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Pulmonary Retransplant for a Patient with Bronchiolitis Obliterans Syndrome
And Hepatitis C Viremia: An Ethical Case Analysis
Patricia A. Maani, F.N. P., DrNP (c )

Abstract

*The purpose of this paper is to discuss and analyze the ethical appropriateness of pulmonary retransplantation as a viable treatment option for end-stage bronchiolitis obliterans syndrome, commonly referred to as chronic rejection. Lung transplantation has become a life-saving treatment for patients with advanced lung disease, but not replantation, for reasons not clearly elucidated. Though statistics show comparable survival of retransplant to primary transplant recipients, this is not an option often considered. Through the course of clinical practice, it became evident that retransplantation had many ethical components that were not fully investigated as part of the retransplantation process. This paper is to identify the relevant ethical considerations regarding pulmonary retransplantation.*

*Keywords: Pulmonary Retransplantation, Thoracic Allocation, Bioethics, Lung Transplant, Hepatitis C Virus.*

Pulmonary Retransplant for a Patient with Bronchiolitis Obliterans Syndrome
And Hepatitis C Viremia: An Ethical Case Analysis

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**Case Study**

A 27-year-old patient underwent bilateral, sequential lung transplantation in March 2002. This patient was critically ill at the time of organ offer: ventilator dependent, in ICU, profound hemoptysis, and multiple blood transfusions for blood loss due to his hemoptysis. When a suitable donor organ became available, the patient was transferred to the transplant center emergently, via mobile ICU.

In the immediate postoperative period, the patient had rising liver functions enzymes and subsequent testing revealed hepatitis C Viremia (HCV), which was believed to be transplant-induced. The recipient screened negative for HCV prior to transplant.

Additionally, the outlying hospital reported all blood products given to this patient were negative for hepatitis viruses.

Approximately 14 months later, the patient had incremental decreases in pulmonary function testing with concomitant bronchiolitis obliterans on biopsy. Despite multiple adjunctive therapies, including fundoplication for gastroesophageal reflux (GERD), Rituxan and photopheresis, bronchiolitis obliterans syndrome (BOS) developed. Coexisting diagnoses included: hypertension, Cytomegalovirus (CMV) mismatch, diabetes, and progressive weight loss, currently 106lbs at 72".

In light of aggressive BOS, the transplant team decided to evaluate this patient for pulmonary retransplantation. Varying ethical dilemmas arose and coincided with alarming statistics of the success (or relative lack thereof) in pulmonary retransplantation. The clinical team found themselves divided on this issue, and this report will examine the clinical, ethical and moral perspectives of this case study.

## Clinical Background

Chronic allograft rejection remains the bane of improving long-term outcomes for lung transplant recipients. BOS is defined as "…a clinical syndrome of irreversible, progressive airway obstruction after lung transplantation, caused by the presence of obliterative bronchiolitis," (Brugière 2003). Bronchiolitis obliterans is a fibrotic process that results in the progressive narrowing of the bronchiolar lumen, with concomitant airflow obstruction (Belperio 2003).

Nearly 50 percent of all pulmonary transplant recipients develop BOS by their fifth postoperative year (Hertz 2002). The earliest clinically detectable BOS is detectable by a 10 percent decline, from best postoperative baseline, in Forced Expiratory Volume in one second ($FEV_1$), and this is called BOS Stage Zero-p (BOS 0-p). Subsequent decline in $FEV_1$ is assigned into incremental stages, ranging from 1-3 (Estenne 2002).

Suspected risk factors for BOS include acute rejection, medication non-compliance, Cytomegaloviral infections, organizing pneumonia, older donor age, prolonged ischemic times, and bacterial/fungal/non-CMV viral infections (Estenne 2002). More controversial suspected risk factors include airway complications, such as bronchial anastamotic stenosis and other such complications (Lau 2003); however, these factors are not convincingly linked to BOS. The Duke University Lung Transplant Group correlated a relationship between BOS and patients with untreated GERD, as diagnosed by pH probe, and found that if the GERD was corrected, via fundoplication, the result was an improvement and/or stabilization of BOS (Davis 2003).

