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The Relationship Between Preexisting Gastroesophageal Reflux Disease in Lung Transplant Recipients and the Development of Post-Transplant Bronciolitis Obliterans

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THE RELATIONSHIP BETWEEN PREEXISTING GASTROESOPHAGEAL REFLUX DISEASE IN LUNG TRANSPLANT RECIPIENTS AND THE DEVELOPMENT OF POST-TRANSPLANT BRONCHIOLITIS OBLITERANS

by

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Abstract

Lung transplant is a treatment modality for patients with end stage lung disease. Bronchiolitis obliterans syndrome (BOS) is the number one cause of morbidity and mortality in patients the first year after lung transplant. There are many risk factors which have been identified to increase the risk of BOS including acute rejection, lymphocytic bronchitis, medication non-compliance, bacterial or viral infections, older donor age, extended ischemic time, donor antigen-specific reactivity, human leukocyte antigen (HLA) mismatch, underlying disease and gastroesophageal reflux disease (GERD).

Advanced practice nurses can help in the primary prevention of BOS through the assessment and treatment of pre-transplant patients with GERD. A descriptive study using retrospective chart reviews of lung transplant recipients was conducted to evaluate the relationship between pre-transplant GERD and post-transplant BOS. The incidence of pre-transplant GERD was 39%. The incidence of BOS at year one was 17% and at year two was 32%. There was not a significant relationship between pre-transplant GERD and post-transplant BOS.

CHAPTER ONE

Introduction

Over 1700 transplants are performed world wide every year for select end stage lung diseases (Trulock et al., 2005). The most common diseases for which lung transplant is an indication are chronic obstructive lung disease, idiopathic pulmonary fibrosis (IPF), cystic fibrosis (CF), pulmonary hypertension, and Eisenmenger syndromes. Less common indications for lung transplant include bronchiectasis, sarcoidosis, and lymphangioleiomyomatosis (LAM) and pulmonary Langerhans cell histiocytosis (Trulock et al., 2005).

One possible complication of lung transplant is chronic rejection, more commonly known as bronchiolitis obliterans syndrome (BOS). BOS is the most common cause of death after the first year post-transplant (Trulock et al., 2005). The cause of BOS is unclear and controversial. Gastroesophageal reflux disease (GERD) is a comorbid condition in end stage lung disease and is a suspected risk factor for the development of BOS in lung transplant recipients (D'Ovidio & Keshavjee, 2006; Trulock et al., 2005). Although there have been multiple studies that have looked at the role of GERD and allograft dysfunction, further research examining GERD and its association with BOS is warranted to optimize prevention and treatment options.

Conceptual Framework

Margaret Newman's model of health as expanding consciousness (HEC) is the theoretical framework used to guide this research. The model has three main concepts: health, pattern and consciousness. Newman defines health as the expansion of consciousness and is inclusive of both disease and nondisease (Newman, 2000). Health is viewed as the recognition of the evolving pattern of human-environment interaction. Newman asserts that disease is not a negative, as one in the medical field may presume, but that "health includes disease and disease includes health" (Newman, 2000, p. 6). With this in mind, the focus of the nurse should be placed on facilitating the individual's recognition of their own expanding consciousness and on recognition of patterns rather than simple identification of symptoms.

Patterns are the individual differences that make a person who they are. Every individual is different. It is important for individuals to recognize that their disease is not a separate entity, but rather to identify it as their own particular pattern. This will allow them to understand themselves and how they fit in the larger pattern of the environment (Newman, 2000).

"Consciousness is defined as the informational capacity of the system: the ability of the system to interact with its environment" (Newman, 2000, p. 33). Every individual is unique and has his or her own pattern that is within the system which is described by Newman. This individual then has to interact and adapt with the environment that is around them which is the act of finding his or her consciousness.

There are three sub concepts that define consciousness: time, movement and space. Time and space are not specifically defined within Margaret Newman's

model. Newman refers to time as it is relevant to the individual person; this was regarded as private time. Coordinated and shared time referred to the time that was spent with family (Newman, 2000). When an individual's space is increased or decreased then his or her time is decreased or increased respectively. With time the individual is in tune with their past, present and future. With this the individual is able to work within their environment with whatever limitations he or she may or may not perceive. Movement is defined as the events that happen in individuals' lives that may change both their reality and their pattern.

Individuals with end stage lung disease live in a chronic disease state that is usually terminal. In this chronic disease state the individual has periods of relatively stable health followed by an exacerbation of the chronic disease. This establishes the pattern that identifies and is specific to that individual (Newman, 2000). Over time the individual's pattern changes depending on the stage of the disease. For individuals who undergo transplantation, their pattern changes once again. The individual's consciousness is expanded by learning how to adapt in the environment as the pattern continuously changes.

In this expansion of consciousness, individuals who are lung transplant recipients must make life changes in order to protect themselves from injury to their transplanted organ. They are in constant movement to become aware of themselves in order to recognize when they may be facing a change in health. Lung transplant recipients are always at risk for decline. It is important for them to be aware of their pattern and to report their symptoms of health to their health care provider so that if there is a problem the provider may intervene.

One pattern that may evolve for lung transplant recipients is BOS. Patients must be educated and aware of the pattern that this disease may portray so that they can inform their provider in order to potentially reverse or halt the progression of the syndrome. Recipients who are expanding their consciousness and always in tune with their pattern and their environment are taking responsibility for themselves and the organ that they received.

Purpose

The purpose of this study was to examine the relationship between pre-transplant GERD and the development of post-transplant BOS among lung transplant recipients.

Research Questions

There were four questions for this study. Among lung transplant recipients:

1. What is the incidence of pre-transplant GERD?
2. What is the incidence of post-transplant BOS?
3. What is the relationship between pre-transplant GERD and post-transplant BOS?
4. What are the sensitivity and specificity of pre-transplant GERD as a predictor of post-transplant BOS?

Definition of Terms

Lung transplant. A surgical procedure to transfer a lung from a person who has died to another living person who has end stage lung disease.

Gastroesophageal reflux disease. GERD is a condition where there is repeated backward movement of stomach contents into the esophagus causing damage to the esophageal tissues (McCance & Huether, 2006).

Bronchiolitis obliterans syndrome. BOS is chronic rejection of the transplanted graft evidenced by persistent airflow obstruction (Trulock, Patterson, & Cooper, 2007).

CHAPTER TWO

Literature Review

This chapter provides a general overview of lung transplant, including history, processes for organ procurement, indications for lung transplant, postoperative complications and prognosis. This will be followed by a discussion of bronchiolitis obliterans (BOS), gastroesophageal reflux disease (GERD), including etiology, symptomology, treatment and prognosis. Finally, a discussion of the suspected role of GERD in the development of BOS after lung transplant will be presented.

Lung Transplant

Lung transplant has become an accepted viable treatment for end stage lung disease, providing an increased quality of life and survival benefit (Trulock et al., 2005). In 1963, the first human lung transplant was performed with very poor results (Blumenstock & Lewis, 1993). Lung transplantation was not attempted again until 1981, when a combination heart-lung transplant was performed (Reitz et al., 1982). In 1983, a single lung transplant succeeded due to improvements in surgical techniques and immunosuppressive agents (Toronto Lung Transplant Group, 1986). In 1986, a double lung transplant was performed at the University of Toronto (Cooper, Patterson, Grossman, & Maurer, 1989). During this time the pharmacologic agent cyclosporine was introduced as an immunosuppressant which enhanced the success of the transplants in the 1980's.

