. Stage 1 is bilateral hilar lymphadenopathy without parenchymal infiltration, stage 2 is bilateral hilar lymphadenopathy with parenchymal infiltration, stage 3 is parenchymal infiltration without hilar enlargement, and stage 4 has hilar retraction, bullae, fibrotic banding, traction bronchiectasis and diaphragmatic tenting (Scadding 1961).

Computed tomography (CT) develops superior views of the thoracic cage and so has superseded the CXR for usefulness in the diagnostic algorithm. CT scanning can identify subtle changes in the parenchyma allowing staging to be more accurately applied to the patient. Identification of ground glass opacification in this way may also identify steroid responsive disease (Murdoch and Muller 1992). In addition parenchymal markings identified before bronchoscopy allows a targeted approach to transbronchial biopsies.

Although no longer part of routine assessment due to poor sensitivity Gadolinium 67 scanning has previously been used. If present a classical distribution of uptake involving the lung parenchyma, hilar nodes, parotid and lacrimal gland (the 'panda' sign) favours a diagnosis of Sarcoidosis (Sulavik, Spencer et al. 1990). It has been suggested however that Gadolinium may be useful in the diagnosis of cardiac Sarcoidosis in combination with other modalities (Niida, Isoda et al. 2009).

A recent report on positron emission tomography (PET) scanning suggests that using fluoro-alpha-methyltyrosine in combination with 18-F-fluorodeoxyglucose-PET may be beneficial in allowing a better distinction between malignancy and Sarcoidosis (Shulman, Latkany et al. 2009). Magnetic resonance imaging on the other hand has been extensively used in the diagnosis of systemic and especially cardiac Sarcoidosis (Mehta, Lubitz et al. 2008). Its use in parenchymal lung Sarcoidosis is limited; however, there is a role for its use to rule out the presence of mediastinal fibrosis as a cause of pulmonary artery impingement syndrome (Dhote, Vignaux et al. 2003).

2.3 Investigations and diagnostics

Historically the Kveim-Siltzbach test has been utilized for diagnosis and involves the intradermal injection of a homogenate of human Sarcoid tissue, this is followed up four weeks after the injection when a papule has formed at the site. The papule is then biopsied and assessed histologically for classical histological features of Sarcoidosis. Currently its use is limited by the lack of commercial antigen availability, current controls with regards the use of human tissue and new preparations requiring validation in vivo therefore it is reserved for use when lesions are not easily accessible, which in reality is uncommon (Iannuzzi, Rybicki et al. 2007).

Histological findings in Sarcoidosis are characteristic but by no means are they pathognomic. The classically described epithelioid granuloma may be found in any organ of the body and usually consists of distinct lesions with epithelioid cells and multinucleated giant cells at the centre. In the lung it usually involves the peri bronchial, interstitial and subpleural compartments. Associated vasculitis is not a common feature and when present other diagnoses should be considered in the differential. Indeed the granulomas themselves may be preceded by an interstitial pneumonitis with macrophage and lymphocyte infiltrates, although the exact relationship between the extent and severity of these activated macrophages and lymphocytes and the extent of granuloma formation subsequently is not well understood. The finding of non–caseating granulomas requires further evaluation in order to exclude other causes some of which are listed in Table 2.

Laboratory investigations have been poor in confirming the diagnosis of Sarcoidosis but helpful in ruling out other possible causes. Non-caseating granulomas associated with Sarcoidosis are known to produce angiotensin converting enzyme and research has shown it to be elevated in 75% of patients with Sarcoidosis (Studdy and Bird 1989). Its use as a diagnostic test, however, has been hindered because the level can be raised in many other diseases some of which are listed in Table 2. Bronchoalveolar lavage samples taken at bronchoscopy have found an associated imbalance in the CD4/CD8 ratio in Sarcoidosis. When this ratio is elevated to greater than 3.5 it has a specificity of 95%, unfortunately the specificity is low at 59% (Costabel, Bonella et al. 2010). Lavage samples also assist in ruling out many of the infective causes of granulomatous disease.

Inflammatory	Sarcoidosis
	Berylliosis
	Granulomatous Vasculitis
	Eosinophilic Granuloma
	Hypersensitivity Pneumonitis
	Crohn's Disease
Infection	Mycobacterial Infections
	Fugal infections
	Syphillis
	Leprosy
	Catscratch Disease
	Parasitic Infection
Neoplasia	Carcinoma
	Lymphoma

Table 2. Differential Diagnosis for Non Caseating Granulomas

Use of lung function testing may contribute to diagnosis if the pattern of spirometry is consistent. Usually however its use is reserved for follow up and assessment of treatment. Most patients have a restrictive deficit on spirometry but in 50% there is a coexisting obstruction as evidenced by a reduced ratio of forced expiration in one second to forced vital capacity. Interestingly, this obstruction has been shown in some patients to be reversible (Baughman, Teirstein et al. 2001; Shorr, Torrington et al. 2001). The advantage of lung function testing in Sarcoidosis is that it may highlight other disease for example in patients with a conspicuously low diffusion capacity for carbon monoxide out of proportion for the spirometric values might suggest a pulmonary vascular component is present. As a means of follow up in patients commenced on treatment lung function is useful with studies suggesting that abnormalities returns to normal in 80% of patients after two years (Judson, Baughman et al. 2003).

Acquiring tissue for histological assessment has also changed over the recent decades. While tests like the Kveim test had their place, the most commonly affected organ is the lung and as a result this has become the most commonly accessed site for most patients. Open or video-assisted thoracoscopic biopsy remains the gold standard as direct visualisation allows identification of granulomas in 90% of cases. Mediastinoscopy has also been performed and while it possesses a high sensitivity rate it is an invasive procedure with a morbidity rate that may render it unjustifiable in many cases.

Development of the fibreoptic bronchoscope has allowed targeted transbronchial biopsies to be performed whish has resulted in a high yield for lesions in a peribronchial distribution. A minimum of four transbronchial biopsies are needed to guarantee sufficient tissue for diagnosis, while reports using this method demonstrated a sensitivity of 90%(Gilman and Wang 1980). The development of endobronchial ultrasound has also advanced the diagnostic capabilities of bronchoscopy. The advantage of this approach is that not only can transbronchial lung biopsies be performed but enlarged mediastinal lymph nodes can also be targeted for tissue sampling. The use of endobronchial ultrasound in many centres have negated the need to perform mediastinoscopy, and in expert hands the sensitivities can

approach 96% with specificities of 100% (Costabel, Bonella et al. 2010). The safety profile of linear endobronchial ultrasound is also superior to that of mediastinoscopy and in many centres where it is available it has become the investigation of choice.