In cardiothoracic transplant, the use of organs infected with HCV is limited to those patients who are critically ill with precarious likelihood of recovery and stablization. With the need for transplant imminent and the scarcity of suitable pulmonary organs, the utilization of HCV infected organs becomes a medically warranted, needs-based actuality (Pfau 2000). Cotler (1991) found 17 percent of lung transplant programs have transplanted HCV(+) lungs into uninfected recipients. By contrast, standard guidelines for lung transplantation advise against transplantation for patients with active HCV disease (confirmed with HCV-RNA and biopsy-proven), as fulminant hepatic failure has been linked to poor outcomes post-transplantation.

## The Pulmonary Organ Dilemma

Treatment options for end-stage lung disease have been transformed by the option of transplantation. However, the availability of acceptable pulmonary organs remains limited. There are nearly 4000 patients listed for lung transplantation, but 941 transplants were performed in 2000. About 500 patients die while waiting for a transplant. (Egan 2003). The shortage of usable donors is also a concern because the lungs are delicate in nature, and most mechanisms of trauma and brain death will more so adversely affect the lungs than the solid organs. As such, the quality of the pulmonary organs is grossly, (sometimes irreversibly), affected (Egan 2003).

There are also greater concerns about the thoracic allocation system, which currently allocates organs based on ABO compatibility, followed by time accrued on the waiting list. Following a directive from the Department of Health and Human Services, the United Network for Organ Sharing's (UNOS) Thoracic and Lung Allocation subcommittees met to develop a new allocations system that would ensure allocation of this limited organ to those most in need (UNOS 2002).

To ensure fair allocation of thoracic organs, four ethical principles must be considered: a) Equity (allocation and selection of recipient is made without bias), b) Justice (providing patients with what is due to them; somewhat righteous in implication; and suggestive of healthcare practitioners arriving at a decision based on personal values, moral, etc.), c) Beneficence (to do no harm), and d) Utility (distribution of scarce resources to ensure optimal outcomes for the many, i.e. efficacy.)

## Ethical Analysis of Retransplantation

Though all principles are key, utility prevails because it is an ethical and moral obligation (Ubel 1993). Organs should be allocated to those patients for whom it will provide the greatest benefit. However, it is the definition of "benefit" that remains ill defined. The pre-existing therapeutic relationship of the transplant center and their post-operative patients establishes a fiduciary obligation to that patient. Thus, retransplantation is of benefit to that patient. Ironically, refusal to consider retransplantation could be a variant of patient abandonment, which then leads to violation of the ethical principle of non-malfecience. Conversely, retransplanting one patient when another has not "had their chance" with a first transplant can also be abandonment, or possibly even neglect.

Does the transplant team "owe" the patient for a primary allograft that failed? Is that team obligated (professionally, morally, or ethically) to provide "restitution" to the patient (vis á vis the second chance retransplant) for his/her suffering? How does the transplant community justify the expense of retransplantation? And for that matter, is retransplantation even a cost-effective measure?

As Ubel (1993) states, "Decisions to transplant or retransplant would be very hard to base on a scale of comparative misery" - a poignant comment when one takes into consideration that the measurement of said misery is subjective and the expression of which will vary from patient to patient. As health care providers, we must balance our obligations of efficacious resource allocation with fidelity to care for our patients.

Moreover, while our delivery of health care must ideally be fiscally responsible, we are duty bound to ensure our treatment for each patient is without regard for financial incentives or at the expense of patient loyalty. There are instances when our strong patient advocacy can, in fact, be unjust. Since survival after retransplantation is lower

than after primary transplantation, a guarded approach remains warranted (Novick 1995; Saeed 2001). New data, however, indicates that retransplant candidates who are ambulatory and not on invasive ventilation have increased survival rates: 64 percent (+/- 5) at one year, which is comparable to national one-year survival for primary transplants (Brugière 2003; Novick 1998).