Christie et al. (2008) describe the survival of lung transplant patients from January 1994 through June 2006. Survival rate for lung transplant recipients at one year was 78%, at five years 51% and at ten years 28%. Causes of death post lung transplant included acute or chronic rejection, malignancy, infection, graft failure, cardiovascular events and technical complications. Chronic rejection, more commonly known as BOS, along with non- CMV infection and graft failure are the most common reason for death after the first year post lung transplant (Christie et al., 2008). BOS clinically evolves as a progressive loss of airflow due to the obstruction of the smaller airways. The course of the disease can be either rapid or slow. The experience is different for each patient.

The number of patients who are currently on the waiting list for transplant exceeds the number of donors that are available. At the end of 2005 there were 3,170 patients listed and waiting for lung transplant with only 1,287 available living and deceased donors (Scientific Registry of Transplant Recipients, n.d.). The average wait time for patients who are listed to be transplanted according to United Network of Organ Sharing (UNOS) is 588 days (Organ Procurement and Transplantation Network, n.d.).

Organ procurement. Due to the shortage of organs, the identification process for the recipients of organs is very selective. Organ allocation in the United States is governed under the United States Department of Health and Human Services (Rudow, Ohler, & Shafer, 2006). The Organ Procurement and Transplantation Network (OPTN) was established by the United States Congress under the National Organ Transplant Act (NOTA) of 1984. The purpose of the OPTN was to establish and maintain a national list of individuals who need organs through a national system in a database with established medical criteria to match organs to the individuals on the list. The OPTN is dedicated to

increasing and ensuring the effectiveness, efficiency, and equity of the organ allocation system and to increasing the number of donated organs that are utilized in transplantation (Rudow et al., 2006).

In 1986, UNOS was awarded the contract to establish and operate the OPTN. Under this contract UNOS developed a system that is used for the collection, storage, analysis and publication of all data pertaining to transplant and to provide guidance to anyone concerned with transplantation and information to increase donor awareness (Rudow et al., 2006). UNOS uses a defined lung allocation system (LAS) for the distribution of organs to those candidates who are on the waiting list. This system was put in place to clarify the order that lung offers are made to the transplant candidates. The candidates are assigned a LAS that is determined by each candidate's medical information criteria. The score allows the sickest candidates with the highest chance of survival the best opportunity of getting a transplant (Rudow et al., 2006). Organ procurement organizations (OPOs) operate under UNOS and are responsible for the recovery of organs and allocation of those organs in their geographic regions in accordance to the UNOS guidelines.

Indications for lung transplant. The common lung diseases that are indications for lung transplant include chronic obstructive pulmonary disease (COPD), alpha-1 antitrypsin deficiency, idiopathic pulmonary fibrosis (IPF), cystic fibrosis (CF), idiopathic pulmonary hypertension (IPAH) and Eisenmenger syndrome (Trulock, 2006b). Lung transplant is considered for patients with end stage lung disease when they are failing medical treatment or an effective medical treatment is nonexistent (Orens et al., 2006). Candidates for lung transplant referred to a transplant center for evaluation is

dependent on many factors including the patient's quality of life, the patient's desire for information regarding lung transplant and the referring physician's clinical decision regarding the patient's survival. Ideally listing of a lung transplant patient should take place when the patient with end stage lung disease's life expectancy is considerably reduced to where it may be affecting quality of life and activities of daily living but does not exceed the waiting time for donor lungs (Orens et al., 2006). To review as it was discussed earlier the average wait time for some one who is listed for lung transplant according to UNOS is 588 days. (Organ Procurement and Transplantation Network, n.d.).

The general guidelines for selection of recipients for lung transplant have been outlined by the International Society of Heart and Lung Transplantation (ISHLT) (see Table 2.1). Upon completion of a comprehensive transplant evaluation and after all potential contraindications have been ruled out the patient is placed on the waiting list.

Postoperative course and potential complications. Postoperatively, the patient spends 24 to 48 hours in the intensive care. Upon arrival to the intensive care, the patient has an endotracheal tube and is placed on mechanical ventilation. Bronchoscopy is performed via the endotracheal tube to assess the anastomosis site and obtain bronchoalveolar lavage for cultures. The patient is usually extubated within 24 hours after transplantation to avoid complications. Hospitalization usually lasts five to fourteen days. Patients are encouraged to start ambulating within 24 hours post transplant. Patients are discharged from the hospital after chest tubes are removed and they are able to resume oral intake.

Table 2.1.
Selection Criteria for Lung Transplant

Age Limits
Single lung transplant: 65 years old
Double Lung transplant: 60 years old

Absolute Contraindications
Malignancy in the last two years
Untreatable Advanced organ dysfunction
Untreatable Chronic extrapulmonary infection
Significant chest wall or spinal deformity
Noncompliance
Untreatable Psychiatric or psychological condition
Substance addiction < six months

Relative Contraindications
Age greater than 65
Critical clinical condition
Limited functional status
Colonization with resistant bacteria, fungus or mycobacterium
Body mass index >30
Severe osteoporosis
Mechanical ventilation
Other comorbidities

Adapted from "International guidelines for the selection of lung transplant candidates: 2006 update - a consensus report from the pulmonary scientific council of the international society for heart and lung transplantation," by J.B. Orens et al., 2006, *The Journal of Heart and Lung Transplantation, 25*(7), pp. 746-747.

Early in the postoperative phase, patients may experience complications with reperfusion injury, primary graft failure, and cardiac arrythmias (Trulock et al., 2007). Reperfusion injury occurs from alveolar damage and increased vascular permeability, which can happen within hours or up to days following the transplant surgery. Primary graft failure is similar to acute lung injury that occurs shortly after the lung is transplanted and may happen because of problems with the donor lung that occurred prior to transplant. These problems include aspiration, contusion during removal or transport,

or inadequate lung preservation. Cardiac arrhythmias are common after lung transplant and are usually atrial in nature because of the proximity of the atrial cuff to the anastamosis site, the trauma and inflammation can impede electric conduction.

Other complications may occur in the first days to weeks after surgery. Vascular complications that may occur include pulmonary artery stenosis and pulmonary venous obstruction increased pulmonary pressures or pulmonary vein thrombosis. Airway complications include bronchial dehiscence or stenosis of the anastamosis. Pleural complications will usually occur in the first month post lung transplant and are usually caused by infection, poor pleural drainage, or rejection. Infection is common after lung transplant and is related to the surgery itself and to ventilator dependence. Infection may also come from the donor lung (Trulock, 2006a).

Long term consequences of lung transplant are the result of physiologic changes that occur because of the pulmonary denervation that happens during surgery. The patient's ability to control breathing is changed due to the cutting of the afferent and efferent nerves to the lung during organ retrieval. Reinnervation does not occur in the post transplant period. Patients also experience impairment of the cough reflex and mucociliary clearance because the afferent limb of the cough reflex is severed and does not regenerate. The patient continues to have the ability to cough by other means such as stimulation from the native lung or from sites in the respiratory tract that are proximal to the airway anastamosis (Trulock, 2003).

