Smoking Relapse After Lung Transplantation: Is a Second Transplant Justified?

Running Head: Smoking Relapse After Lung Transplant

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INTRODUCTION

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Robert M. Sade, MD

One of the recurrent problems in health care is the question of how best to allocate scarce resources. If we think of scarce medical resources as medications, devices, or other materials that cannot be supplied in sufficient quantities to fill the need for them, even if financial resources to pay for them is unlimited and the time needed to acquire them is not an issue, then seemingly only one medical resource is truly scarce: vital organs for transplantation. Ever since human organ transplantation began in earnest in the early 1980s, the need for organs has always outstripped their availability. For example, in 2019 the waiting list comprised nearly 120,000 candidates, and over 10,900 candidates died in that year either while on the waiting list or after being removed from the list when they became too sick to transplant. [1] None of those deaths would have occurred if organs had not been in scarce supply.

Because of the scarcity of organs, transplant centers must be selective in adding patients to the transplant waiting list to compete for available organs. General criteria for the selection process are provided by the Organ Procurement and Transplantation Network and specific criteria are applied by transplant centers. Among the criteria is the patient's reliability in following post-transplant regimens — a patient's unreliability suggests that the transplanted organ may be at increased risk of failure.

Multidisciplinary selection committees, generally composed of broadly representative membership, make selection decisions, and placement on a waiting list is literally a matter of life

and death for many patients with end-stage organ failure. The following fictional vignette illustrates a problematic decision faced by a lung transplant selection committee.

Smoking Relapse After Lung Transplant

Morris Philips is 53 years old and underwent a lung transplantation three years ago. He had begun smoking at age 15 and within a few years was smoking two packs a day. He developed severe chronic obstructive pulmonary disease (COPD), stopped smoking for a year, and underwent a lung transplantation at the age of 50. His home was in a rural community 200 miles from the transplant hospital, so for the first year after his operation, he lived with a friend close to the transplant center. He did quite well, maintaining normal pulmonary function, with both FEV1 and FVC in the 90% range.

Mr. Philips returned to live at home 12 months after his operation. Three months after moving back to his rural community, 15 months postop, his followup visit to the transplant center revealed still normal pulmonary function, but he admitted he had started smoking again, a pack a day. He was warned that smoking could damage his transplanted organ, so he had to stop, as he had before his operation. At his next visit at 18 months postop, his pulmonary function had deteriorated — FEV1 and FVC 70% and 75%, respectively — and his exercise tolerance seemed lower than it had been. He admitted to smoking even more, 1½ - 2 packs a day. He was strongly admonished and told he had to stop smoking or he might lose his new organs.

At his 21 month postop visit, Mr. Philips reported increasing shortness of breath, his pulmonary function was still worse — FEV1 and FVC in the 60% range — and he had managed to reduce

his smoking to ½ -1 pack a day. He was again admonished and told that any smoking at all was unacceptable — he had to stop totally, and this would be tracked with cotinine testing.

At his 2-year postop visit, he had stopped smoking entirely for the 3 months since his previous visit, but his shortness of breath had worsened and his lung function had deteriorated even further. Over the next 3 months several additional studies were done, and multiple endoscopic lung biopsies showed widespread bronchiolitis obliterans. It was now clear that his grafts were failing and he was in need of a new lung transplant. There was vehement disagreement among members of the pulmonary transplant selection committee as to whether re-transplant was justified. They decided to seek the counsel of two lung transplant experts: should Mr. Philips be listed for another transplant?

PRO:

Jacob Klapper, MD

Mr. Philips should be placed on the waiting list for lung transplantation.

Near the end of his all too brief life, F. Scott Fitzgerald wrote in the notes to his final novel, *The Last Tycoon*, "There are no second acts in American lives". These words written at a true low point in the author's life, as he was very near his own death, may have been an expression of what he felt to be the American mentality of being unforgiving or perhaps

indifferent to the failings of our fellow countrymen and women. Given the continued popularity of this quote, one might think that Fitzgerald had put his finger on a feature of the American psyche.

