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Lung Transplantation for Cystic Fibrosis

Narrator:
Welcome to the ReachMD activity: Lung Transplantation for Cystic Fibrosis. This segment is sponsored by Prova Education. Your host is Dr. Barry Mennen who welcomes Dr. Denis Hadjiliadis, Paul F. Harron, Jr. Associate Professor of Medicine, Perleman School of Medicine at the University of Pennsylvania, and Program Director of the Adult Cystic Fibrosis Center in Philadelphia, Pennsylvania. Prior to beginning the activity, please be sure to review the goals of this educational activity, or, if you're listening to this as a podcast, go to this activity on ReachMD.com/Prova on your computer, smartphone, or tablet device.

Dr. Mennen:
Lung transplantation is often considered for patients with cystic fibrosis. Today, we will discuss how patients are evaluated and listed, common complications, medications that are used, and survival after lung transplantation. You are listening to ReachMD, and I am your host, Dr. Barry Mennen. Dr. Hadjiliadis, welcome to ReachMD.

Dr. Hadjiliadis:
Thank you for having me here.

Dr. Mennen:
Now, Dr. Hadjiliadis, when do we consider lung transplant for patients with CF?

Dr. Hadjiliadis:
We usually consider lung transplantation for patients with CF when they have really advanced disease and we expect that their survival, because of their cystic fibrosis, to be relatively limited. This is not always a very easy question to answer for most patients and we use a lot of different variables and clinical knowledge to try and predict when is the right time to refer a patient. There are some multiple studies that have tried to answer that question and some of the factors that are associated with problems in survival, limited long-term survival, are: lung function, FEV1 more specifically, that is the forced expiratory volume in the first second; age; gender, in this case women tend to do worse than men; weight, patients that are malnourished do worse; being diabetic; having many exacerbations every year; having bacteria that are more difficult than the average bacteria; obviously if you have pancreatic insufficiency that means you have more severe CF; the same is true if you have mutations that give you more severe CF; and then some other factors like in the past needing admission to the intensive care unit or having an elevated carbon dioxide. All those things, including also quality of life, have been found together to predict which patients might have worse survival than other ones. So, a clinician looks at all of them and tries to make a best estimate on when to refer a patient for lung transplant. One of the other issues that we have, however, to acknowledge, is the fact that survival has been improving. Approximately 25 years ago, an FEV1 of less than 30% was associated even with 2-year survival, and we look at about 15 years ago it was associated with a 50% 5-year survival; however, most recently, a study from the UK showed that the median survival in the early 2000s might have been around 5 years instead of 1.2 years in 1991. And another study from Italy showed exactly the same thing, that a cohort of patients that were having the same characteristics, like a cohort in 1999, they had about 34% fewer deaths. So, during that period, in the original group of patients there were 10% that died and then in the later period there were about only 6.4%. So, those are some of the factors that come into play when we try to decide when to refer a patient.

Dr. Mennen:
Now, how do patients get evaluated for lung transplant?

Dr. Hadjiliadis:
This is a very, very complicated and well-choreographed process. The key answer for somebody to be a good candidate for lung transplant would be to make sure that they have lung disease which is what the transplant will do, will take away the old lungs and put

new lungs in, but at the same time, try and have the rest of the organ systems of the body as good as possible so that they can be able to withstand a big operation that is a lung transplant. So, the evaluation process includes a multitude of tests. So, you have a test of cardiac function to see how the heart is working and this also gives you an idea on how sick the patient is. You have tests of looking at the lungs like a CAT scan and ventilation perfusion scan to give you an idea how severe the disease is and also some idea on how difficult the operation itself might be. You have a lot of blood tests to find out what specific infections the patient might be at risk of, and to make sure they don't have other infections like hepatitis, HIV, and other infections that might make things more complicated or very difficult to transplant. And then, you have tests of fitness to make sure that the patient is fit enough and strong enough to be able to undergo the operation. And then, a lot of consults usually with a lot of team members that center around nutrition, to make sure that the nutrition is okay; social work with or without a psychologist, it depends on the program, to make sure that they are okay as far as their ability to follow medical care, they have enough social support, they don't' have a history of recent drug use or other things that might make them poor candidates for lung transplant; and finally, with anything like that you need also education from the nursing and the surgical team; and also education from a financial person because this is an expensive operation, even if it is covered by insurance. So, all those, with some variation, all those things are done in order to identify who is a good candidate for lung transplant.