In the post transplant period the patients are followed periodically for a lifetime to monitor for acute and chronic rejection, infection, and immunosuppression levels. Immunosuppressive medications are indicated to prevent organ rejection immediately

post transplant. These medications are implemented immediately prior to or immediately after surgery. Induction therapy is the use of immunosuppressive medications such as cytolytic agent, monoclonal antibodies, and humanized monocolonal interleukin 2 receptor antagonists in the first five to seven days after transplantation. Common medications that are used in the post transplant period include calcineurin inhibitors such as cyclosporine or tacrolimus, azathioprine or mycophenolate mofetil, and corticosteroids. Labs are monitored at regular intervals to determine therapeutic levels and adjust medications as needed (Trulock & Mandel, 2006).

Infection. Patients in the post transplant period are more prone to infections due to the immunosuppressive medications needed to avoid rejection in the post-transplant period, impaired cough reflex, and impaired mucociliary clearance. The pathophysiology of infection may include the presence of acute inflammatory cells, alveolar inflammation, viral inclusions, and infectious pathogens identified by special stains (Reilly, 2005). Some infections that may occur in post-transplant patients include bacterial pneumonia (Pseudomonas species, Enterobacter, Staphylococcus aureus, Enterococcus species, and Hemophilus influenzae), viral infections (cytomegalovirus, herpes simplex virus, respiratory syncytial virus, and influenza), and fungal infections (candida and aspergillus).

Acute transplant rejection. Acute rejection is a celluar mediated immune response that usually occurs frequently in the first few months after lung transplant and decreases over time. Approximately 40% of patients will develop acute rejection in the first month after transplant (Trulock et al., 2007).

Patients with acute rejection may have no symptoms at all or may experience low grade fever, shortness of breath, nonproductive cough, and drop in oxygen saturation or drop in spirometry. The pathology representing acute rejection includes endothelial inflammation and lymphocyte infiltration in the alveolar walls and the airways. Acute rejection is diagnosed by clinical and diagnostic tools such as bronchoscopy with biopsies and bronchoalveolar lavage to rule out rejection versus infection. Acute rejection is graded by guidelines provided by the ISHLT (See Table 2.2). Acute rejection is graded by the pathology of the lung tissue and the degree of airway inflammation with lymphocytic bronchitis. Rejection versus infection can be a difficult diagnosis to make because both cause inflammation of the lung parenchyma (Stewart et al., 2007). Formal measurement of lung function with pulmonary function testing can be performed to assess for acute rejection. Chest x-ray can be used to rule out infiltrates or pleural effusion which may represent acute rejection.

Treatment for acute rejection depends on several factors including, severity of the rejection, clinical symptoms of the patient, and the presence of infection. In practice grade three and grade four rejections are always treated. The treatment of grade one and grade two rejection is more variable depending on the factors mentioned above. Steroid boluses for three days are used to treat acute rejection. Spirometry or follow up transbronchial biopsies may be performed to follow up the resolution of acute rejection (Reilly, 2006).

Table 2.2 Classification and Grading of Pulmonary Allograft Rejection	
A: Acute Rejection	
Grade 0	None
Grade 1	Minimal
Grade 2	Mild
Grade 3	Moderate
Grade 4	Severe
B: Airway Inflammation	
Grade 0	None
Grade 1R*	Low grade
Grade 2R*	High grade
Grade X	Ungradable
C: Chronic airway rejection – obliterative bronchiolitis	
0	Absent
1	Present
D: Chronic vascular rejection – accelerated graft vascular sclerosis	

* Revised grade to avoid confusion with 1996 scheme
From "Revision of the 1996 working formulation for standardization of nomenclature in the diagnosis of lung rejection," by S. Stewart et al., 2007, *The Journal of Heart and Lung Transplantation, 26*(12), p. 1230.

Bronchiolitis Obliterans Syndrome

BOS, chronic transplant rejection, is the primary cause of morbidity and mortality following the first year of lung transplantation can manifest itself in two classifications: chronic airway rejection or chronic vascular rejection (Reilly, 2006). Chronic airway rejection, the more common manifestation results in occlusion of the airways. Chronic vascular rejection is caused by atherosclerosis of the pulmonary vasculature, resulting in BOS. BOS can have a very unpredictable clinical course. Some individuals have a slow progression with gradual loss of lung function while others have a rapid progression into respiratory failure (Estenne et al., 2002).

Pathophysiology. BOS develops with submucosal lymphocytic inflammation resulting in the disruption of the epithelium in the small airways. Following the inflammation of the small airways, there is a fibromyxoid granulation which ultimately causes partial or complete occlusion of the airway (Reilly, 2006).

ISHLT has defined three categories of risk factors for BOS: probable, potential and hypothetical according to reliability and quality of evidence in the research available (Estenne et al., 2002). Probable risk factors are acute rejection, lymphocytic bronchitis, medication non-compliance and cytomegalovirus (CMV) infection. Potential risk factors include organizing pneumonia, bacterial, fungal and non-CMV viral infection, older donor age, longer ischemic time, and donor antigen-specific reactivity. Hypothetical risk factors include genotype of the recipient for certain cytokine gene polymorphisms, human leukocyte antigen (HLA) mismatch, underlying disease, and GERD with aspiration.

Nonimmunologically mediated risk factors that may contribute to the development of BOS include acute rejection, lymphocytic bronchitis, ischemic injury, GERD and bacterial, viral, or fungal infections. The most common risk factor for BOS is acute rejection. Multiple episodes of rejection may increase the risk of developing BOS. Lymphocytic bronchitis, or inflammation of the tissue in the airways from either acute rejection or infection may also predispose individuals to BOS. Some experts hypothesize that ischemic injury after transplantation may play a role in the development of BOS. GERD has been identified to be a predisposing risk factor of BOS. Respiratory infections from bacteria, virus, or fungus have been established as a cause of BOS (Sharples, McNeil, Stewart, & Wallwork, 2002).

BOS continues to be an ongoing challenge in lung transplantion. BOS may occur due to many different factors and much research needs to be done in the future regarding the multiple risk factors. The mortality and morbidity of lung transplant recipients is significantly affected by BOS. The development of BOS by five years after lung transplant is a significant complication. Between April 1994 and June 2004, 43% of lung transplant patients had developed BOS (Trulock et al., 2005). BOS continues to be the number one cause of death in this population one year or greater post transplant.

Diagnosis. BOS is diagnosed either by clinical suspicion after all other causes of functional decline are eliminated or by histological confirmation by transbronchial biopsy or open lung biopsy. The ISHLT has defined the diagnostic criteria for BOS based on pulmonary function using forced expiratory volume in one second (FEV_1) (Estenne et al., 2002). The baseline FEV_1 is the average of the two highest measurements obtained at least three weeks apart post lung transplant (Estenne et al., 2002). The percent of decline in the individual's FEV_1 post transplant can then be calculated. The mid-expiratory flow rate (FEF_{25-75}) is a pulmonary function measurement that may show decline before the FEV_1 the ISHLT uses both measurements as defining factors in the early stages of BOS (Estenne et al., 2002) (see Table 2.3).

Treatment. There is not a single proven treatment for BOS. Many pharmacologic agents have been used in an effort to stabilize the drop in FEV_1 in lung transplant patients. Some of these treatments have been effective in halting the progression of BOS. These include high dose steroids, azithromycin, cytolitic therapy, a change in calcinurin inhibitor, total lymphoid irradiation, plasmapheresis, photopheresis and retransplantation

Table 2.3
Bronchiolitis Obliterans Syndrome (BOS) Classification

BOS Grade	*BOS Criteria*
BOS 0	$FEV_1 > 90\%$ of baseline and $FEF_{25-75} > 75\%$ of baseline
BOS 0-p	FEV_1 81% to 90% of the baseline and/or $FEF_{25-75} \leq 75$ of baseline
BOS 1	FEV_1 66% to 80% of baseline
BOS 2	FEV_1 51% to 65% of baseline
BOS 3	FEV_1 50% or less of baseline

Note: FEV_1 forced expiratory volume in one second
FEF_{25-75} mid-expiratory flow rate

From "Bronchiolitis obliterans syndrome 2001: An update of the diagnostic criteria," by M. Estenne et al., 2002, *The Journal of Heart and Lung Transplantation, 21*(3), p. 299.