It is a bit harsh to paint an entire continent of people with such a broad brush. In fact, it is debatable whether a heterogeneous nation such as ours could ever possess a national mindset. Certainly, we have, at times, yielded to, as Lincoln said, the "better angels of our nature". In brief intervals of progressive spirit, we have made allotments for those among us who have not had the advantages of others. Major programs designed to give our fellow citizens a leg up (see the GI bill post World War II) or a safety net to prevent their descent into destitution, eviction, and bankruptcy (see Medicaid/Medicare and Social Security). There was even a time when we built large "penitentiaries" not "prisons", a failed yet noble exercise from a more innocent time, but based nevertheless on our momentary belief that we could reform those who had violated our laws.

In the last 40 years, this country has intentionally distanced itself from the progressive periods of the 1910's, 1930's, and 1960's. We have lamented the erosion of our manufacturing base and with it the loss of our vibrant middle class, but our leaders have no appetite or desire for the expansive social programs that are a necessity in times of immense change. Remember after all, the guiding spirit of this age is signified best by that famous quote from a cold day in January of 1981: "Government is not the solution to our problem, government is the problem". Perhaps. But what is worse than bad governance is doing nothing, and nothing has truly been done.

Instead we have gotten what we didn't pay for; wide disparities in wealth and tragic results in our public health. Inarguably, the very few have prospered generating enormous disparities in wealth that are reminiscent of another era of robber barons. Consequently, the

cultivation of these fortunes has come at a cost, born by those less fortunate. Our state hospitals have not only been closed, but their alternatives underfunded. Meanwhile, even when we make attempts at social welfare, such as the Affordable Care Act with its vital expansion of Medicaid, we have hell-bent ideologues in certain states that deny this supplement. As a result, in states such as Alabama, the lack of federal dollars has further limited health care access. In 1980, for instance, 45 out of 54 of Alabama's rural counties had hospitals that offered obstetric services. In 2019, that number was sixteen, a consequence of poor hospitals in rural areas needing to cut vital services to keep the doors open.[2]

So where am I going with this? Why this expansive liberal view of the last forty years of American life? Because ultimately what has and has not happened on a macro level filters down to a micro level to affect the most vulnerable. And among the most vulnerable areas of this country in 2020: our rural towns and communities. This brings us to the patient in question. Who is Morris Philips and what is his community like?

The work of the Princeton economists Anne Case and Angus Deaton are illuminating of the current status of Mr. Phillip's community. Their research has focused on what they term "deaths of despair" and they have been at the forefront of highlighting the dramatic rise in premature death amongst the rural poor over the last twenty years. It's not just the opioid crisis, but also the unraveling of the social fabric in our rural communities. Diminished rates of church attendance and marriage, wage stagnation or decline, and minimal job prospects have created rural communities where vital social services are lacking and the nuclear family has fissured in remarkable ways. The results have been dramatic. From 1978 to 1998, the mortality rate for US whites aged 45-54 fell by 2% per year, but then unfathomably, from 1998 to 2014, white

non-Hispanic mortality has risen by a percent a year![3] A remarkable reversal that is emblematic of what the journalist George Packer has termed America's "unwinding".

A pretty bleak picture of rural America and Mr. Phillip's peers to be sure, but a harsh reality. In all likelihood, for a patient like Mr. Philips, this is the status of the community he returns to after his transplant. Add to this the fact that quitting and continuing to abstain from tobacco use is difficult. For instance, in a trial published two years ago in the *NEJM*, researchers studied the effectiveness of five different approaches to smoking cessation. In this study, over 6000 individuals were randomized from a population of smokers from 54 companies across the country. The primary endpoint was sustained smoking abstinence for 6 months after the target quit date. Each trial participant was given access to some cessation aid whether it be encouraging text messages, nicotine replacements, e-cigarettes, or even financial incentives. Regardless, rates of smoking cessation were low across all the various interventions (2.9% in the most successful cohort).[4]

Would we think for a moment that Mr. Philips had access or the money to afford such aids when he returned to his community? Unlikely, given the money he is required to spend on his medications and basic necessities. But you might say, he quit before surgery, so he proved he could do it. For sure, but ultimately what I am suggesting is that we must focus less the on the act of returning to smoking and rather what smoking represents. While in close proximity to his transplant center and his friend, he maintains some semblance of the social structure that allows him to abstain from cigarettes. Then, however, he returns home to a community far less equipped to support a member in need.