It remains difficult to devise a severity index for Sarcoidosis although there have been some attempts. The six minute walk test has significant age and racial variability however lung function and diffusion capacity race, immunosuppression use and organ involvement have all been incorporated into an algorithm of severity however it remains to be validated (Wasfi, Rose et al. 2006; Alhamad 2009).

3. Treatment

Most patients with Sarcoidosis will recover spontaneously and don't require any pharmacological treatment, in those that do the most commonly used agents are corticosteroids. These are usually indicated when patients are significantly symptomatic, have decreasing lung function or diffusion capacity over a 3-6 month period, or have advancing radiological disease. Treatment is also indicated for extrapulmonary disease including neurological, ocular, renal calcification or hypercalcaemia (Baughman, Costabel et al. 2008). Other agents have also been assessed for use but these are usually reserved for those who have had a poor response to corticosteroids, have side effects or in patients who have coexistent adverse events and are intolerant of lower doses of corticosteroids (1999). Alternative therapies have included methotrexate, most commonly, but also azathioprine and leflunamide (Baughman, Costabel et al. 2008). These agents can be used either alone or in combination, however, if the response is still unsatisfactory Infliximab (tumour necrosis factor-alpha antagonist) can be considered as an alternative. While a number of other agents have been considered useful their use has delivered unsatisfactory results. Some of the agents trialled include colchicine, cyclophosphamide, mycophenylate mofetil, pentoxyphylline and non-steroidal anti-inflammatory agents (Fazzi 2003).

3.1 Timing of transplantation

Referral for transplantation has always been the Achilles heal of Sarcoidosis treatment. Of particular concern in Sarcoidosis is the difficulty gauging the extent of organ involvement, identifying which patients will respond to treatment, and which test is the best prognostic indicator. Factors that need to be considered when deciding about the timing of lung transplant referral include making sure all avenues of treatment have been exhausted leaving lung transplantation as the 'last option', prognosis needs to be within the transplantation window where the patient has a survival advantage from surgery, while the patient also needs to be in sufficient health to survive the procedure. Most transplantation centres accept a combination of factors to decide when patients should be accepted for transplant workup.

Extensive fibrocystic disease in stage 4 disease is more likely to derive benefit from lung transplantation. Other stages of disease also need to be observed closely in the outpatient setting to watch for worsening radiological changes and clinical status as this may be the onset of treatment failure. Arterial blood gases revealing a $PaCO_2 > 6.7$ kPa (50 mm Hg) or a $PaO_2 < 7.3$ kPa (55 mm Hg) are suggestive of more advanced disease, although, while they are evidence of more extensive disease they have not been found to be useful in terms of prognosis or identification of progressive disease. Lung function is also a useful indicator when following patients and a forced vital capacity between 40-50% with or without a declining diffusing capacity below 40% are likely to be symptomatic on exertion if not at rest

and should be referred for consideration (Judson 1998). Another factor to take into consideration is the impact of disease on quality of life and the patient's ability to cope with the disease. If the patient satisfies some or all of these parameters then referral for transplant assessment is prudent.

Recently the development of pulmonary hypertension has been shown to be a good discriminator for future survival (Corte, Wells et al. 2010). Research has revealed that the likelihood of mortality on a lung transplant waiting list with a diagnosis of Sarcoidosis was equivalent to that for patients with idiopathic pulmonary fibrosis although Sarcoidosis patients were less likely to receive a transplant. For Sarcoidosis patients pulmonary hypertension had more impact on the disease than for those with idiopathic pulmonary fibrosis and may have contributed to the Sarcoidosis deaths (Shorr, Davies et al. 2002). Evidence of clinical decline with or without a decline in lung function or diffusion capacity should prompt investigation with an echocardiogram, if there is evidence of onset of pulmonary hypertension referral for consideration of lung transplantation should be considered.

3.2 Lung transplantation workup

Screening is used in order select the most appropriate patients for the process of lung transplantation. The process ensures not only the appropriate choice of recipient but also ensures that the donor families can see that due diligence is performed with respect to the ultimate allocation the donor organs. Recent data shows that for all deceased donor lung transplants the 1, 5, and 10 year survival is 83, 54 and 29 percent respectively (OPTN/SRTR 2009). Patients with a 20-30% one year survival should be considered appropriate for lung transplant work up (Christie, Edwards et al. 2008).

There are a number of tests that are performed as part of transplant workup that are in no way particular to one or other of the many diseases that are considered suitable for lung transplant. These are investigations required to assist in guiding the patient successfully through the process and are listed in table 3. Sarcoidosis is a multisystem disorder and therefore potentially represents a higher risk to transplant recipients in terms of post-operative complications. A number of other organs may be involved and so diligent pretransplant screening needs to be undertaken to optimize decision making prior to surgery.

Additional factors that are of particular concern when assessing patients with Sarcoidosis include the involvement of the thoracic cage. Patients with advanced disease, especially stage 4 disease associated with fibrocystic changes may present with mycetomas or pneumothoraces. Mycetomas causing haemoptysis may cause significant difficulty prior to surgery however most difficulty arises after transplantation with immunosuppression treatment (Rafferty, Biggs et al. 1983). If any fungal infection is brought through the operation there is a significant risk of anastomotic breakdown. Therefore patients with any evidence of cystic lesions on radiology investigations receive bilateral lung transplants decreasing this risk. Multiple pneumothoraces or prolonged thoracotomy tube placed as therapy may also result in pleural reaction and fibrosis that can hinder dissection at the time of transplantation. If this is extensive or if pleurodesis has been carried out the case may be too difficult with a high risk of bleeding, more often than not however, patients can be wait-listed with extra dissection time added into the protocol on the night.

In addition to pleural disease patients who have extensive mediastinal involvement need careful assessment as mediastinitis also can result in difficult dissection during surgery, in