(Trulock & Mandel, 2006). The outcomes for these treatments have not been promising. The best treatment for BOS continues to be aggressive primary prevention.

Gastroesophageal Reflux Disease

GERD is a condition that in which there are symptoms associated with reflux of gastric contents into the esophagus (Devault & Castell, 2005). GERD affects five in every thousand persons in the United States each year (Kahrilas, 2006).

Pathophysiology. The lower esophageal sphincter (LES) is responsible for keeping acid out of the esophagus by maintaining a high pressure region that does not allow for gastric contents to enter the esophagus (McCance & Huether, 2006). Reflux occurs when the pressure between the LES and the stomach is decreased due to relaxation or weakness of the sphincter. The presence and severity of reflux is influenced by factors that increase abdominal pressure, such as vomiting, coughing, lifting and bending. Other conditions that increase the incidence of esophageal reflux include hiatal hernia and delayed gastric emptying (McCance & Huether, 2006).

The risks of esophageal reflux are inflammation to the esophageal wall which increases capillary permeability resulting in edema, fragile tissue, erosions and ulcerations. The severity of reflux depends on the gastric contents, the length of exposure the contents have with the esophagus, and the epithelial resistance to acid exposure (McCance & Huether, 2006).

Symptoms. Individuals with a diagnosis of GERD have symptoms of heartburn, regurgitation, upper abdominal pain within one hour of eating and dysphagia. These symptoms usually worsen when the individual is in a supine position or if the intrabdominal pressure increases. The symptoms are relieved by the use of antacids. Other symptoms of GERD include chest pain, hypersalivation, chronic cough, wheezing, sore throat, hoarseness, eructation, and nausea (Kahrilas, 2006).

Diagnosis. GERD is usually diagnosed based on the patient's history. Diagnostic testing such as endoscopy should be considered in individuals with complicated disease such as patients at risk for Barrett's esophagus, a complication of GERD that is predisposed to esophageal adenocarcinoma (Devault & Castell, 2005). All patients with a history of GERD for five years should undergo endoscopy to evaluate for Barrett's esophagus. Other diagnostic tests include ambulatory esophageal pH monitoring, esophageal manometry, Berstein test, and barium swallow (Kahrilas, 2006).

Treatment. Treatment for GERD includes lifestyle modifications, pharmacotherapy, and surgery (Kahrilas, 2006). Lifestyle modifications include elevating the head of the bed, decreasing fat intake, abstinence from smoking, and avoiding a supine position three hours after eating. Dietary modifications include avoidance of foods

known to lower the pressure of the LES, such as chocolate, alcohol, peppermint, and coffee (Devault & Castell, 2005).

Medications used for the treatment of GERD include over the counter antacids and acid suppressants, histamine 2-receptor blockers, proton pump inhibitors and promotility agents. Most individuals who experience intermittent symptoms of GERD respond well to over-the-counter antacids such as calcium carbonate, aluminum hydroxide, and simethicone. Histamine-2 receptor blockers such as cimetidine, famotidine, nizatidine, and ranitidine or proton pump inhibitors such as esomeprazole, lansoprazole, omeprazole, and pantoprazole are used for individuals who have continuous symptoms. Although both classifications of drugs act to suppress acid production, the proton pump inhibitors are more effective in patients with severe GERD (Goyal, 2007). Promotility agents such as metoclopramide, may be used in conjunction with histamine 2-receptor blockers or proton pump inhibitors, but not as monotherapy (D'Ovidio et al., 2005). Promotility agents increase the motility of the upper gastrointestinal tract.

Antireflux surgery can be used as a maintenance treatment for individuals with severe gastroesophageal reflux disease. The purpose of the surgery is to restore the LES. This can be done by Nissen fundoplication, Belsey Mark IV, and Hill repair. The Nissen fundoplication can be preformed either surgically or laparoscopically, where they surgically place a wrap around the LES to control reflux. The Belsey Mark IV is a partial fundoplication which allows mobilization of the esophagus. The Hill repair involves the overlapping of the gastric curve around the esophagus with attachment of the complex to the medican arcuate ligament, closing the diaphragm (Sampliner, 2006). This treatment option remains controversial for its long term efficacy (Devault & Castell, 2005).

Role of Gastroesophageal Reflux in Lung Transplant and Bronchiolitis Obliterans

GERD is a known comorbidity in end stage lung disease, occurring in as many as 63% of patients awaiting lung transplantation (D'Ovidio et al., 2005). GERD is also suspected to be a nonimmunologically mediated risk factor that causes both allograft dysfunction and BOS in lung transplant recipients (D'Ovidio & Keshavjee, 2006).

There are several theories for worsening GERD post lung transplant. Immunosuppressive agents, including calcineurin inhibitors and prednisone, are administered to the transplant recipients to prevent rejection. These medications also delay gastric emptying and increase the incidence of GERD by prolonging the time that the food is in the stomach to potentially reflux into the esophagus (D'Ovidio & Keshavjee, 2006). Iatrogenic vagal nerve injury during lung transplantation may occur. Such an injury causes diaphragm paralysis and the denervation of the lungs that occurs with the transplantation produces suboptimal cough reflex and mucociliary clearance (Trulock, 2003). With these impaired lung defenses, the lungs may not be able to appropriately eliminate offending gastric contents that may get aspirated (D'Ovidio & Keshavjee, 2006).

It is known that the severity of GERD worsens after lung transplant surgery (Young, Hadjiliadis, Davis, & Palmer, 2003). The suspicions of the relationship between GERD and BOS are beginning to be demonstrated empirically. In two animal studies of lung transplant in rats it was found that lungs exposed to aspiration demonstrated severe rejection with increased monocyte infiltration and fibrosis (Hartwig et al., 2006; Li et al., 2008). A study of lung transplants in miniature swine was designed by aspirating gastric contents via a gastrostomy tube to replicate reflux. The results of the study concluded that

acid reflux enhances an indirect alloresponse, revealing that GERD may be injurious to the transplanted lung (Meltzer et al., 2008).

In studies of humans, the incidence of GERD in patients post lung transplant is 70% to 90% (Benden et al., 2005; Hadjiliadis et al., 2003). Several studies have measured bile acid in bronchoalveolar lavage fluids and found that exposure to bile acids in the transplant lung shortened the time to diagnosis of BOS (D'Ovidio et al., 2006; D'Ovidio et al., 2005; Blondeau et al., 2009). Blondeau et al. (2008) conducted a study that evaluated pepsin and bile acid and their association with BOS. They concluded that pepsin was a general marker whereas bile acid was a more specific marker that may lead to the development of BOS. They also examined treatment with proton pump inhibitors and found that they did not stop nonacid reflux and gastric aspiration.

