Review Article

Ethical subjects in lung transplant and current era

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Abstract: Ethical issues in palliative care often arise in chronic and terminal diseases because of concerns about how much care and what kind of care make sense for someone with a limited life expectancy due to chronic disease. There is often conflict between health care team including clinicians, nurses, and patients, and their families about how to define appropriate care and how to deliver it especially once patients approach death. The four principals of Ethics which are: autonomy, beneficence, non-maleficence, and justice are not always straightforward to implement in rapidly evolving medical technology and increasing life expectancy for example. In the United States, this question of "who decides" has undergone a major transition from paternalism (where the health professional decides) to autonomy (where the patients or their surrogate decides). Lung transplantation like any other solid organ transplantation requires a skilled team to navigate through many ethical and social issues to be fair and just in scarce pool of donated organs. In such process, considering the fundamental principles of ethics, is the alphabet of such program to succeed. So when clinicians explore the patient's values and goals and use that knowledge to make an informed recommendation the process will be fair and unbiased. This article discusses the ethical issues surrounding lung transplant by addressing few question like how can we respect equity of access and also equality of outcome and how do we allocate the available resources and how do we avoid the provider own bias in the process and also addresses the ethical dilemma around single *vs.* double lung transplant and expanding the donors pool. Also, in this article we explain the palliative care role in lung transplant.

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General principals of biomedical ethics

Lung transplantation has become a viable treatment option for many patients with terminal pulmonary disease, but the lack of available donors adds more constrains to already difficult and lengthy process. Sadly, many patients listed for lung transplant die while awaiting transplantation (1).

Due to the fact that organs recovered from deceased donors offer substantial (and sometimes superior) benefits to potential recipients, with no risk to a healthy live donor, the efforts to maximize the use of organs from deceased donors must not be impeded by the development of live organ donation (2).

Understanding the fundamental principles of biomedical ethics will help analyzing the complex medical situation that physicians often encounter such as organ transplantation.

There are four principles: Beneficence which means "do good", non-maleficence "do no harm", autonomy which means making sure that the patients fully understand their options and that their decisions are respected, and Justice which means trying to advocate and invest the medical resources equally to all patients regardless of any factor including social economic status (3).

Applying general biomedical ethical concepts in lung transplant

In lung transplant, Beneficence means that this ethical principal is clearly being met in all transplant patients as a group. In other words, the quality of life of some patients is

positively impacted after a lung transplants but this might not be the case in all patients due to the fact that some may not be lucky enough to enjoy a successful outcome but as long as the physicians explain and act toward those patients in good faith and present them with the facts about their illness then the principal of beneficence is clearly met.

Nonmaleficence in lung transplant means that alternative therapies to lung transplant should be explored if they are considered less risky but potentially effective alternative therapies in other words in a patient who is to be considered for lung transplantation as a therapeutic option, it is mandatory to discuss with the patient the survival rate of living with or without lung transplantation. As an example, some of patient with advanced emphysema might have similar longevity with or without lung transplantation but symptomatically patients with lung transplantation have improved respiratory symptoms and exercise tolerance so it all depends on the patient overall goals of care (3).

Does the patient want to go through expensive surgery and lengthy rehab or rather choose to let the disease takes its course?

When it comes to autonomy, once again the patient should be fully informed of the limitation of lung transplant and that continuation of conservative management still an option and that the physician should not make a paternalistic decision on behalf of the patient in regard to making decision to consider lung transplantation or not to consider it.

How far physicians can go to "influence" the autonomy of a patient who is considered for lung transplant? For example, some providers often request such patient to avoid choosing "Do Not Resusitate" (DNR) around their transplant time or not to refuse medical interventions if needed. So, taking all this into account and couple it with the scarcity of organs available for transplant, it seems ethically appropriate for the provider to engage in fully informed decision with the patients to discuss such issues and palliative care service can help in such discussion by offering support to the patient during the process.

One scenario that often encountered is a donation after brain death in case that the next of kin can override the potential donors "presumed consent" to donate if this was indicated on the donor driver's license or other legal documents. But what matter the most is to not violate in any way the individual or his next of kin or surrogate's autonomy by making a purely medical decision to harvest someone's organs without the patients or their surrogate consent (3,4).

When it comes to justice which implies equity and fairness or impartiality with no bias or discrimination in selecting an organ recipient for any given donor, but some ethical dilemmas arise from conflicts between equity and utility.

Does age matter? It seems that age comes up in solid organ in general and in lung transplant in specific due to the lack of larger pool. The main question is: do we transplant a young adult with cystic fibrosis or middle age man with idiopathic pulmonary fibrosis? Will it be a single or double lung transplant? Does baseline and posttransplant performance status play a major role in determining of the "likelihood" that someone will be a candidate for lung transplant or a combination of few other factors including socioeconomic status and the affordability of antirejection drugs? And do we offer this organ to a local young patient who lives around the corner from the transplant center or we offer it to middle age patient who lives thousands of miles away? Or will transplanting younger patients preferentially result in more years of life saved? (4).