Overwhelming to be sure and quite daunting for someone who must re-establish himself all while being unmarried and unemployed. In all likelihood, this situation is a source of stress

and anxiety, vital ingredients for depression. We may also surmise, given his condition and his surroundings, that Mr. Philips suffered from some level of depression prior to transplant. Add to this that we know from studies of patient reported outcomes after transplant, that depression is not uncommon and increases the risk of mortality by 65%. In addition, it is acknowledged that lung transplant recipients have issues of self-esteem, anxiety, and even post-traumatic stress disorder.[5] Taken in this context, it is not hard to fathom how Mr. Philips returned to the "crutch" that served him well since he was 15.

In the end, however, Mr. Philips was provided with a wonderful gift. A generation ago, he would have died from his disease. Without a doubt, he must be held responsible for understanding the enormity of what has been done for him and must guard and protect his lungs. I don't deny this but I also believe that we must appreciate the totality of the individual. What does his smoking represent? Is this truly a casual disregard or is it something more complex? A manifestation, if you will, of an individual suffering with the enormity of taking care of his lungs while meeting the regular stressful requirements of daily living.

Ultimately, we are all byproducts or our environment and the methods that we develop for coping and adjusting to the realities of our lives are predicated upon the resources at our disposal. Admonishing a patient like Mr. Philips, instead of attempting to contextualize his smoking as part of a larger picture is to do him a disservice. Enrolling him in a smoking cessation program, addressing his likely depression, or the stresses in his life, that is hard and time-consuming. But don't we owe it to him? After all we are his physicians not judges. Life and the lives we lead are complex, and all too often we distill our modern existence into the binary right and wrong; a mindset that is far easier to maintain than to appreciate the subtle

nuance of the individual and his condition. Eighty years ago, Fitzgerald suggested we lacked the capacity to provide second chances. I should hope we have learned something in the interim.

CON:

Chadrick Denlinger, MD

Mr. Philips should not be added to the waiting list for lung transplantation.

The US Department of Health and Human Services recognizes that the number of patients potentially benefiting from organ transplantation greatly exceeds the number of available organs. As a result, the organ procurement and transplantation network (OPTN) has been charged with the responsibility of allocating organs to patients most likely to derive the greatest benefit from transplantation. In 2005, the United Network for Organ Sharing (UNOS) established the lung allocation scoring (LAS) system to prioritize patients on the waiting list such that patients with the greatest risk for dying on the wait list received the highest priority. Those possessing the greatest benefit of a lung transplant are most likely to receive organ offers. The LAS system incorporates both the risk of dying on the wait list as well as the risk of death following lung transplantation, although a greater emphasis is placed on risks for wait list mortality. While the LAS system was born out of rigorous statistical analysis of UNOS databases, the risk model has recognized deficiencies where risks of an individual may not be adequately objectified by the calculated LAS score. To accommodate inherent deficiencies, UNOS created a mechanism where transplant programs can apply for exceptions on behalf of

their patient whose clinical acuity is not sufficiently represented by the calculated LAS, and thereby be assigned a higher score. The allowance for exceptions underscores the concept that clinicians understand countless nuances which contribute to the risks and probable long-term outcomes of lung transplantation for specific patients.

With this concept in mind, the hypothetical patient described should NOT be considered for a second transplant. The adverse effects of smoking on pulmonary function are well established and smoking is the predominant contributing factor for the development of COPD, emphysema and chronic bronchitis.[6] The detrimental effects of smoking relate to chronic inflammation leading to release of proteolytic enzymes by neutrophils that degrade the infrastructure of lung parenchyma. Macrophages are the predominant inflammatory cell type located in respiratory bronchioles and alveoli and are a central factor in the progression of COPD. However, several other inflammatory cells are also consistently present such as neutrophils, and T helper cells. Importantly, these same cells are also implicated in chronic lung allograft dysfunction following transplantation.[7,8] The damaging effects of smoking are more associated with the immunological response to toxins than they are to the smoke itself and this recruitment of inflammatory cells is particularly problematic following a lung transplant.