addition, if there is any evidence of impingement of the pulmonary artery with right heart failure then stenting of the pulmonary arteries may improve symptoms significantly delaying or negating the need for listing (Figure 1C). Ventilation/perfusion scans are unreliable in this instance as the significance of the obstruction may be difficult to assess and a Magnetic Resonance Angiogram gives a detailed outline of the mediastinal structures completing the workup.
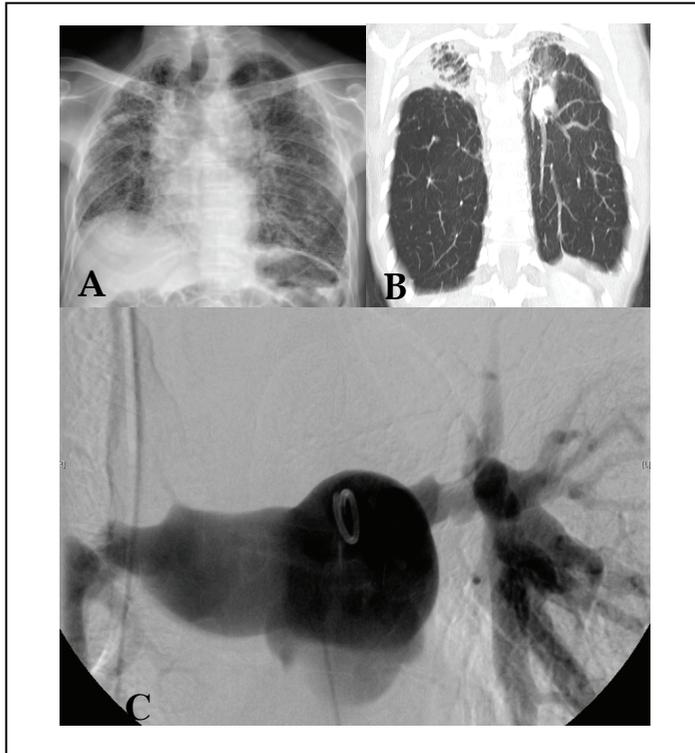

Fig. 1. Sarcoidosis Complications impacting on surgery: A) Tracheal deviation, B) pleural reaction, C) mediastinitis causing pulmonary artery outlet obstruction.

The skin, the second most common organ to be involved with up to 25% of patients affected to some degree, usually manifests itself in the form of macules, papules, plaques or indeed the classical lupus pernio involvement of the lips, cheeks and nose (Yanardag, Pamuk et al. 2003). While this type of disease is not a contraindication to lung transplantation one needs to be mindful of the potential for impaired site healing or indeed wound infection if the cutaneous region around the potential incision site is involved.

The liver and spleen may also be involved with 10 percent of patients having an elevation in their alkaline phosphatase and aminotransferases (Baughman, Teirstein et al. 2001). CT analysis of the hepatosplenic system in Sarcoidosis patients found that the liver developed granulomatous lesions in 5 percent of patients with the spleen having granulomatous involvement in 15 percent. While these figures might be higher than

previously thought the nature of liver disease in Sarcoidosis is mainly of insidious onset and clinically quiescent (Scott, Berman et al. 1997). Less than 1 % of the time does significant liver disease like portal hypertension, variceal bleeding, hepatopulmonary syndrome and liver failure occur and in terms of lung transplant work up a CT scan of the abdomen in combination with laboratory parameters is usually sufficient to assess the integrity of the liver and spleen unless indicators such as haematemesis or refractory hypoxia are present.

Cardiovascular investigation represents an important area in patients with Sarcoidosis. Clinically cardiac involvement is thought to be 5 percent however cadaveric studies have shown the figure to be around 25 percent in one series (Iannuzzi, Rybicki et al. 2007). There is a low yield with cardiac biopsies and this hinders the identification of cardiac involvement. The likely reason for this is that the left free wall and septum are more commonly involved resulting in cardiomyopathy or arrhythmias. While these may be identified on routine echocardiography and electrocardiograms the use of MRI/PET with gadolinium are useful in screening for cardiac involvement (Ohira, Tsujino et al. 2008).

Immunosuppression and steroid induced diabetes post lung transplantation results in a higher risk of renal impairment. Macrophages in Sarcoidosis granulomas activate 25-hydroxy-vitamin D to 1,25-dihydroxyvitamin-D resulting in hypercalcaemia (11%), hypercalciuria (40%) and renal calculi (10%) while intrarenal calcium deposition can result in renal failure (Berliner, Haas et al. 2006). All represent a potential risk to patients post transplantation and so patients are screened with 24-hour urinary calcium excretion examination, 24-hour creatinine clearance, and CT abdomen is also performed.

Eighty percent of patients have ocular Sarcoidosis manifest by anterior and posterior uveitis. (Atmaca, Atmaca-Sonmez et al. 2009). This needs to be flagged in the pre-transplant clinic, as there is the added complication of steroid induced cataracts in the post-operative period. In addition there is an increased incidence of neurological Sarcoidosis associated with anterior uveitis, while neurosarcoid is only symptomatic 10% of the time any neurological symptoms should be investigated with an MRI with gadolinium (Menezo, Lobo et al. 2009). A positive result with significant symptoms would rule out transplantation.

3.3 Types of surgery

Sarcoidosis has been subject to most modes of lung transplantation over the decades however some are more advantageous than others. Heart lung transplantation was initially performed and can still be offered if the heart is deemed likely to be unrecoverable post transplant. This is not commonly performed now because experience has taught us that the heart can recover quite well after transplantation (Bando, Armitage et al. 1994), however, even for those in whom the heart is too impaired the paucity of donors has meant the numbers have dwindled over time.

Single lung transplantation on the other hand maximizes the donor pool and increases the chance for more patients on the list to be successfully transplanted. There is some debate as to whether single lung transplantation leaves the patient more susceptible to earlier decline in lung function due to the deficiency of the extra tissue. However we have previously published on our data showing a strong long-term survival in patients receiving a single lung transplant for interstitial lung disease of all types (Keating, Levvey et al. 2009).

Laboratory Studies	Full blood count & Coagulation testing Urea, creatinine and electrolytes Calcium, phosphorous, amylase Liver & Thyroid function tests Total protein and albumin Fasting lipids 24-hour urinary creatinine clearance Urine analysis including cotinine
Microbiology and Serology	Sputum analysis - bacterial and fungal cultures Tuberculosis – Quantiferon Testing Syphilis - RPR, VRDL Urine culture Cytomegalovirus, Epstein Barr virus, toxoplasmosis, Varicella-zoster virus, herpes simplex virus, Human immunodeficiency virus Hepatitis A, B, and C virus
Immunologic Assessment	ABO blood typing Lymphocytic cytotoxic antibody crossmatch Human leukocyte antigen typing Lymphocyte cytotoxicity screen Quantitative immunoglobulin and subclasses
Cardiac Assessment	12-lead electrocardiogram Cardiac gated blood pool scan Echocardiogram Thallium stress testing Cardiac catheterization – if > 40 yrs coronary arteries & ventriculogram, +/- right heart catheter +/- Cardiac Magnetic Resonance Imaging
Pulmonary Assessment	Spirometry, DLCO, lung volumes, arterial blood gases Computed Tomography of the chest Ventilation-perfusion scan Chest x-ray - PA and lateral, and AP supine Exercise capacity - 6-minute walk test with pulse oximetry
Vaccines	Human papilloma vaccine in females Pneumococcal Vaccine Hepatitis A (if seronegative) Hepatitis B (if seronegative)
Miscellaneous	Gynaecological exam & Mammogram > 35 years DEXA scan of spine and hips Prostate-specific antigen >55 years Nutritional assessment including BMI Dental evaluation Psychosocial Evaluation Physiotherapy consultation

Table 3. Lung Transplant work-up protocol

Others have also suggested that due to the shorter operation time single lung transplantation may be preferable for those who might benefit from a brief anesthetic exposure (Low, Trulock et al. 1992).