Dr. Mennen:
What issues might exclude patients from being good candidates for lung transplantation?

Dr. Hadjiliadis:
So, there are multiple issues that might come into play when we consider that somebody is a candidate for lung transplant. There are some absolute contraindications to lung transplantations that apply beyond cystic fibrosis and some of those include having active infection with very virulent or resistant micro-organisms. An example would be having active tuberculosis. Another one, if you have sepsis, which means infection that is systemic. So, those are some of the very significant things that might exclude a patient. Other things that are very significant is having a very poor social support, untreated psychiatric illness, unable to adhere to therapy or having active substance abuse. Patients like that are not able to follow complicated medical regimen, so in their case, it is not possible to do a transplant. Another factor that sometimes might be significant in patients with CF is severe chest wall deformity because that might make it very difficult to explant the lungs, and then in addition to that, find an appropriate pair of organs that can fit in a smaller chest wall and a bigger side of the chest wall. So, those are usually very complicated situations. Another factor is malignancy. If you have a cancer within the last 2 years, for a low-risk cancer, or 5 years for a high-risk cancer, then you cannot do a transplant because the immunosuppression after transplant will make the cancer explode and take over the patient. So, in general, you want the cancer to be cured and a consultation with oncology is needed. Finally, if you have non-pulmonary vital organ dysfunction that includes kidneys, liver, bad diabetes, another organ system that is failing, obviously a lung transplant will not fix that problem. Sometimes you might be able to combine more than one organ transplant, like if you have a bad liver and bad lungs, maybe you can do both, but generally speaking a lung transplant alone will not be enough. Something that's not as common in our CF patient population is if they have coronary disease or if they have very high weight. Those can also lead to problems with transplantation. Finally, if you are not a good rehabilitation candidate, that means if you have an inability to be able to walk and get stronger and be able to make it better, that might also exclude you from transplant. There are also other problems that usually, on their own might not be enough, but they might make altogether the condition very difficult. So, if you are much older, not very common in our patients, if you have worsening malnutrition, that is common and is a problem, if you have other diseases at the same time, rheumatologic diseases, if you have problems with your esophagus, like your swallowing, those sometimes can be problems.

Specifically, for cystic fibrosis, there are a couple of factors that come into play and one of them is the presence of certain micro-organisms that are very difficult to treat. The most common one that everybody knows about is Burkholderia cepacia and, more specifically, Burkholderia cenocepacia. And the reason behind it is patients that have an infection with this organism before transplant they have a terrible time post-transplant. Approximately 25 to 30% lower survival, so that is a huge decrease. In this group, but with maybe not as dramatic effect, although we do not have enough data to be certain about it, includes another form of Burkholderia that's called gladioli, Mycobacterium abscessus, and another one that is very scary to most of us is Scedosporium. Interestingly enough, some patients, even if they're very, very sick, they can be supported with ECMO, that's extracorporeal membrane oxygenation. It's a special life support that cleans your blood, gives you oxygen, takes away the carbon dioxide. So this has been able to be done for patients with cystic fibrosis. So there are a lot of different options that might help our patients get better. And the other thing about it, even if patients are hospitalized and ventilated, they have decreased survival; however, patients with CF seem to have the ability to do okay even in cases like that.

Dr. Mennen:
Now, once the CF patient is okayed for lung transplant, how do you prioritize the list?