After transplantation, the allograft is impacted by combined insults of cellular rejection and inflammation that is exacerbated by smoke inhalation.[9] Smoking recidivism following lung transplant occurs in approximately 10% of all lung transplant recipients, and this rate may be even greater among patients transplanted for COPD. In other solid organ transplants, chemically confirmed smoking recidivism after transplant was associated with a decreased median survival, a dramatic increased risk for malignancy and increased graft coronary artery disease, thus corroborating previous reports.[10,11] The impact of smoking on pulmonary function following

transplantation has not been well investigated and data directly addressing this issue remains limited.[12,13] Perhaps, the near certainty of apparent outcome may have suppressed intellectual curiosity on this matter. However, the existing data does suggest that smoking recidivism following lung transplant contributes to diminished pulmonary function with spirometry patterns similar to patients with bronchiolitis obliterans (BOS) despite the lack of histological evidence for BOS.[13] Thus, patients who resumed smoking after lung transplantation suffered from diminished lung function at a rate comparable to other patients suffering from the disease process responsible for the vast majority of post-transplant deaths.

Smoking recidivism after transplant raises additional concerns related to long-term survival and overall outcomes as it has been associated with poor medication compliance in several non-transplant related disease states as well as following solid organ transplantation.[10,14-16] Obviously, compliance with medications is of utmost importance following transplantation in order to minimize risks for rejection as well as opportunistic infections. All patients are counseled regarding the importance of remaining tobacco-free following transplantation and smoking recidivism raises strong concerns about compliance in general which would jeopardize his candidacy for a second lung transplant.

Undoubtedly, patients suffering from bronchiolitis obliterans after transplantation benefit from consideration of a second lung transplant provided their general health would support a second operation. In a similar way, clinical beneficence applies to all other patients currently listed for lung transplant or being considered for listing. The perceived survival benefit and improved quality of life following transplant applies in a similar way to all patients awaiting organ offers from a limited number of viable donors. Given the perennial problem of potential recipients vying for a limited resource, utility and fairness become dominant facets for

consideration. While the current LAS system is weighted in favor of estimating a patient's risk of mortality while on the waiting list, the potential for years gained and improved quality of life following transplant are also appropriately considered.

Post-transplant survival and patient well-being have always been important considerations for transplant programs, which is evident by the rigorous evaluation process for potential recipients. In addition to a comprehensive health evaluation, patients are also assessed to determine that they have the necessary social support systems and financial resources to support their care after transplantation. Compliance is also assured by reviewing their medication compliance history, attendance at group educational meetings and participation in pulmonary rehabilitation programs. This comprehensive evaluation optimizes the likelihood that recipients will be good stewards of their allograft. Remaining free of the injurious effects of tobacco use is also a critical component of appropriate stewardship.

The United Network for Organ Sharing's statement on Ethical Principles and Regulatory Requirements notes, "The principle of utility, applied to the allocation of organs, thus specifies that allocation should maximize the expected amount of overall good." The statement continues:

> Developing an allocation policy grounded in the principle of utility requires that the various goods and harms be compared using standardized outcome measures so that at least a rough estimate can be made in determining which allocation produces the greatest good. Good consequences of transplantation include, but are not limited to: saving life, relieving suffering and debility, removing psychological impairment, and promoting well-being. Data measuring predicted graft survival, predicted years of life added, and even more importantly, predicted quality adjusted life years (QALYs) added are relevant to such determinations.

The guiding ethical principles of UNOS indicate that transplant programs must consider post-operative expectations, including proper stewardship, for individuals in order to fairly allocate the limited resource of solid organs available for transplantation.

In the described vignette, the patient's history of non-compliance and smoking recidivism places that particular patient at a disturbingly high risk for worse long-term outcomes following a potential second transplant. While this patient may deserve consideration for a second transplant in the setting of an unlimited resource, the harsh reality of our current limited organ supply mandates that available organs ought to be allocated to patients with a higher probability of proper stewardship of this gift. Therefore, it is the responsibility of the transplant center involved in the care of this individual to NOT consider listing him for a second transplant for the benefit of all patients with advanced lung disease.