There are however particular situations where bilateral sequential lung transplantation is more advantageous. This particularly applies to Sarcoidosis patients who have stage IV disease. In this setting the presence of traction bronchiectasis and the presence of resistant microbes make the necessity for this procedure absolute. It is not advisable to leave a potentially infected native lung in situ if there is evidence that it harbors resistant organisms such as pseudomonas aeruginosa, scediosporum profligans or aspergillus. So while there is no research suggesting one form of surgery is superior to another in survival terms, some authors suggest bilateral transplantation should be performed on patients with severe secondary hypertension, fibrocystic Sarcoidosis, mycetomas, and bronchiectasis (Alalawi, Whelan et al. 2005).

Sarcoidosis patients most commonly have a restrictive lung disease and as a result lung size is diminished. In order to accommodate the change in size the lung function is used to compute the size a potential match should be. If there is a size discrepancy it may be necessary to perform cadaveric lobar lung transplantation. This may also be the result if there is a pediatric recipient, when the decision to perform a lobar cut down can be electively taken at the time of listing. Outcomes from this type of surgery are similar to other surgeries allowing patients previously discriminated against based on size mismatch to be transplanted successfully (Keating, Marasco et al. 2010). For similar reasons living donor lobar lung transplantation was developed in order to decrease waiting list times. While there is a theoretical 300% mortality risk, to date this has procedure has shown itself to be well tolerated (Barr, Schenkel et al. 2005). Its use has diminished recently following the introduction of the lung allocation score in the United States however it is still used in countries where culture differences with regards to brain death are still hindering donor procurement.

While the type of surgery being performed has changed, so too has the method by which it is performed. Bilateral sequential lung transplantation has superseded the en bloc approach. The use of lung transplantation over heart-lung transplantation has also developed as our experience has grown. The approach has also differed from midline approach to a clamshell horizontal incision. This now has also been modified in certain individuals to a bilateral thoracotomy incision that allows adequate access to the thoracic cavity but leaves the sternum intact. When patients such as those with Sarcoidosis have had significant exposure to corticosteroids then sternal healing may be impaired and by using this approach a more satisfactory outcome can be achieved.

3.4 Perioperative considerations

A number of issues need to be considered on the night of transplant specifically when considering the multiorgan involvement associated with Sarcoidosis. It is crucial that while on the waiting list that all personnel with a role in the transplant process are kept abreast of any new developments that might arise. This is usually achieved by regular outpatient review with follow up debriefing session with staff. It is through this attention to detail that allows coordinators, physicians and operators to organize a smooth transition through the procedure.

As part of workup patients are screened for renal impairment, if there is any suggestion that renal function may deteriorate as a result of the procedure it is possible during the perioperative period to consider alternative strategies. This might include include withholding preoperative immunosuppression and alternatively using Basiliximab a chimeric monoclonal Interleukin-2 receptor antibody with less nephrotoxicity than calcineurin inhibitors Tacrolimus and Cyclosporin. It acts as an antagonist at the interleukin-2 binding site of the p55 subunit of the high affinity Interleukin-2 receptor on the surface of the activated T lymphocytes and has been shown to decrease the incidence of acute rejection but not chronic rejection in lung transplant recipients (Borro, De la Torre et al. 2005).

3.4.1 Anesthetic considerations

As the fibrotic component of the disease advances Sarcoidosis patients develop tracheal deviation (Figure 1A). While in the majority of the cases this is not a significant issue there is a minority of patients who present on the night of transplant with a severely distorted trachea. This represents a particular problem for anesthetic staff with responsibility for inserting a double lumen endotracheal tube to allow independent lung ventilation necessary to perform a bilateral sequential lung transplant. In most cases this can be achieved, however it adds to the ischaemic time if there is a large time delay.

Routine preoperative anesthetic care involves the insertion of an epidural to adequately titre pain relief post operatively. In patients with severe end stage fibrosis this may be essential as they may have been treated preoperatively with opioid agents for excessive dyspnoea and distress thereby blunting their response to regular doses of analgesia. While in the usual setting this procedure is more routine, in the case of end stage fibrosis patients with labile oxygenation and possible vertebral fractures is requires a greater level of competence and expertise to ensure success.

3.4.2 Intraoperative considerations

Likewise for patients with stage III disease the process may extend to abut or involve the pleura. In this scenario it may be surgically challenging to remove the recipient lungs from the thoracic cavity. This can be assessed by using computed tomography of the chest and assessing the pleural involvement visually, if there is evidence of pleural thickening or adhesion it would be prudent to allow more 'dissection time' when organizing the procedure.

As stated previously the identification of pulmonary hypertension prior to listing is a useful indicator for prognosis in patients with Sarcoidosis. In addition this information is also crucial on the night of transplantation as there is a higher incidence of patients with pulmonary hypertension needing cardiac bypass. This procedure results in deoxygenated blood being removed via large bore cannula placed usually in the vena cava, being externally oxygenated, filtered, warmed and then returned to the circulation via a second large bore cannula usually placed in the ascending aorta. Some debate exists about the need for cardiac bypass in routine lung transplantation, however in the setting of pulmonary hypertension it can prevent hemodynamic collapse when the pulmonary artery is clamped. In addition is prevents any sudden increase in pulmonary pressures after clamping which might increase the after-load on the right ventricle. With underlying hypertension this could result in right heart failure and decompensation. As a result most centres will have cardiopulmonary bypass on standby in transplant cases where there is evidence of increased

pulmonary pressures preoperatively (Marczin, Royston et al. 2000). In some patients with severe pulmonary hypertension and high oxygen requirements a decision to commence cardiopulmonary bypass prior to induction of anesthesia may be made. This allows the anesthetist time to correctly position the endotracheal tube without the risk of sudden and catastrophic desaturation occurring. When this is performed a different approach is used with cannulation of the femoral artery and vein.

Hyperacute rejection is one of the more devastating complications that occurs following lung transplantation surgery. On releasing the cross-clamp the flow of blood into the new lung results in an immediate reaction within minutes that can herald a terminal decline. The mechanism is thought to be pre-existing antibodies formed against ABO blood groups, endothelial cells or human leukocyte antigens (Frost, Jammal et al. 1996). This results in parenchymal damage that pathologically resembles diffuse alveolar damage characterized by mononuclear and polymorphonuclear accumulation, intravascular thrombosis and intramural vascular necrosis. Many centres now use more sensitive antibody testing such as Luminex, which allows a better assessment of the match between donor and recipient. This has decreased the incidence of hyperacute rejection and while it still represents a significant immediate complication there is some possibility that the patient can be stabilized, transferred onto extracorporeal membrane oxygenation and urgently relisted.