Additionally, Brugière's data showed improved survival for patients who were greater than two years post-transplant (Brugière 2003). Kotloff (2003) urges the transplant community to maintain equilibrium between "…the competing goals of maximizing the distribution of a scarce resource to the greatest number of patients vs. optimizing the outcome of the individual patient."

One suggestion was to hold retransplant candidates to the same criteria as primary transplant patients (Novick 1995), which could contribute to improved outcomes post-transplant. Another proposed solution is to establish an annual limit on organs allocated for retransplantation. Is this a potentially fair solution? While no answer remains obvious, there is data to suggest long-term viability. Ubel (1995) found while subjects strongly favored prognosis as the key component in allocation (90 percent favored organ allocation to patients with a better prognosis), they demonstrated a conviction that prognosis alone was not enough. Study subjects demonstrated their "…reluctance to abandon any group of candidates…as if saying that although prognosis is important, some amount of organs should be set aside to give hope to other candidates," (Ubel 1995).

Societal attitudes on retransplantation are, therefore, not purely utilitarian. There is concern for efficacy maximization on varying levels to ensure that some benefit is brought to all potential patients, even those who may be at a disadvantage (Ubel 1995).

Theories of just allocation remain central to the ethical analysis of retransplantation and thoracic organ allocation. Resource allocation is defined as the allotment of supplies to the populace. McKneally (1997) stratified allocation within the context of healthcare: macroallocation (government distribution); mesoallocation (hospital distribution); and microallocation (patient distribution.) It is at the level of microallocation that we examine retransplantation.

Due to the scarcity of donor organs, the wait list mortality for thoracic patients remains high. Because of this limitation, rationing of resources must utilize justice and fairness, but what is just and fair remains negotiable. A "fair chance" is not equivalent to a better outcome, and this forces the examination of sicker patients to determine their "worthiness." And because patient deaths will occur while waiting for transplant, it is important to accept the impossibility of a system without wait list mortality.

Bioethical theories on organ allocation are created in an effort to optimize/ensure the fairest method of distribution for a limited resource, i.e. ensure efficacy as dictated by utilitarian principles. Historically, allocation criteria included considerations of age, social worth, financial stability, need, and quality of life (Ubel 1999). And while this does not favor the primary transplant candidate, neither does it favor the retransplant candidate. Both patients are of equal need, and the utilitarian analysis would mandate we toss the proverbial coin to determine allocation (Ubel 1993).

Interestingly, utilitarianism advocates efficacy: transplant the patient with the greater likelihood of survival. Thus, efficacy remains "…a morally relevant criterion for distributing scarce transplant organs," (Ubel 1993). Interestingly, in the Netherlands and

Germany, allocation statutes stipulate: "In designating the recipient, account is to be taken of no other factors than the blood compatibility and histocompatibility of the donor and the recipient of the organ, the medical urgency for the recipient, and other circumstances associated with the state of the organ, and also, if these factors are not decisive, then length of time the recipient must wait," (Price 2000, p.457)

## Conclusion

The issue of retransplantation is a complex and intricate decision with various ethical principles that warrant examination while determining the allocation of an insufficient supply. Most centers will consider retransplantation on a case-by-case basis and agree there is an obligation – fiduciary, social, and moral - to patients transplanted at their center. In this instance, we have a patient who was infected with HCV through the course of his transplant surgery and now has aggressive BOS warranting earnest consideration for retransplantation.