There is evidence that fundoplication surgery may be useful in the prevention of early allograft dysfunction and the development of BOS (Hartwig, Appel, & Davis, 2005). Other studies have found that fundoplication can improve the outcome of patients who are undergoing or who have undergone lung transplantation. A single patient case study described dramatic improvement in both reflux symptoms and pulmonary function after fundoplication surgery (Palmer et al., 2000). Cantu et al. (2004) studied 127 lung transplant patients and reported that 76% had abnormal esophageal acid evaluated by pH probe. Fourteen of these patients met the diagnosis of BOS and did undergo fundoplication. They were again evaluated after the fundoplication and their BOS improved or ceased. This suggested that GERD did contribute to the development of BOS. Davis et al. (2003) found similar results in their study of 128 lung transplant patients and reported that 73% had abnormal esophageal acid evaluated by pH probe.

Forty-three patients underwent fundoplication and 26 of these patients met the diagnosis of BOS. The 26 patients were again evaluated after the fundoplication and their BOS improved or ceased. Additional studies have been conducted to disclose the same conclusion that fundoplication can be performed safely in selected lung transplant candidates in order to improve or abate reflux symptoms and ultimately improve their lung function (Lau et al., 2002; O'Halloran et al., 2004). Other studies have shown that performing fundoplication in patients with end stage lung disease prior to lung transplantation can also be done safely and successfully with positive outcomes. (Gasper et al., 2008; Linden et al., 2006).

Summary

Although lung transplantation increases the quality of life for many patients with end stage lung disease, BOS continues to be a devastating complication for lung transplant recipients one year after transplantation. It has been suggested that GERD can be a predisposing factor for the development of BOS. Multiple studies of lung transplant patients in this area have supported the concept, but it still remains to be fully understood and accepted. Continued study in this area is warranted as lung transplant is an evolving treatment for end stage lung disease in the last two decades.

CHAPTER THREE

Methodology

This Level II correlational study utilized a retrospective chart review to determine the relationship between pre-transplant GERD and the development of post-transplant BOS among lung transplant recipients.

Sample and Setting

The study population consisted of the medical records of all patients who received a lung transplant at a major medical research and teaching facility in the southeastern United States between June 2001 to October 2005. This medical facility is a 224-bed institution with an average of 30 lung transplants performed each year. A power analysis revealed that the sample size needed to determine a significant relationship with $\alpha = .05$ in a two tailed test, a medium effects size and a power = of .80 would be 88 subjects.

Data Collection

The data were collected through a retrospective chart review. Medical records of all patients undergoing lung transplant between June 2001 and October 2005 were reviewed and examined. The data were extracted regarding demographic and study variables (see Appendix for data collection tool).

The diagnosis of GERD was assessed by (a) history, (b) esophagogastro-duodenoscopy with or without Bravo capsule, (c) pH probe, (d) barium swallow or (e) documented use of proton pump inhibitors. The diagnosis of BOS was be assessed by the

percent drop of the FEV_1 post transplant, and the number of months post-transplant that the BOS started to develop.

Protection of Human Subjects

Institutional Review Board (IRB) approval Expedited Status to conduct the study was obtained from the University of North Florida IRB and from the IRB of the facility where data were collected. The principal investigator was the only person with direct access to the medical records. No personal identifying information was collected and there was no direct interaction with patients

CHAPTER FOUR

Results

The data were entered into a spreadsheet and checked for accuracy. Data analysis was accomplished using Microsoft Excel 2003® and SPSS 16.1 for Windows®. This chapter presents sample characteristics and a description of the results for each research question.

Sample Characteristics

One-hundred patients met the inclusion criteria. There were a total of 102 transplants, with 2 patients who were re-transplanted during the study period. The patients were between 16 and 74 years-of-age (M= 55.99, SD = 12.91) with a median of 59 years-of-age. Further characteristics of the sample may be found in Table 4.1.

The survival of the lung transplant patients was from 0 to 91 months (M = 41.76 Months; SD=25.69 months) with a median of 44 months. The survival rate at one year was 84 %, two years 74% and three years 63%.

Research Question One

The first research question was: what is the incidence of pre-transplant GERD? Of the 100 patients whose records were reviewed, 39 had pre-transplant GERD. Eighteen (46.15%) were on medical treatment and also had symptoms which lead to a clinical diagnosis of GERD. Fourteen (35.90%) were on medical treatment without clinical symptoms but in the presence of risk factors for GERD, 3 (7.69%) were diagnosed by

Table 4.1
Patient Demographics (n=100 patients)

Characteristics	N
Gender	
Male	54
Female	46
Blood Type	
O	43
A	39
B	16
AB	2
Diagnosis	
Idiopathic pulmonary fibrosis	44
COPD/Emphysema	37
Pulmonary hypertension	5
Cystic fibrosis	3
Eisenmenger's Syndrome	3
Lymphangioleiomyomatosis	3
Re-transplant	2
Bronchiectasis	2
Other*	3

* Other diagnoses leading to the need for lung transplant were silicosis, bronchoalveolar cell carcinoma, and Shwachman-Diamond syndrome with one case in each category.

barium swallow and pH probe, 2 (5.13%) by EGD, and 1 (2.56%) by bravo capsule and EGD. All of these patients were also on medical treatments because of clinical symptoms. One (2.56%) patient had already had a fundoplication for previous diagnosis of GERD.

The incidence of pre-transplant GERD varied by gender. Twenty-four (61.53%) of the individuals with GERD were male and 15 (38.46%) female.

Research Question Two

The second research question was: what is the incidence of post-transplant BOS in lung transplant recipients? Only 84 of the 100 patients were able to be evaluated for first

year post-transplant information because 16 patients did not survive the first year. Fourteen (16.67%) of the 84 patients developed BOS within one year after transplant: 8 (57.14%) with BOS grade 1, 2 (14.29%) with BOS grade 2, and 4 (28.57%) with BOS grade 3. An additional 10 patients did not survive the second year, so only 74 patients were able to be evaluated for second year post-transplant information. Twenty four (32.43%) of the 74 patients developed BOS within two years after transplant: 12 (50%) with BOS grade 1, 3 (12.5%) with BOS grade 2, and 9 (37.5%) with BOS grade 3. (See Figure 4.1)

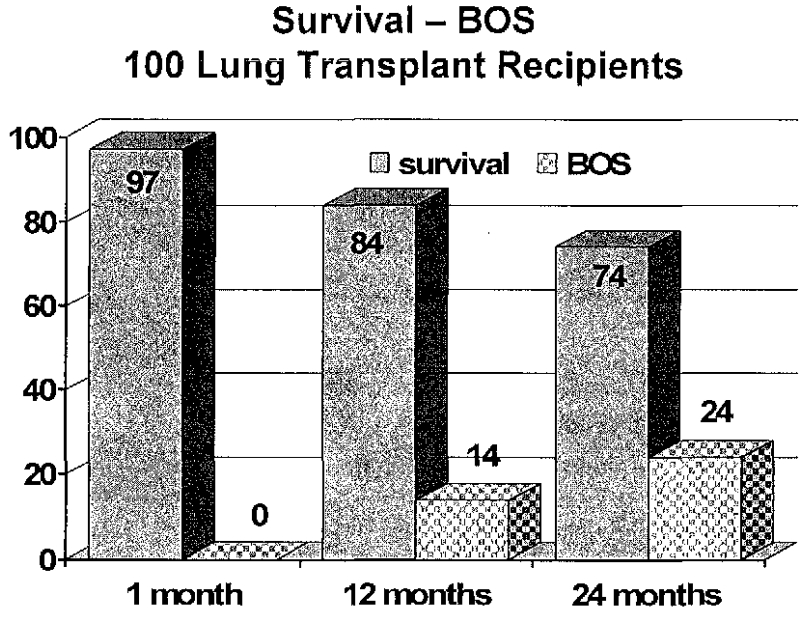

Figure 4.1
Survival Rate and Incidence of Post-transplant BOS

The incidence of post-transplant BOS varied by gender in the first year, but not in the second. Nine (64.28%) of the individuals with BOS at 1 year post-transplant were

female and 5 (35.71%) were male. Thirteen (54.16%) of the individuals with BOS at 2 years post-transplant were female and 11 (45.83%) were male.