3.4.3 Early post-operative considerations

Most of the gains that have been achieved in lung transplantation over the last two decades have been as a result of early post-operative management. The recognition of problems that might arise not just as a result of transplantation but also in relation to the recipients underlying disease has allowed physicians to pre-empt issues rather than react to them as they arise. Some of the problems that affect Sarcoidosis patients are related to the transplant process, however some they will have a predilection to.

Immunosuppression is commenced pre-operatively and continued post operative while being closely followed using serum measurements of trough levels. Most centers use a triple immunosuppression regimen consisting of a calcineurin inhibitor (Cyclosporin or Tacrolimus), Azathioprine or mycophenylate, and corticosteroids. Basiliximab may be used in preference to the calcineurin inhibitors initially to preserve renal function. Preoperative assessment in Sarcoidosis patients usually highlights those that should be prescribed the Interleukin-2 inhibitor electively. All agents can be given intravenously initially and changed to the oral route when feasible (Snell and Westall 2007).

Ischemia reperfusion injury is used to describe non-cardiogenic edema that usually occurs approximately 24 hours after lung transplantation in up to 97% of patients. It peaks by day four, resolving usually by day seven however, it may continue for up to six months. Putative contributing factors include surgical trauma, donor lung ischemia, and interruption of bronchial circulation, lymphatic flow and donor lung innervation (Collins 2002). Features of reperfusion injury on Computed Tomography differ from those of hyperacute rejection with evidence of perihilar ground glass opacities, peribronchial and perivascular thickening and reticular interstitial or airspace opacities especially in the middle and lower lobes. In this setting it is important to rule out other causes with similar profiles such as rejection, infection, fluid overload or cardiac failure especially in Sarcoidosis patients with an increased incidence of cardiac involvement (Krishnam, Suh et al. 2007)

To avoid healing problems that may occur it is important not to induce barotrauma either to the parenchyma, which might induce an upregulation of the immune response, or direct positive pressure injury to the anastomotic area. While strategies need not necessarily be tailored for Sarcoidosis patients a strategy of low positive end expiratory pressure (5cmH$_2$0) and tidal volumes (8-10 mL/Kg) are preferred. When patients receive single lung transplants this is especially important as the native lung will have altered compliance due to fibrosis putting the allograft at greater risk of injury using what appears to be acceptable pressures

Early weaning from mechanical ventilation is of paramount importance for a successful transplant outcome. Many patients can be weaned from the ventilator within twenty-four hours. This has significant benefits in terms of weaning of sedation, less need for airway access via suction, while the risk of infection is considerably reduced. In addition the discontinuation of positive pressure and the initiation of more natural negative ventilation helps to protect the anastomotic integrity from any barotrauma that might cause rupture. An early extubation strategy for Sarcoidosis recipients is encouraged as many patients will have been treated with prolonged courses of steroids. While this is not a contraindication for transplantation there are a number of problems that might arise if the overall burden of steroid preoperatively is excessive. Of particular concern is the patients' wound healing ability following surgery. This does not only apply to the cutaneous and underlying subcutaneous structures but also the anastomoses. The arterial and venous connections may also be compromised by significant corticosteroid doses. As a general rule most centres suggest doses of steroids to be less than 10 milligrams per day prior to transplantation, which in the majority of Sarcoidosis cases can be achieved.

Weaning from mechanical ventilation may also be affected more profoundly by the onset of critical care myopathy. While there is no indication that this affects patients with Sarcoidosis more than any other transplant recipients the long-term use of steroids in high doses certainly results in preponderance for muscle wasting (Weber-Carstens, Deja et al.). The wasting of intercostal muscles in particular may result in failure to wean from the mechanical ventilator resulting in the need to progress to tracheostomy placement and non-invasive ventilation strategies to aid recovery. A prolonged period on non-invasive ventilation through a tracheotomy leads to thicker secretions, increased frequency of infections and increased length of stay.

The diaphragm represents the main muscle of respiration and normal ventilation requires it to be healthy and functioning. Normal diaphragmatic contraction results in decreased intrapleural pressure, an expanded rib cage through its zone of apposition by generating a positive intra-abdominal pressure, and expansion of the rib cage using the abdomen as a fulcrum (Rochester 1985). The reported incidence of phrenic nerve injury in the literature varies from 3% to 30% and is dependent on the methods used to detect the defect (Maziak, Maurer et al. 1996). The putative causes of the injury include direct phrenic nerve injury during mediastinal dissection, stretch injury of the nerve as the pericardium is manipulated, and hypothermic injury during the operative period. Interruption of this phrenic nerve function leads to increased work of breathing and difficulty in weaning patients from mechanical ventilation in addition to an increased incidence of atelectasis, ventilator associated pneumonia, and hypoxemia resulting in prolongation of ICU stay in most cases (Maziak, Maurer et al. 1996; Ferdinande, Bruyninckx et al. 2004)

Physiotherapy input at this stage and indeed in the preoperative work up is essential to improve patient outcome (Kress 2009). Breathing techniques to facilitate airway secretion clearance and daily assessment of muscle function help to expedite patients' recovery and decrease infections. An earlier initiation of treatment and regular follow up exercise, in a controlled environment, has long term benefits on patients exercise capacity, lung function and quality of life (Munro, Holland et al. 2009).

3.4.4 General ICU considerations

Usually an epidural catheter placed preoperatively allows adequate analgesia to be applied at a local level and decreasing the reliance on systemic agents. If this is not possible higher doses of systemic agents may result in significant cognitive depression delaying weaning from mechanical ventilation. In addition any prolongation of mechanical ventilation should be accompanied by an attempt to awaken the patient on a daily basis to assess cognitive function, pain threshold and ability to perform even limited physiotherapy.

Although more commonly seen as a result of gastric surgery there has been a recent increase in the reported incidence of vagus nerve injury following fundoplication surgery and bariatric surgery. However, there have been reports of cases in transplantation also (Shafi and Pasricha 2007; Paul, Escareno et al. 2009)with the incidence reported to be of the order of five percent. Most cases can be managed conservatively; however there may be significant problems post lung transplantation in terms of maintaining adequate immunosuppression and nutritional absorption. Most injuries resolve over a two-year period and additional intervention is not usually required.

Malabsorption however can have additional consequences with patients often having difficulty maintaining electrolyte levels. While patients with cystic fibrosis are generally at greater risk any Sarcoidosis patients who may have occult cardiac involvement may manifest this during a period of electrolyte instability by the onset of cardiac arrhythmia. Patients are monitored daily with blood analysis while immunosuppression levels are increased to achieve adequate levels. Any evidence of renal impairment or electrolyte imbalance is treated early to avoid any cardiac arrhythmias.