Another question will be: should we transplant children before adults? Then if this is the case, we should define who is a child? Is it the 16 years old or the 19 years old with cystic fibrosis? do young adults who raise their own kids and are the main source of their income be given priorities? How about patients with similar pathologies but no families of their own to raise?

How do we ensure equity of access to transplant and inequality of the outcome? how do we allocate the available organs in as such scarce available pool? And where is personal bias and justice stand in all of this?

Ever since lung transplantation considered a viable option for patients with terminal lung disease the consensus internationally was to consider age over 60 a contraindication for bilateral lung transplant and age over 65 is a contraindication against single lung transplant. But later, age limit was increased to less than 75 years old (5).

Another ethical principle is justice and how do we look at individuals with specific lifestyle and social habits who contributed to their own heart or lung disease by personal choices (like in case of smoking and obesity) who need to be transplanted and compare them against those who acquire lung disease due to random event, lung failure due COVID 19 by example or inherited genes? This argument is also encountered in heart transplant as well.

Although obesity and social habits including polysubstance

including alcohol use might be a relative contraindication for consideration for lung transplant and quitting such habits for 6 months will increase the chance of such consideration but the damage has already been done to their organs so who would we consider giving lung transplant to? is it for long time smoker with chronic obstructive pulmonary disease (COPD) or a child with inherited cystic fibrosis or someone who, not knowingly, contracted COVID-19? This is not an easy decision for a physician to make to avoid being judgmental.

On the other hand, beneficence is the act of kindness and for physician specifically, is a moral obligation to do good to others which is a corner stone of a good ethical medical practice.

In organ transplant field, utility means making the best use of a scarce resource. It makes no sense to transplant an organ into a patient who, because of illness or comorbidities, will not be able to engage in robust rehab program due to poor quality of life or poor performance status or overall prognosis that is measured in few months to few years.

Lung re-transplantation

One other potential ethical dilemma arises in lung re-transplantation. Lung re-transplantation is performed in about 4–5% of total lung transplantations performed throughout the world, according to the International Society for Heart and Lung Transplantation (ISHLT) database, the 1-year survival for re-transplantation lags considerably compared with primary transplantation at 69% versus 84% (5). Another study revealed similar outcomes with 1-year survival at 61% versus 82% and 3-year survival was 41% versus 67%, they concluded that the long-term survival results in lung retransplant recipients are poor (6).

In a recent study about lung re-transplantation while the patient on extracorporeal membrane oxygenation (ECMO) support, the authors point to the fact that lung re-transplantation may not be advisable based on study done on 15 patients on ECMO underwent re-transplantation. Nine patients with the Hannover protocol and 6 in the historical cohort. In both cohorts only, half of the patients survived to 1-year posttransplant (7). Patients on ECMO are understandably sicker and should not be completely excluded from consideration for lung transplant but with the overall poor post-transplant outcome do we offer the organ to a patient who is on ECMO or a patient who is not?

Lung transplantation and donation after cardiac death

According to Modified Maastricht Classification for Donors after Circulatory Death (DCD), the DCD could be divided clinically into uncontrolled donation after circulatory death (uDCD) when the patient died before arrival to the hospital category I, or unsuccessful resuscitation in the hospital category II, and controlled donation after circulatory death (cDCD) in case of awaiting for cardiac arrest in patients opted for withdrawal of care category III, or in patients with cardiac arrest awaiting while in brain death category IV (8).

Lung transplantation from DCD donors has been increasing in recent years. A recent ISHLT DCD Registry included 11,516 lung transplants, of which 1,090 (9.5%) were DCD transplants. DCD-III category comprised 94.1% of the DCD cohort. Among the participating centers, the proportion of DCD lung transplant increased from 0.6% in 2003 to 15.2% in 2017. One- and 5-year actuarial survival was 97% and 90% in DCD, *vs.* 90% and 61%, for 503 DBD lung transplants, respectively (9).

Lung transplantation through cDCD has slowly gained universal acceptance with reports of similar outcomes to those through donation after brain death. In contrast, uDCD lung use is controversial and difficult as it requires legal, ethical, and medical complexities be addressed in short period of time. However, the concept of using DCD lungs is not legally allowed in some countries like Germany, which is the country in Euro transplant region with the largest number of potential donors, but with the lowest number of actual donors per inhabitant population (10).

Lung transplantation *ex vivo* lung perfusion (EVLP)

EVLP including both preservation systems in cold or normothermic has recently emerged as a new technology to safely prolong cross-clamp time for standard-criteria donor lungs, and to re-evaluate questionable lungs from extended-criteria donors such as older donor lungs, DCD lungs, lungs with low oxygenation capacity, and lungs with expected long ischemic time due to logistics or unexpected delay of reperfusion time (10,11).

These strategies may help to increase the donor pool in the future in countries with lower organ donation rates.