Research Question Three

The third research question was: What is the relationship between pre-transplant GERD and post-transplant BOS in lung transplant recipients? Fourteen out of the 39 individuals (35.89%) with pre-transplant GERD developed post-transplant BOS by one year post-transplant. At two years post-transplant, 24 out of 39 individuals (61.53%) developed post-transplant BOS. There was not a significant relationship between preoperative GERD and postoperative BOS at either one year ($r = -.09$, $p = .41$) or two years ($r = .02$, $p = .83$) post-transplant. (See Figure 4.2)

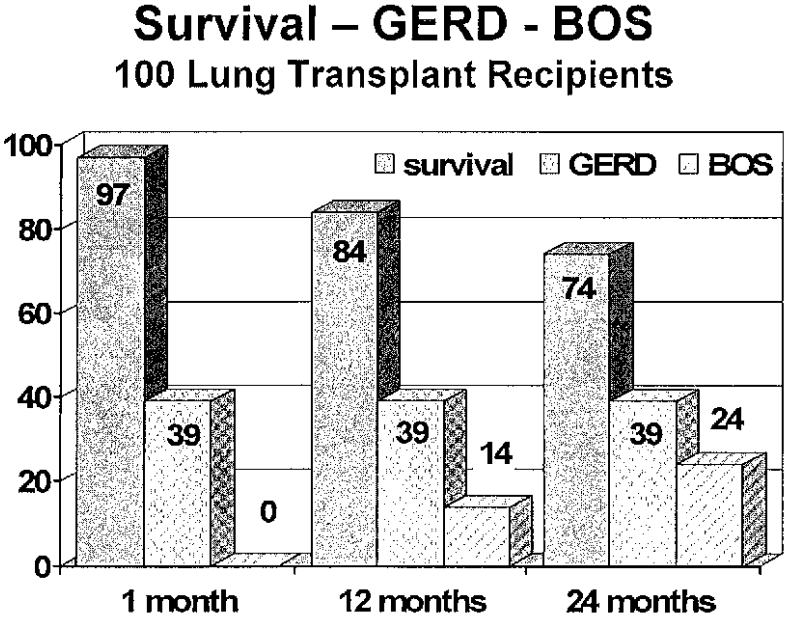

Figure 4.2
GERD and BOS Comparison from 1month to 2 years

Research Question Four

The fourth research question was: What is the sensitivity and specificity of pre-transplant GERD as a predictor of post-transplant BOS among lung transplant recipients? At year one the sensitivity was 36% and the specificity was 51% of pre-transplant GERD as a predictor of post-transplant BOS in lung transplant recipients. At year two the sensitivity was 58% and the specificity was 50%.

CHAPTER FIVE

Discussion

This study was a retrospective chart review to evaluate the relationship between pre-transplant GERD and the development of post-transplant BOS among lung transplant recipients. The records of 100 of patients who received a lung transplant between June 2001 to October 2005 were reviewed.

The survival rate for lung transplant recipients was 84% at one year, 74% at two years and 63% at three years. This is comparable to national average of 78% at one year, and 63% at three years for the period January 1994 to June 2006 (Christie et al., 2008).

The incidence of pre-transplant GERD was 39% in this sample, 61.53% of whom were male. The overall incidence of GERD in the United States is five per thousand (Kahrilas, 2006). Among those awaiting lung transplant the reported incidence is up to 70% (Benden et al., 2005; Hadjiliadis et al., 2003).

The incidence of post transplant BOS was 16.67% for the first year and 32.43% in the second year in this sample, with 64.28% in the first year and 54.16% in the second year being female. This incidence is somewhat lower than that reported in the US as a whole where the overall incidence of BOS is 33.70% (Christie et al., 2008). Among those receiving lung transplants the reported incidence is 27% at 2.5 years and 51% at 5.6 years (Christie et al., 2008). Blondeau et al. (2008) found similar results in their study off of proton pump inhibitors resulting in 63.63% of patients having BOS grade 1 or greater.

The relationship between pre-transplant GERD and post transplant BOS was 35.89% at one year and 61.53% at the second year in this sample. The hypothesis that there is a relationship has been validated in many studies who have examined the relationship between pre-transplant GERD and post transplant BOS (Benden et al., 2005; Blondeau et al., 2009; Blondeau et al., 2008; D'Ovidio & Keshavjee, 2006; D'Ovidio et al., 2006; D'Ovidio et al., 2005; Hadjiliadis et al., 2003; Hartwig et al., 2006; Li et al., 2008; Meltzer et al., 2008; Palmer et al., 2000; Young, Hadjiliadis, Davis, & Palmer, 2003).

The sensitivity and specificity of pre-transplant GERD as a predictor of post-transplant BOS in this study was 36% and 51% at one year and 58% and 50% at two years respectively. Sweet et al. (2006) examined the utility of symptomatic screening and found the sensitivity and specificity of distal reflux to be 67% and 26% and proximal reflux to be 62% and 26% respectively.

Limitations of the Study

The fact that these data were all obtained from one facility is a limiting factor to the generalizability of the results. The sample size should have been more than adequate to find a relationship between pre-transplant GERD and post-transplant BOS (power analysis indicated a desired n of 88 and there were 100 in this sample). This, however, was not the case, and is contrary to reports of an association found in an animal studies (Hartwig et al., 2006; Meltzer et al., 2008) and several other preliminary studies in humans (Benden et al., 2005; Blondeau et al., 2009; Blondeau et al., 2008; D'Ovidio et al., 2006; D'Ovidio et al., 2005; Hadjiliadis et al., 2003).

The retrospective nature of the data collection proved to be a limiting element, especially with respect to the diagnosis of pre-transplant GERD. Given the discrepancy between the incidence of pre-transplant GERD in this study (39%) and other reports of up to 63% (D'Ovidio et al., 2005), it is possible that GERD was underdiagnosed in this sample, since the pre-transplant diagnosis was made by a variety of mechanisms, including clinical judgment with or without specific testing. Unless the clinician was specifically looking for GERD, it may have been missed. When using retrospective data, one is also hampered by having to rely on what was previously documented in the medical record.

Future Research

Prospective studies that include screening for GERD in all patients awaiting transplant would add to the evidence that has already been generated. When designing these studies, the vulnerable state of the pre-transplant patient should be taken into consideration, since the patient may not be strong enough to endure the testing of a pH probe or EGD to make a definitive GERD diagnosis. Use of a validated, self-administered questionnaire such as the Reflux Disease Questionnaire (Shaw et al., 2001) might be a useful tool, with anyone scoring positively on the tool treated presumptively for GERD.

Since persons with GERD may be totally asymptomatic, studies might also be designed to investigate both clinically symptomatic and asymptomatic GERD and its relationship with the development of BOS post-transplant. Additionally, with the presumed relationship between pre-transplant GERD and post-transplant BOS, a study

investigating prophylactic treatment for GERD in all patients awaiting lung transplant is also warranted.