Hyperammonemia has been reported to occur in up to four percent of lung transplant patients with mortality estimated to be of the order of seventy percent (Lichtenstein, Yang et al. 2000). It presents as a clinical syndrome with deteriorating neurological function despite liver function tests in the normal range within the first three months after surgery. Hyperammonemia is thought to be related to immunosuppressive agents however underlying liver and genetic abnormalities have also been suggested as alleged mechanisms of disease. Sarcoidosis patients although not shown to be at higher risk post lung transplant, may have occult disease wither due to granulomatous infiltration or to immunosuppressive agents such as azathioprine prescribed preoperatively. While the prognosis if diagnosed is poor there have been reports of patients being successfully managed, physicians however, need to maintain a high level of clinical suspicion to facilitate early intervention (Moffatt-Bruce, Pesavento et al. 2008)

3.4.5 Infections

Early infections are usually of donor origin however in the setting of severe bronchiectasis as in stage IV Sarcoidosis it is possible to have native tracheal colonization with microbes. Early antibiotic regimens are usually broad spectrum covering the commonest pathogens

with the addition of cover for any microbes identified in the recipient preoperatively. Donor harvest washings are also taken to tailor the treatment if empiric treatment proves to be incomplete.

Bacterial pneumonia is frequently observed following lung transplantation; however the incidence has decreased over the last few decades. The initial six-month post operative period is when the patients are subjected to the peak level of immunosuppression and it is during this time that likelihood of bacterial infection is at its greatest. Bacterial identification has been reported in up to eighty percent of patients. In one Spanish study there was an incidence of 72 episodes of pneumonia per hundred lung transplants per year and of the established etiologies bacterial infections accounted for eighty two percent. Pseudomonas, Acinetobacter and staphylococcus accounted for the majority of the cases (Aguilar-Guisado, Givalda et al. 2007). Assessment and sampling of donor lungs during harvesting suggests that many of the early pneumonias are of donor origin; use of this information has allowed a tailoring of the post lung transplant antibiotic regime resulting in improved outcome (Dauber, Paradis et al. 1990; Weill, Dey et al. 2002). Antibiotic prophylaxis against opportunistic infections is also important and the use of sulfamethoxazole and trimethoprim three times a week has been efficacious in the prevention of Pneumocystis Jiroveci infection while it also has an effect on other microbes such as Listeria, Toxoplasma and Listeria (Fishman 2007).

Cytomegalovirus (a human herpesvirus) is probably the most important viral pathogens associated with lung transplantation due to its ability to latently infect the host allowing reactivation to occur at any stage throughout the recipients lifetime (Zamora 2004). Seronegative recipients receiving a seropositive allograft are at greatest risk of infection while previously exposed recipients have a lesser risk. CMV primary infection and reactivation is associated with a reported mortality ranging from 2- 12 percent (Fishman and Rubin 1998). While the acute effects from CMV have been identified the long term risk from latent infection or repeated activation does not have a linear relationship with the development of chronic allograft failure (Sharples, McNeil et al. 2002).

Epstein Barr Virus is a well-documented pathogen following lung transplantation with historical reports of post transplant lymphoproliferative disease in 2-5% of all lung transplant recipients and up to 30% of donor/recipient Epstein Barr virus mismatches. More recently, routine use of current antiviral prophylaxis strategies, more judicious use of immunosuppression regimens in at risk recipients, and improved treatment options have anecdotally been associated with improved outcomes (Malouf, Chhajed et al. 2002).

Other viruses such as the alphaherpesviridae (Herpes Simplex Virus 1 and 2, and Varicella Zoster Virus) were previously associated with an unacceptably high mortality however with cytomegalovirus prophylaxis the 10 percent mortality associated with these viruses has been almost eradicated (Manuel, Kumar et al. 2008)

While fungal infections post lung transplantation may include Candida, Scediosporum and Fusarium species the most problematic is Aspergillus. Aspergillus, also the commonest affecting 6.2% of all lung transplant recipients (Singh and Husain 2003), may take the form of tracheobronchitis, anastomotic infection of parenchymal invasion, although disseminated disease can also occur. Complicated surgery in addition to immunosuppressive therapy and renal impairment are recognized as risk factors for fungal infection, suggesting that extra vigilance may be warranted in Sarcoidosis patients in the weeks post procedure. Diagnosis of fungal infection is difficult but the instigation of regular surveillance bronchoscopies in

most centres allows regular viewing of the anastomosis and bronchoalveolar lavage of the parenchyma, which improves the detection rate. Treatment in most centres involves fluconazole or in the case of aspergillus voriconazole or posaconazole which has been reasonably efficacious in managing the disease although eradication has proven difficult especially in the setting of single lung transplant recipients where the native lung acts as a reservoir for infection. Prophylaxis is not routinely prescribed unless isolated from the donor harvest bronchoalveolar lavage.

3.4.6 Medium and late complications

A number of conditions are associated with lung transplantation as a consequence of the long-term effects of immunosuppression. These include osteoporosis (Aris, Neuringer et al. 1996) which many Sarcoidosis patients will have a predilection to as a result of prior corticosteroid use, chronic renal failure related in part to Tacrolimus or cyclosporine (Parekh, Trulock et al. 2004) as is systemic hypertension (Morrison, Short et al. 1993). Corticosteroids and the calcineurin inhibitors can also induce diabetes mellitus (Jindal 1994), Obesity, Anaemia (End, Stift et al. 1995), hypercholesterolemia and hypertriglyceridaemia (Stephany, Alao et al. 2007). Gastroesophageal reflux disease (GORD) disease however appears to be a direct result of surgery through mechanical manipulation or impingement of the vagus nerve causing gastroparesis (Davis, Lau et al. 2003).

Lung transplantation surgery has evolved so that the recipient airway is relying on collateral and retrograde perfusion from the pulmonary artery for blood supply. Initially the bronchial arteries were re-anastomosed but this resulted in prolongation of the allograft ischaemic time; this led to the cessation of this technique. Currently evidence of diminished airway perfusion may be observed during surveillance bronchoscopies usually as variegated violet change on the endobronchial surface. These changes may subsequently develop into ischaemic injury with blackening and ulceration of the surface. Some of the sloughed endobronchial surface may result in airway obstruction with evidence of decreased FEV1 and a scalloped flow loop on lung function testing. Any sloughed areas can be debrided via the bronchoscope and closely followed to insure that secondary infection is identified and treated as early as possible.