CONCLUDING REMARKS:

Robert M. Sade, MD

One of the most daunting tasks of transplant centers is determining who should be placed on a specific organ waiting list. UNOS has provided some criteria for guidance, as Denlinger has described, but the guidance leaves some wiggle room for decision makers, as some exceptions are permissible.

In arguing for including Mr. Philips on the waiting list for lungs, Klapper is on the side of the angels in saying, "After all we are his physicians not judges" — physicians generally should not make treatment decisions based on non-medical factors, such as socioeconomic status, social

conditions, or patients' contributions to their illness.[17] Transplant waiting lists present a categorically different situation from most clinical circumstances, however, because of the severely limited availability of medically suitable organs for transplantation and the requirement to make the best use of those organs — or in the words of UNOS, to produce "the greatest good". Both are open to interpretation, however: what is "the best use" and what is "the good"?

UNOS's lung allocation system is largely objective and fairly specific in how determinations of suitability for listing should be made, but it also allows for exceptions based on considerations of individual patient factors. Both Denlinger and, using that fudge factor, Klapper can make different professional determinations of Mr. Philips' suitability for listing, Klapper in favor, Denlinger against. Such decisions are not made by individual physicians, however; they are made by multidisciplinary selection committees. Denlinger's case against listing seems *prima facie* to be most consistent with UNOS guidance, but Klapper's "second chance" argument could carry the day by persuading a sufficient number of selection committee members to adopt his view. Such is the nature of decision making by committee.

References

1. Organ Procurement and Transplantation Network. National data: Removal reasons by year. Available at: https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/#. Accessed November 9, 2020.

2. Press E. A Deadly Principle. The New Yorker. April 2020.

3. Case A, Deaton A. Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century. Proc Nat Acad Sci. 2015;112:15078-15083.

4. Halpern S, Harhay M, Saul, et al. A Pragmatic Trial of E-cigarettes, incentive, and drugs for smoking cessation. NEJM. 2018;378:2302-10.

5. Kolaitis N, Singer J. Defining success in lung transplantation from survival to quality of life. Semin Respir Crit Care Med. 2018;39:255-268.

6. Han MK, Criner GJ. Update in chronic obstructive pulmonary disease 2012. Am J Respir Crit Care Med. 2013;188:29-34.

7. Spurzem JR, Rennard SI. Pathogenesis of COPD. Semin Respir Crit Care Med. 2005;26:142-153.

8. Yamada Y, Brustle K, Jungraithmayr W. T helper cell subsets in experimental lung allograft rejection. J Surg Res. 2019;233:74-81.

9. Bharat A, Narayanan K, Street T, Fields RC, Steward N, Aloush A, et al. Early post-transplant inflammation promotes the development of alloimmunity and chronic human lung allograft rejection. Transplantation. 2007;83:150-158.

10. Botha P, Peaston R, White K, Forty J, Dark JH, Parry G. Smoking after cardiac transplantation. Am J Transplant. 2008;8:866-871.

11. Nagele H, Kalmar P, Rodiger W, Stubbe HM. Smoking after heart transplantation: An underestimated hazard? Eur J Cardiothorac Surg. 1997;12:70-74.

12. Bauldoff GS, Holloman CH, Carter S, Pope-harmann AL, Nunley DR. Cigarette smoking following lung transplantation. J Cardiopulm Rehab Prev. 2015;35:147-153.

13. Hofmann P, Benden C, Kohler M, Schuurmans MM. Smoking resumption after heart or lung transplantation: a systematic review and suggestions for screening and management. J Thorac Dis. 2018;10:4609-4618.

14. Kiortsis DN, Giral P, Bruckert E, Turpin G. Factors associated with low compliance with lipid-lowering drugs in hyperlipidemic patients. J Clin Pharm Ther. 2000;25:445-51.

15. Zaghloul SS, Goodfield MJD. Objective assessment of compliance with psoriasis treatment. Arch Dermatol. 2004;140:408-14.

16. Han E, Sohn HS, Lee JY, Jang S. Health behaviors and medication adherence in elderly patients. Am J Health Promot. 2017;31:278-86.

17. Council on Ethical and Judicial Affairs. Opinion 11.1.3 Allocating limited health care resources. In: *Code of Medical Ethics.* Chicago, IL: American Medical Association; 2017:185.