Advance Nursing Practice Implications

Knowledge regarding GERD and BOS gained from this study and others can guide the advanced practice nurse in the primary care of lung transplant recipients, allowing for identification of the conditions in their early phases of disease. This may have a positive impact on lung transplant outcomes. In the pre-transplant period this would include helping patients become aware of what Newman (2000) calls evolving patterns, those symptoms that may indicate GERD: pyrosis, regurgitation, dysphagia, chest pain, hypersalivation, globus sensation, odynophagia, and nausea. The Reflux Disease Questionnaire (Shaw et al., 2001) described above could be used to identify the patterns and make a presumptive diagnosis. Identification of the pattern could then be followed, as appropriate, by testing to make a definitive diagnosis by EGD, espophageal pH monitoring, esophageal manometry, barium swallow, and response to antisecretory therapy.

Once the diagnosis is made, either presumptively or through specific testing, patient teaching would include avoiding foods that exacerbate symptoms, avoid lying down for two to three hours after eating, stop smoking, lose weight, eat smaller and more frequent meals, and elevate the head of the bed by six inches. Given the albeit moderate association between pre-transplant GERD and post-transplant BOS, appropriate pharmacologic management using antisecretory therapy such as H_2 blockers, proton pump inhibitors should be strongly considered in both preoperative and postoperative periods.

In the post-transplant period, helping patients understand patterns related to post-transplant worsening of GERD and/or the development of BOS would be important. Patient education should include symptoms of worsening GERD, pyrosis, regurgitation, or dysphagia or beginning BOS, non productive cough, dyspnea at rest or on exertion, or a decrease in FEV_1 readings. Additionally, patients should be assisted to modify or eliminate patterns that increase the likelihood of the development of BOS, such as preventing episodes of acute rejection, cytomegalovirus pneumonitis, noncompliance with immunosuppressive medications and the occurrence of primary graft dysfunction.

In the ways described above, the APN in primary care can effectively compliment any lung transplant team. The addition of an APN to the lung transplant team should also be considered, as this individual can be a valuable as part of the transplant team, utilizing broad nursing and medically-based education to facilitate comprehensive patient management for this population. This could enhance all aspects of lung transplant care through the coordination of multidisciplinary efforts and communication among team members.

Appendix: Data Collection Tool

Subject	TxDate	DeathDate	Survival	Alive	CurrentAge	AgeatTx	Sex	ABO

Subject	TxDx1	TxType	DateEgd	PreTxEgd	EGD+/-	DateEgd	PostTxEgd	EGD+/-

Subject	DateBravo	PreTxBravo	Bravo+/-	DateBravo	PostTxBravo	Bravo+/-	DatepHProbe

Subject	PreTxpHProbe	Probe+/-	DatepHProbe	PostTxpHProbe	Probe+/-	DateBaSw

Subject	PreTxBaSw	Ba+/-	DateBaSw	PostTxBaSw	Ba+/-	DateDx	PreClinicalDx	Medication

Subject	TxDate	Date	BOS1Yr	BOS1YrGrade	Date	BOS2Yr	BOS2YrGrade

References

Benden , C., Aurora, P., Curry, J., Whitmore, P., Priestley, L., & Elliot, M. J. (2005). High prevalence of gastroesophageal reflux in children after lung transplantation. *Pediatric Pulmonology, 40*(1), 68-71.

Blondeau, K., Mertens, V., Vanaudenaerde, B. A., Verleden, G. M., Van Raemdonck, D. E., Sifrim, D., et al. (2009). Nocturnal weakly acid reflux promotes aspiraiton of bile acids in lung transplant recipients. *The Journal of Heart and Lung Transplantation, 28*(2), 141-148.

Blondeau, K., Mertens, V., Vanaudenaerde, B. A., Verleden, G. M., Van Raemdonck, D. E., Sifrim, D., et al. (2008). Gastro-oesophageal reflux and gastric aspiration in lung transplant recipients with or without chronic rejection. *European Respiratory Journal, 31*(4), 707-713.

Blumenstock, D. A., & Lewis, C. (1993). The first transplantation of the lung in a human revisited. *Annals of Thoracic Surgery, 56*(6), 1423-1425.

Cantu , E., Appel, J. Z., Hartwig, M. G., Woreta, H., Green, C., Messier, R., et al. (2004). Early fundoplication prevents chronic allograft dysfunction in patients with gastroesophageal reflux disease. *Annals of Thoracic Surgery, 78*(4), 1142-1151.

Christie, J. D., Edwards, L. B., Aurora, P., Dobbels, F., Kirk, R., Rahmel, A., et al. (2008). Registry of the international society for heart and lung transplantation: Twenty-fifth official adult lung and heart/lung transplantation report-2008. *Heart and Lung Transplantation, 27*(9), 957-977.

Cooper, J. D., Patterson, G. A., Grossman, R., & Maurer, J. (1989). Double lung transplant for advanced chronic obstructive lung disease. *The American Review of Respiratory Disease, 139*(2), 303-307.

Davis, R. D., Lau, C. L., Eubanks, S., Messier, R. H., Hadjiliadis, D., Steele, M. P., et al. (2003). Improved lung allograft function after fundoplication in patients with gastroesophageal reflux disease undergoing lung transplantation. *General Thoracic Surgery, 125*(3), 533-542.

Devault, K. R., & Castell, D. O. (2005). Updated guidelines for the diagnosis and treatment of gastroesophageal reflux disease. *American Journal of Gastroenterology, 100*(1), 190-200.

D'Ovidio, F., & Keshavjee, S. (2006). Gastroesophageal reflux and lung transplantation. *Diseases of the Esophagus, 19*(5), 315-320.

D'Ovidio, F., Mura, M., Ridsdale, R., Takahashi, H., Waddell, T. K., & Hutcheon, M. (2006). The effect of reflux and bile acid aspiration on the lung allograft and its surfactant and innate immunity molecules SP-A and SP-D. *American Journal of Transplantation, 6*(8), 1930-1938.

D'Ovidio, F., Mura, M., Tsang, M., Waddell, T. K., Hutcheon, M. A., Singer, L. G., et al. (2005). Bile acid aspiration and the development of bronchiolitis obliterans after lung transplantation. *The Journal of Thoracic and Cardiovascular Surgery, 129*(5), 1144-1152.

Estenne, M., Maurer, J. R., Boehler, A., Egan, J. J., Frost, A., Hertz, M., et al. (2002). Bronchiolitis obliterans syndrome 2001: An update of the diagnostic criteria. *Journal of Heart and Lung Transplantation, 21*(3), 297-310.

Gasper, W. J., Sweet, M. P., Hoopes, C., Leard, L. E., Kleinhenz, M. E., Hays, S. R., et al. (2008). Antireflux surgery for patients with end-stage lung disease before and after lung transplantation. *Surgical Endoscopy, 22*(2), 495-500.

Goyal, R. K. (2007). Harrison's Internal Medicine. *Diseases of the esophagus (chap. 273)*. Retrieved April 23, 2007, from http://www.accessmedicine.com

Hadjiliadis, D., Davis, R. D., Steele, M. P., Messier, R. H., Lau, C. L., Eubanks, S. S., et al. (2003). Gastroesophageal reflux disease in lung transplant recipients. *Clinical Transplantation, 17*(4), 363-368.