For the majority of cases conservative management is sufficient however in 5% of patients the injury progresses to bronchial dehiscence with ulceration, perforation or stricture formation (Weder, Inci et al. 2009). It has been suggested that the technique of telescoping of the airways to adjust for size discrepancy and to add stability to the airway wall may also result in an increase in airway complications. Usually management is successful using balloon dilatations with or without the added radial cuts with argon plasma coagulation. This approach usually abrogates the need to use endobronchial stent placement. In some patients the need for stenting is unavoidable and in this scenario temporary polyflex stents can be placed which allow for their removal when the integrity of the airway wall has stiffened with scaring. Occasionally covered or uncovered stents may be placed and usually this will add architecture to the airway, however the disadvantage is that stents can fracture leading to retention of secretions around the loose wires. This may result in infection, obstruction or both and dealing with these can be problematic as the stents become embedded in the walls. On the other hand vascular anastomotic problems are not as common. Usually if present they result in pulmonary infarction on the arterial side and often occur in the early postoperative period.

Surveillance bronchoscopy is carried out regularly after transplantation at weeks 2,4,8,12,24,36, and 52. While initially this is done to assess the anastomosis and also to preempt any infection that might arise subsequently more subtle infections such as CMV and EBV can be identified earlier by using bronchoalveolar lavage thereby allowing physicians to augment therapy and avoid chronic impairment (Westall, Michaelides et al. 2004).

Bronchoscopy is also performed to monitor for acute rejection which in the early post operative period is generally diagnosed using clinical criteria. Clinically acute rejection is recognized as a constellation of symptoms including dyspnoea, fatigue, dry cough, low-grade fever, a 10mmHg decrease in PaO2, and a 10% drop in FEV1 in conjunction with radiological opacification. These clinical features are not specific and usually develop when acute rejection is more severe. Subsequently surveillance biopsies taken at bronchoscopy assist to diagnose the process. Acute rejection occurs when the host organ recipient recognizes the donor organ as foreign, based on a lack of recognition of human leukocyte antigens, and as a result attacks the organ causing it to fail. Acute rejection is classified based on the severity and extent of perivascular lymphocytic cuffing and parenchymal infiltration. No abnormality (grade A0) at one end of the scale is counterbalanced by severe rejection (grade A4) that involves the interstitium and airspaces in addition to damaged pneumocytes and vascular changes (Stewart, Fishbein et al. 2007). Most lung transplant recipients will develop at least one episode of acute rejection in the first three months and the presence of rejection grade A2 or higher is managed with a 'pulse' of methylprednisolone (500mg-1g IV x three days). Baseline immunosuppression is also augmented following this. Resistant cases may need further treatment with antilymphocyte antibody.

Chronic rejection remains the elusive 'holy grail' of transplantation. It remains the main cause of morbidity and mortality after the first year not just due to obliterative bronchiolitis but also due to increased infections (Burton, Carlsen et al. 2007). Chronic rejection is more difficult to diagnose and has a more languid onset than acute rejection. Patients usually develop a cough that may be productive and clinically produce audible squeaks on examination. Risk factors to be noted in the history include persistent or severe episodes of acute rejection, CMV infection or recurrence, organising pneumonia, ischaemic-reperfusion injury, and gastro-oesophageal reflux (Estenne, Maurer et al. 2002). Lung function may show a progressive obstruction which has been used to grade the severity of bronchiolitis obliterans syndrome while the pathological entity obliterative bronchiolitis may or may not be evident on transbronchial biopsies leaving clinicians with a diagnosis of exclusion. Treatment is generally unsatisfactory despite courses of pulsed corticosteroids, cytolytic therapy, inhaled cyclosporin, switching from Cyclosporin to Tacrolimus, total lymphoid irradiation, plasmapheresis and photopheresis, leaving retransplantation in most cases the only option provided the patient passes the assessment criteria a second time (Neuringer, Noone et al. 2009).

4. Results

Considering the numbers of transplants performed for Sarcoidosis are limited compared with other diagnosis, the specific survival data is difficult to extrapolate from the documented figures provided in international databases. Lung transplantation figures have generally improved recently, due mainly to careful choice of donors and improvements in

patient management postoperatively. Recent data shows that for all deceased donor lung transplants the 1, 3, and 5 year survival is 83, 65 and 51 percent respectively (UNOS 2011). In order to address the donor shortage donor organs from patients deceased following cardiac death have been utilised, and interestingly the early outcome data suggests that the survival is improved in this cohort theoretically due to diminished neurological mediators released at the time of death although the exact reason remains to be elucidated (Snell and Levvey 2009). No direct comparison of data has been published; however one paper has shown excellent long term outcomes for all interstitial diseases following transplantation, which appears comparable to survival numbers in other organs (Keating, Levvey et al. 2009).

	Living		Deceased		Lost to Follow up		Retransplanted		Total
Year	N	%	N	%	N	%	N	%	N
2000	10	38.46	16	61.54	0	0	0	0	26
2001	7	22.58	22	70.97	0	0	2	6.45	31
2002	5	15.63	24	75.00	1	3.13	2	6.25	32
2003	9	42.86	11	52.38	1	4.76	0	0	21
2004	16	41.03	21	53.85	1	2.56	1	2.56	39
2005	19	39.58	27	56.25	1	2.08	1	2.08	48
2006	36	64.29	18	32.14	1	1.79	1	1.79	56
2007	25	58.14	17	39.53	1	2.33	0	0	43
2008	32	74.42	11	25.58	0	0	0	0	43
2009	37	82.22	7	15.56	0	0	1	2.22	45
2010	45	83.33	9	16.67	0	0	0	0	54
All	241	55.05	183	41.78	6	1.37	8	1.83	438

Table 4. Survival Data from UNOS for Sarcoidosis Recipients since 2000

Other research shows that Sarcoidosis patients, when compared to other lung transplant recipients, have a predilection for severe, acute rejection. Acute rejection is a recognised risk factor for the development of BOS or chronic rejection suggesting Sarcoidosis patients might have a worse long term outcome after transplant (Johnson, Duncan et al. 1993). On review the evidence for an increased incidence of BOS in Sarcoidosis patients is lacking and suggests that the numbers involved in this study are too small to draw definitive conclusions on long term outcomes while others have shown equivocal outcomes to other transplant diagnosis (Padilla, Schilero et al. 1997; Wille, Gaggar et al. 2008; Keating, Levvey et al. 2009).