Dr. Hadjiliadis:

First of all, the whole United States is divided into regions, UNOS regions, and then organ procurement organizations, so there are smaller local areas where all the organs are allocated first. So, what happens is, if an organ becomes available first it's given to the local programs and the local patients, and then it's given out to much larger areas if it's not utilized. Obviously, if there is no program in that local area then it's given directly to the larger radius. So, what happens, every patient is placed on the list based on their blood group, that's something that's obviously in the listing process, but programs also take into account size because obviously you cannot fit a very big lung in a small person and vice versa; it's very difficult to do that. This is usually done internally so it does not have anything to do with your score and your priority, but every program puts some parameters. After that, what happens is there is a very complicated algorithm that gives you a score that's called the lung allocation score. And that score tries to take into account what your survival is within a year of having a transplant and without a transplant. So, it takes into account your transplant benefit, meaning how many days are you going to live if you get a transplant versus if you don't. But then, it double counts the number of days that you live without a transplant with the idea that that works as a tie-breaker. So, if you have somebody, two people have the same transplant benefit that means they benefit both from the transplant equally, but one person cannot wait, they take priority. And that score basically comes from very, very many different factors and then it gets normalized to a score from 0 to 100. So, patients are prioritized based on this with priority given to the patients that are most likely not to make it if they don't receive a transplant.

Dr. Mennen:
Now, what is the survival for CF patients after lung transplantation?

Dr. Hadjiliadis:
Overall, the survival of lung transplant is not the greatest. That's part of the reason when we talked about it; we have to have patients with end-stage disease to be able to get a benefit from receiving a lung transplant. So, we were talking about survival that's limited, it's probably less than 5 years that we want to offer the transplant to a person, but that's because we have to take into account what the survival post-transplant is. Despite that, patients with CF tend to have the best short-term and long-term survival from any other group of patients that receive lung transplant. So, according to the most recent statistics, the 5-year survival for patients with CF, it's a little over 60%; and the median survival, that means half the patients will survive beyond 8.6 years, and actually, if the patient survives the perioperative period, the more high-risk time and you look at the patients that have survived already 1 year, then the median survival for somebody with CF pushes closer to 11 or 12 years. The survival has been very slowly getting better. It's not where we would like it to be, but we do a better job around the operation time and we do a better job in taking care of the patients afterwards.

Dr. Mennen:
Now, what are the common complications after lung transplantation?

Dr. Hadjiliadis:
So, the first one that can happen is what we call primary graft dysfunction. Primary graft dysfunction is you basically put the lungs in, and even though everything was perfect at the donor, and when you took them out they looked perfect and the recipient was doing well, the lungs don't work upfront. So, there is an action where the lungs start leaking fluid. So, you end up with a situation, in medical terms we call that ARDS after lung transplant, and you end up with a situation where the lungs are not doing their job, exchanging oxygen and carbon dioxide and you've already gone through a major operation. As you can imagine, this can lead to a lot of other organs to start to fail. Sometimes you get the kidney, sometimes you get heart, sometimes you get infections, so this is a very, very serious complication. It occurs in about 10 to 15% of patients in the severe form. The good news about it is that the lungs recover. They recover with maybe a little bit of long-term effect, but not much. They actually recover very, very well. So, the key thing about this complication is helping the patients get through with it, and pretty much all the early deaths happen because of this and that is probably about maybe 3% of patients that succumb to this. Obviously, a smaller percentage, but still that is the most devastating complication that can happen early on. Later on, you have a lot of other issues that can happen. So, starting a few weeks after transplant, you can get acute rejection and this can happen because the way that we treat the patients with immune medications, or immune suppressive medications, is good, but it's not perfect, and the body's too smart and sometimes can still go ahead and reject the lungs. This is treated with usually steroids and goes away, but it's the major risk factor for chronic rejection. That usually happens after the first year post-transplant and it shows itself by dropping of the lung functions; similar to what happens in CF before transplant, you have a lower lung function. And it is a major problem because in the long run this is the most common reason why patients don't do well and they might die. In addition, because you're on a lot of immunosuppressive medications, you're at higher risk for infections. So, you can get your usual infections that you had before with CF, but more importantly, you can get other infections like fungal, mycobacterial, viral infections including CMV, and most of the time you can recover from those. But, if you think about how we are bombarded with infectious organisms all the time of our lives, it can be devastating because you never know which one might be more serious than the others. A third reason why people end up in trouble is malignancy. So, it's not uncommon, because of the immunosuppression, to have an increased risk of developing many cancers. Some of them are more likely than others. In patients with CF, a common cancer is post-transplant lymphoma, because many