Hartwig, M. G., Appel, J. Z., & Davis, R. D. (2005). Antireflux surgery in the setting of lung transplantation: Strategies for treating gastroesophageal reflux disease in a high risk population. *Thoracic Surgery Clinics, 15*(3), 417-427.

Hartwig, M. G., Appel, J. Z., Li, B., Hsieh, C. C., Yoon, Y. H., Lin, S. S., et al. (2006). Chronic aspiration of gastric fluid accelerates pulmonary allograft dysfunction in a rat model of lung transplantation. *The Journal of Thoracic and Cardiovascular Surgery, 131*(1), 209-217.

Kahrilas, P. J. (January, 2006). Complications of gastroesophgeal reflux in adults. *UpToDate*. Retrieved March 5, 2007, from http://uptodateonline.com

Lau, C. L., Palmer, S. M., Howell, D. N., McMahon, R., Hadjiliadis, D., Gaca, J., et al. (2002). Laparoscopic antireflux surgery in the lung transplant population. *Surgical Endoscopy, 16*(12), 1674-1678.

Li, B., Hartwig, M. G., Appel, J. Z., Bush, E. L., Balsara, K. R., Holzknecht, Z. E., et al. (2008). Chronic aspiration of gastric fluid induces the development of obliterative bronchiolitis in rat lung transplants. *American Journal of Transplantation, 8*(8), 1614-1620.

Linden, P. A., Gilbert, R. J., Yeap, B. Y., Boyle, K., Deykin, A., Jaklitsch, M. T., et al. (2006). Laparoscopic fundoplication in patients with end-stage lung disease awaiting transplantation. *The Journal of Thoracic and Cardiovascular Surgery, 131*(2), 438-446.

McCance, K. L., & Huether, S. E. (2006). Alterations of digestive function. In S. Huether (Ed.), *Pathophysiology the biologic basis for disease in adults and children* (5th ed., pp. 1385-1445). St. Louis, MO: Mosby.

Meltzer, A. J., Weiss, M. J., Veillette, G. R., Sahara, H., Ng, C. Y., Cochrane, M. E., et al. (2008). Repetitive gastric aspiration leads to augmented indirect allorecognition after lung transplantation in minature swine. *Transplantation, 86*(12), 1824-1829.

Newman, M. (2000). *Health as expanding consciousness*. St. Louis, MO: Mosby.

O'Halloran, E. K., Reynolds, J. D., Lau, C. L., Manson, R. J., Davis, R. D., Palmer, S. M., et al. (2004). Laparoscopic nissen fundoplication for treating reflux in lung transplant recpients. *The Journal of Gastrointestinal Surgery, 8*(1), 132-137.

Orens, J. B., Estenne, M., Arcasoy, S., Conte, J. V., Corris, P., Egan, J. J., et al. (2006). International guidelines for the selection of lung transplant candidates: 2006 update- a consensus report from the pulmonary scientific council of the international society for heart and lung transplantation. *Journal of Heart and Lung Transplantation, 25*(7), 745-755.

Organ Procurement and Transplantation Network. (n.d.). *All Kaplan-Meier median waiting times for registration listed: 1999-2004*. Retrieved March 11, 2007, from http://www.optn.org/latestData/rptStrat.asp

Palmer, S. M., Miralles, A. P., Howell, D. N., Brazer, S. R., Tapson, V. F., & Davis, R. D. (2000). Gastroesophageal reflux as a reversible cause of allograft dysfunction after lung transplantation. *Chest, 118*(4), 1214-1217.

Reilly, J. J. (2005, November). Evaluation and treatment of acute lung transplant rejection. *UpToDate*. Retrieved April 23, 2007, from http://uptodateonline.com

Reilly, J. J. (2006, May). Chronic lung transplant rejection: Bronchiolitis obliterans *UpToDate*. Retrieved March 5, 2007, from http://uptodateonline.com

Reitz , B. A., Wallwork, J. L., Hunt, S. A., Pennock, J. L., Billingham, M. E., Oyer, P. E., et al. (1982). Heart-lung transplantation: Successful therapy for patients with pulmonary vascular disease. *New England Journal of Medicine, 306*(10), 557-564.

Rudow, D. L., Ohler, L., & Shafer, T. (2006). Organ allocation. In W. Graham, L. McGaw, K. Johnson, D. Sampson, C. Sommers, & R. Brown (Eds.), *A clinician's guide to donation and transplantation* (pp. 321-334). Lenexa, KS: Applied Measurement Professionals.

Sampliner, R. E. (2006, September). Treatment of refractory gastroesophageal reflux disease in adults. *UpToDate*. Retrieved April 23, 2007, from http://uptodateonline.com

Scientific Registry of Transplant Recipients. (n.d.). Retrieved April 25, 2007, from http://www.ustransplant.org

Sharples, L. D., McNeil, K., Stewart, S., & Wallwork, J. (2002). Risk factors for bronchiolitis obliterans: A systematic review of recent publications. *The Journal of Heart and Lung Transplantation, 21*(2), 271-281.

Shaw, M.J., Talley, N.J., Beebe, T.J., Rockwood, T., Carlsson, R., Adlis, S., et al. (2001). Initial validation of a diagnostic questionnaire for gastroesophageal reflux disease. *American Journal of Gastroenterology, 96*(1), 52-57.

Stewart, S., Fishbein, M. C., Snell, G. I., Berry , G. J., Boehler, A., & Burke, M. M. (2007). Revision of the 1996 working formulation for the standardization of nomenclature in the diagnosis of lung rejection. *Journal of Heart and Lung Transplantation, 26*(12), 1229-1242.

Sweet, M. P., Herbella, F. A., Leard, L., Hoopes, C., Golden, J., Hays, S., et al. (2006). The prevalence of distal and proximal gastroesophageal reflux in patients awaiting lung transplantation. *Annals of Surgery, 244*(4), 491-497.

Toronto Lung Transplant Group (1986). Unilateral lung transplantation for pulmonary fibrosis. *New England Journal of Medicine, 314*(18), 1140-1145.

Trulock, E. P. (2003, October). Physiologic changes following lung transplantation. *UpToDate*. Retrieved March 5, 2007, from http://uptodateonline.com

Trulock, E. P. (2006a, January). Overview and outcomes of lung transplantation. *UpToDate*. Retrieved March 5, 2007, from http://uptodateonline.com

Trulock, E. P. (2006b, March). Indications; selection of recipients; and choice of procedure for lung transplantation. *UpToDate*. Retrieved March 11, 2007, from http://uptodateonline.com

Trulock, E. P., Edwards, L. B., Taylor, D. O., Boucek, M. M., Keck, B. M., & Hertz, M. I. (2005). Registry of the international society of heart and lung transplantation: Twenty-second official adult lung and heart-lung transplant report-2005. *The Journal of Heart and Lung Transplantation, 24*(8), 956-967.

Trulock, E. P., & Mandel, J. (2006, May). Immunosuppression following lung transplantation. *UpToDate*. Retrieved April 23, 2007, from http://uptodateonline.com

Trulock, E. P., Patterson, G. A., & Cooper, J. D. (2007). Lung transplantation: Introduction. In *Harrison's internal medicine (chap. 248).* Retrieved March 10, 2007, from http://www.accessmedicine.com

Young, L. R., Hadjiliadis, D., Davis, D., & Palmer, S. M. (2003). Lung transplantation exacerbates gastroesophageal reflux disease. *Chest, 124*(5), 1689-1693.

Vita

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