This candidate would be declined based on his initial assessment of HCV status; however, further deliberation is necessary because it is believed the transplant infected the recipient. The consideration of pulmonary retransplantation is a patient specific process in which the candidate is re-evaluated as a new referral. Updated diagnostics studies and measures of functional status, i.e. six minute walk test, cardiopulmonary exercise test, chest radiographs, and computerized tomography scans, are obtained and found to be well within acceptable limits for transplant candidacy. Potential complications and co-morbidities were reviewed, and the patient's repeat liver biopsies show chronic HCV without active disease, fibrosis, or scarring.

The argument for patient fidelity and ethical obligation prevails. The co-morbidity of HCV, possibly transplant-induced, is an otherwise relative contraindication for lung transplant and becomes the central focus of this retransplantation decision. The HCV was left untreated, as research has shown that there is an increased risk of allograft rejection when treatment with antiviral therapies is initiated. As such, the risk exceeds the benefit of treatment for HCV in lung transplant recipients (Chan 2004.) The principles of beneficence (the duty to promote the individual patient's best interest), fairness (equitable distribution of resources), and utility (ensure the best outcomes for the best recipients) must equilibrate and balance (Biggins 2002).

In addition, transplant teams must consider their reasons for re-transplantation of individual patients. The fiduciary responsibility must balance with efficacy, and we must select interventions that will be most effective. Additionally, the use of diseased organs for transplantation may give rise to the potential for fault liability, possibly even breach of contract (Price 2000). The fundamental obligation of all transplant programs is to optimize the well being of their patients through the life-saving measure of organ transplantation. However, McKneally (1997) believes we must "…advocate for one's own patients but avoid manipulating the system to gain unfair advantage to them."

The Code of Ethics obligates us to promote fair access to health care resources without losing cost-effectiveness (McKneally 1997). Patient trust remains a key focus, since it is during times of critical illness that patients are most vulnerable and their trust in the health care team most indomitable. The resiliency of trust is exemplified in the setting of retransplantation – what other time would require such conviction and faith in your transplant team than when contemplating retransplantation? (Hall 1998).

This patient has multiple factors meriting consideration for retransplantation: greater than two years post-transplant, ambulatory, no invasive ventilation, and no active HCV disease. The recurrence of BOS is not appreciably greater for retransplant patients (Laohaburanakit 2003), and retransplantation should be a viable consideration for patients who have progressive BOS despite rescue measure therapy.

Another consideration is the fiduciary obligation to this patient. Frankly, the unintentional transplant induced HCV compels the transplant team to consider retransplantation since it is nearly a breach of contract and thus in violation of the team's intent, which has a lesser role in arguments of distributive justice and efficacy, to optimize health status. Moreover, the prior relationship with this patient requires the transplant center to undertake all efforts within their realm of possibilities to save this patient's life. Any disregard for this patient's condition is a violation of beneficence, and could result in death.

In the final analysis, the transplant team must examine the case from multiple perspectives: ethical, social, moral, and perhaps even financial. We must work in the interest of our patients, as well as for candidates awaiting primary transplant. In this case, we have a patient who was dealt an inequitable hand when transplanted – HCV transmission, and progressive BOS. We must remember our ethical obligations to this patient and trust the data we have on retransplantation to formulate a determination of survival benefit. The patient is greater than two years post-transplant, free of invasive ventilation, ambulatory and free of active HCV. The patient also developed BOS after the first post-operative year.

Additionally, HCV was transplant induced. Diagnostic measures remain within acceptable limits, and there is no other indication to refuse retransplantation. In this case, we have decided to move forward with listing the patient for pulmonary retransplantation, and we hope that our decision will bring about an improved quality of life for him.

It is my hope that our decision will set precedent and enable a more thoughtful and cautious analysis of pulmonary retransplantation for patients. If this option is completely withheld from them, their lives will inevitably and abruptly cease. The implication of a rushed death is remarkably unethical. As lung transplant clinicians, we strive to prolong and improve the quality of our patients' lives, and we hope that our efforts simplify the previous complexity of their lives due to progressive, end-stage lung disease. After all, "What is so intricate, so entangled as death?" (*John Dunne 1628*).

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