The outcomes are encouraging and comparable to transplant without EVLP. However, this technology still evolving, and there are ethical questions in regard the use,

indications, and also the trial and the concept of offering "questionable" lungs to a recipient, all of these questions need to be answered and discussed ethically and revisited regularly around the world involving transplant teams with ethical experts to help guide such approach to lung transplantation.

Lung transplant and hepatitis C

One more challenging question was related to harvesting lungs from people with polysubstance use disorder. With the unfortunate ongoing epidemic of death resulted from opioid overdose, there has been an increase in the availability of ready to transplant organs from patients affected by hepatitis C despite self-decreased potential waiting times for patients in need for lung transplantation in individuals who are hepatitis C negative.

This approach came to lung transplant field because of the effectiveness of current treatment for hepatitis C.

Even though hepatitis C infected heart and lung transplantation trials showed encouraging results, most of these studies were small and lack long term follow up. It will be probably wise not to adopt such strategy as standard of care before performing larger clinical trials with longer term follow up. But nevertheless, there is an ethical issue surrounding this practice as some transplant professionals feel that there is more harm to be done than good by not trying to utilize hepatitis C virus (HCV) infected organs and put them in the pool of available organs to be transplanted to patients who are in need. Hence the use of HCV infected organs and solid organ transplantation is an available option (12).

Ethics surrounding single *vs.* double lung transplant

Single *vs.* double lung transplant is another ethical debate in limited pool of donated lungs.

The question is it better or more acceptable to split a pair of lungs and give one to each recipient in order for them to live and reduce the wait list time and decrease overall mortality which will impact the overall cost to each individual who is waiting for bilateral lung transplant?

It seems that individuals who received bilateral lung transplant get more benefits compared to single but it is on the expense of transplanting fewer patients.

Studies have shown that double lung transplant has superior survival rate compared to single lung transplant in patients with idiopathic pulmonary fibrosis but there was no significant difference in patients with COPD as far as receiving single versus double lung transplantation (13).

The ethical question hers is offering the patients the option of single lung transplant or the option to remain on the waiting list in hope that they will get bilateral lung transplant in the future.

It might seem that the ethical argument here suggest that single lung transplant may provide more utilization of the existing donor pool but this might not be the right conclusion as it all depends on the age, comorbidities and most importantly the etiology behind the lung disease itself and for that matter considering the overall long-term survival post-transplant is as important as increasing the number of potential recipients.

The lung allocation score was implemented the United States in the year of 2005 and the idea behind it was to better understand the mortality between patients who are on the transplant waiting list and patient who survived post-transplant (14).

Sequential bilateral lung transplant

In such approach, the patient will have single lung transplant and then be relisted for another single lung transplant in the future. The question is how utilizing this approach will affect other patients on the waiting list? Such approach will expose the patients to two operations and expose them to risks that they could have avoided and may be doing reasonably well by undergoing single lung transplant (SLT)? So, whether sequential bilateral lung transplantation (SBLT) approach is a viable option or not is yet to be determined as it remains a controversial option and further studies are needed (15,16).

Palliative care role in lung transplant

The role of palliative care overall in caring for patients who are in need for lung transplantation faces few barriers on different levels. Those barriers are related to patient, family, provider, institution, or program/lung allocation system.

Family factors include unrealistic patient/family expectations, a common scenario we see in almost all patients with terminal diseases from overestimating survival to avoiding end-of-life care discussion due to concerns about abandonment or suboptimal care after enrollment in a palliative care program, let alone family members themselves disagreements about goals of care for

their loved ones.

As far as institutional related barriers it all evolve around the allocation system but pretransplant requirement related to the patient themselves like maintain acceptable body mass index (BMI) or quitting social habits like smoking is also important factors.

Physicians barriers included the moral conflict by asking the patient to "hang on" placing their lung disease/transplant as priority or focusing on optimizing symptomatic treatment of such patients utilizing palliative care service? Strategies recommended to improve palliative care involvement in such patients' population include routine advance care planning for patients awaiting transplantation, access to palliative care specialists, training of transplant physicians in symptom management, and regular meetings among transplant physicians, nurses, patients, and families (17,18).

What palliative care literature has approved in lung transplant candidates is that palliative care and opioids, in particular, can be safely provided without compromising eligibility for transplantation and that palliative care should not be delayed until patient is deemed ineligible for transplant (19).

Although clinician overall positive attitudes toward integrating palliative and lung transplant care teams, the actual utilization of palliative care services is still low due to some misconceptions outlined above.

Conclusions

Although organ donation is considered the best altruistic gift that an individual gives selflessly for the wellbeing of others, the lung transplantation raises many ethical considerations, many of which focus on the need to expand the donor pool, the limiting step in achieving ongoing growth in lung and other solid organ transplantation and taking the ethical principle into account will make the transplant algorithm fair for all.

Given current circumstances, no fair allocation system can eliminate deaths in people who are in desperate need for lung transplant and already made it to waiting list and for the same exact reason we are obligated to make the best use of these precious organs and be ethically sound to allocate them wisely and fairly.

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