A number of cases of Sarcoidosis have recurred post lung transplantation (Bjortuft, Foerster et al. 1994; Gisvold, Crotty et al. 2000), however only 533 patients with Sarcoidosis are registered as receiving a transplant since 1998 (OPTN/SRTR 2009). Because of the small number of recipients with a primary diagnosis of Sarcoidosis the actual prevalence of recurrence is not known definitively. To date around 21 cases are recorded with two further reports of recurrence in an undocumented number (Collins, Hartman et al. 2001). The estimated frequency is calculated as 50% but the range between reported series has been between 25 and

80% (Johnson, Duncan et al. 1993; Bjortuft, Foerster et al. 1994; Walker, Mikhail et al. 1998; Burke, Stewart et al. 2001; Milman, Burton et al. 2005). Although rates are varied Black Americans seem to have a higher recurrence rate at 66% compared to other races (Nunley, Hattler et al. 1999). Sarcoidosis, however, is not the only disease that recurs following lung transplant and a list of the other reported conditions is in Table 2.

In the majority of cases, recurrence of Sarcoidosis is not preceded by an increase in respiratory symptoms and signs (Johnson, Duncan et al. 1993; Nunley, Hattler et al. 1999). Usually cases of recurrence are identified as part of surveillance bronchoscopies carried out routinely post procedure. Recurrence is evidenced by the identification of the characteristic non-caseating granulomas present before transplantation however other causes of this such as fungal or mycobacterial infection need to be ruled out first. Radiologically the features may be of solitary or multiple nodules, or there may be no specific changes present (Collins, Hartman et al. 2001). In some cases however there may be evidence of graft dysfunction with the onset of respiratory symptoms, and in these patients there is a greater likelihood that there are coexisting infiltrates on radiological investigations (Judson 1998).

Sarcoidosis
Lymphangioleiomatosis
Diffuse Panbronchiolitis
Pulmonary alveolar proteinosis
Desquamative interstitial pneumonia
Pulmonary Langherhans Cell Histiocytosis
Bronchioloalveolar Carcinoma
Idiopathic Pulmonary Hemosiderosis
Giant Cell Interstitial Pneumonia
Alpha-1-Antitrypsin Deficiency
Pulmonary Veno-occlusive Disease

Table 5. Table of conditions known to recur after lung transplantation.

Recurrence can occur at any stage post transplantation documented from as early as 2 weeks out to 2 years (Johnson, Duncan et al. 1993; Martel, Carre et al. 1996). Some have suggested that rejection and Sarcoidosis may utilise a common pathway via the activation of T-lymphocytes however, the weight of evidence is against this. Immunosuppression used in lung transplantation to target interleukin-2, part of the CD8 cytotoxic T-lymphocyte response, has been found to be ineffective in suppressing Sarcoidosis, the granulomas of which appear to be due to a process driven by CD4 T-lymphocytes (Semenzato, Zambello et al. 1993; Wyser, van Schalkwyk et al. 1997). The recurrence of Sarcoidosis in lung transplant recipients early post operatively when immunosuppression is at its zenith would concur with a disparate immunological basis between the two pathological processes.

Notwithstanding the debate as to the frequency of recurrence of Sarcoidosis the impact of recurrence appears to be negligible. The majority of patients who have recurrence have an incidental finding with little or no effect noticeable on pulmonary function testing. Indeed while recurrence is associated with a more severe course of acute rejection, there is no evidence for increased frequency and there is no association with an increase in BOS over and above the normal LTx population.

Appropriate patients are considered for retransplantation if they are in robust enough health to allow transition through a second procedure. The evidence suggests that while the survival figures are improving retransplantation outcomes are not as good as those undergoing their first procedure. This is especially so for those who require early retransplantation within 30 days (Trulock, Edwards et al. 2003). A recent paper suggested Sarcoidosis was not a significant cause for retransplantation; of 389 patients requiring retransplantation between 1980 and 2006, only 84 patients had diffuse lung disease as the reason for initial transplantation, this number included all Sarcoidosis patients. The reason for retransplantation included BOS (52%), primary graft dysfunction (16%) and acute rejection (3%) while all other and unknown causes accounted for only 27% (59/389) (Kawut, Lederer et al. 2008). The specific Sarcoidosis numbers among these figures were not commented on, however, a previous study showed that there was no evidence to suggest a higher incidence of chronic rejection with Sarcoidosis (Padilla, Schilero et al. 1997). This taken in conjunction with the UNOS data in Table 4 shows that very few Sarcoidosis patients progress to retransplantation (n=8, 1.83%).

5. Conclusion

Sarcoidosis continues to affect significant numbers of the population and while many among this cohort spontaneously recover some progress to respiratory failure. The historical difficulty in Sarcoidosis patient receiving lung transplantation is likely to be multifactorial as the natural progression of the disease is not consistent, with no reliable markers to predict those who progress despite treatment. This meant that timing for lung transplantation was difficult to assess accurately. Recently pulmonary hypertension has been identified as a reasonable prognostic marker and all patients who develop increased pulmonary pressures on echocardiogram should be considered potential candidates. The multisystem nature of Sarcoidosis means patients still need to undergo a rigorous pre-listing assessment, but once lung transplantation has been performed outcomes are equivocal to other indications. Recurrence of Sarcoidosis is the commonest for all the indication for transplantation however it has limited impact on the long-term outcome of the recipient. The development of an LAS in score in the United States may result in Sarcoidosis receiving greater priority in the future, especially those patients with associated pulmonary hypertension. Early recognition of declining clinical and radiological status should prompt referral for lung transplant assessment with outcomes likely to improve with further improvements in transplantation.

6. Acknowledgements

7. References

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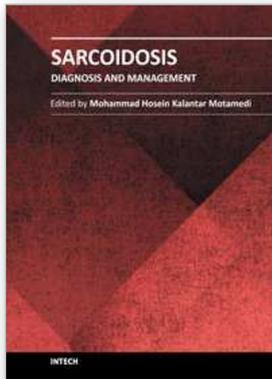
Sarcoidosis Diagnosis and Management

Edited by Prof. Mohammad Hosein Kalantar Motamedi

Sarcoidosis is a type of inflammation that occurs in various locations of the body for no known reason. Normally, when foreign substances or organisms enter the body, the immune system will fight back by activating an immune response. Inflammation is a normal part of this immune response, but it should subside once the foreign antigen is gone. In sarcoidosis, the inflammation persists, and some of the immune cells form abnormal clumps of tissue called granulomas. The disease can affect any organ in the body, but it is most likely to occur in the lungs. It can also affect the skin, eyes, liver, or lymph nodes. Although the cause of sarcoidosis is not known, research suggests that it may be due to an extreme immune response or extreme sensitivity to certain substances. It also seems to have a genetic component as well, and tends to run in families. Sarcoidosis most commonly develops in people between 20 and 50 years of age. African Americans are somewhat more likely to develop sarcoidosis than Caucasians, and females are somewhat more likely to develop sarcoidosis than males. The symptoms of sarcoidosis depend on the organ involved. This book deals with the diagnosis and treatment of this mysterious disease of unknown etiology.

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