of our patients have not had a primary infection with mononucleosis, EBV, that's the name of the infection. And most people get that when they're young, but some of them don't. And since our population is younger, it's more likely to have a donor that has it and a recipient that doesn't and that increases your risk. In addition to that, cancers that are immune-mediated, skin cancers, especially if you have a lot of exposure to the sun, and another one in cystic fibrosis which is much more common is cancers in the GI tract and, specifically, colon cancer. So, that's another cause of problems. Finally, you have complications that come with chronic use of medications. Those include kidney failure, worsening of diabetes, high blood pressure, and a lot of other organs can start being affected because of them that can lead to more issues.

Dr. Mennen:
Picking up the point about medications, what are the common medications that are used after lung transplantation?

Dr. Hadjiliadis:
I'm going to go over mainly the immunosuppressive medications because those are the newer medications that people use. So, there is a group of medications, the cornerstone of the immunosuppression, the calcineurin inhibitors as they are called, and those, the two that we have are tacrolimus and cyclosporine. They are basically the most common ones. They both have similar, but slightly different, side effects. So, tacrolimus sometimes is worse for diabetes but it's easier on the stomach. Cyclosporine causes a lot more cholesterol and high blood pressure problems, is more difficult on the stomach, but is a little less problematic with diabetes, and you use one or the other. Most programs nowadays use tacrolimus because it's a little easier to tolerate and maybe slightly better as an immunosuppressive medication. Then, the second group of medications includes ones that are called mycophenolate and azathioprine. Those are medications that make your white cells weaker so that you don't reject. And they're the ones that if there is something that makes us need to decrease the immunosuppression, we tend to take them a little further down or take them completely away, but they are a very important group of medications. Their main side effects are that they might decrease your white cell count and make you more prone to infection and, obviously, together with everything else, they might make you more prone to have cancers and other things. Finally, everybody is on prednisone which is a common immunosuppressive medication. It is a steroid which starts pretty high in the beginning, although after the first year they usually run a very small dose, might be 5 mg, might be 10 mg, but something that's much lower. There are a couple of other alternatives that sometimes we use; one is called sirolimus and another everolimus. And those can replace either one of the first 2 groups of medications for different reasons and they have a different set of side effects and problems. In addition, patients have to be on some other medications, usually prophylactic, for infections. The most common one is sulfa medications which help prevent a specific infection that is called PJP. And then, either for a long, long time, or sometimes only for a short time at the beginning, they might need to be on antifungal medications like voriconazole is a common one, or valganciclovir, an antiviral medication to prevent CMV infections. So, those are some that come on and sometimes they stay and sometimes they go away. Specifically, for CF patients, very frequently in the early period of the transplant, we also use IV antibiotics obviously, but then for a little more prolonged period we use nebulized antibiotics to try and help keep at bay their old infections which might still be harbored in their sinuses.

Dr. Mennen:
Dr. Hadjiliadis, thank you for joining us today and sharing your insights on Lung Transplantation for Patients with Cystic Fibrosis. I am your host, Dr. Barry Mennen, for ReachMD.

Dr. Hadjiliadis:
Thank you very much for having me.

Narrator:
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