So I have a few disclosures, I have no financial disclosures unfortunately, not much money. I have a lot of slides and I’ll say I’m primarily a clinician, there are a lot of people in this audience, you know who you are who have forgotten more about immunology than I’m ever going to know, but I’m going to try and summarize some of the difficult areas of lung transplantation for you.

So these are some of the objectives for a short talk. I want to talk a little bit about history, indications; contraindications; evolution of the system for listing patients because you need to know how we list them; and some of the very basics of the transplant immunology that we deal with our patients and with that immunosuppressive therapy; complications and results and then at the end if you can stick around that long there’s going to be the important part of this talk, we are going to talk about some of the challenges, controversies and where we are heading with lung transplantation in the future.

So this is a lot to talk about, this is my favorite slide, the road to enlightenment is long and difficult which is why I asked you to bring sandwiches and a change of clothing. And by the way do I have a pointer here? I do. This is not me, okay remember this, I’m one of these guys, okay. I’m still learning this stuff just to be clear on that. But the dream of transplantation is that it existed for a long time. Some of the saints written about Cosmos and Damian, they were brothers who were physicians and surgeons respectively in the 3rd Century A.D. They undertook and carried out the transplantation of a lower limb from a “deceased Ethiopian moor” to replace the gangrenous leg of a sextant of a local church and this is actually centuries later they actually found some of the papers and early photographs of this, and this is a reproduction done by a painter in the 15th Century. This
is Cosmos the physician, this is Damian the surgeon, these are the angels who were also serving as the scrub nurse and the circulating nurse and they found out, what’s interesting is in the archeological findings they found that – they didn’t find all the records but they found out that Damian the surgeon was awarded 16.8 RBUs for doing this, and Cosmos who took care of the patient before and after got 1.3. So this just shows that the more things change the more they change the same, stay the same, okay.

We move forward to 1963, J. D. Hardy at the University of Mississippi after doing – practicing if you will or experimenting with many, many dog lung transplants carried out the first human lung transplant. The donor had been deceased, the recipient was in a Mississippi prison and had unresectable lung cancer. He got in this case an isolated lung, he survived 18 days, he was – it was an avian compatible transplant, there were minimal findings and projection. He died of renal failure after 18 days. So this is J. D. Hardy here.

For the next well almost 20 years a lot of research was done on surgical techniques that led to improved anastomoses, the problem was found to be in the suturing together of the bronchi among other things. The only immunosuppressants available at that time were Azathioprine, they had a radiation, total body irradiation and corticosteroids and by 1978 there were 38 reported recipients, only 9 had lived for more than 14 days, nobody survived longer than a year. So we had a long ways to go.
So after 1978 we had the Cyclosporin revolution. Calne in 1978 used it in kidney transplants, this is Sir Roy Calne. A guy named Starzl whom some of you may have heard about here bouncing into the scene started with livers in 1981 and then moved to Pittsburgh soon thereafter and that transformed the University of Pittsburgh Medical Center into the transplant center of the world for quite some time. It was – there were so many livers done here that actually they wanted to rename the stadium 3 Livers Stadium but because some patients got that many. That’s a joke, just I’m kidding there. And the first time I ever heard the word Cyclosporin was from this guy, Bruce Reitz who at that time looked a lot younger, he and I were essentially trainees together at Stanford. And I still remember sitting in the audience hearing him talk about doing heart-lung transplants in primates and showing a picture of his hands, his two hands holding the heart-lung block of a small Rhesus monkey that he was about to transplant, and that was where I heard for the first time the word Cyclosporin sitting in the audience saying this is going to revolutionize cystic fibrosis, all my patients are going to be transplanted, everything is going to be great. And I was wrong.

I want to say that this quote is a favorite of mine, probably the most interesting period of medicine has been that of the last few decades so rapid has been this advance, this new knowledge developed that the truth of each year was necessarily modified by new evidence, making the truth an ever changing factor. And that should sound familiar to all of you because it was said by Charles Mayo in 1919. So again the more things change the more they stay the same. There is a lot we are learning and a lot to be learned. And I think this, this statement is still true today as it was in 1919.
If you look at the number of lung transplants these are the numbers done in adults. I want you to just concentrate on the high numbers here because the next slide is going to show you what we are doing in pediatrics. This is data from ISHLT, International Society for Heart Lung Transplant. You’ll see this again on many slides. It’s dated 2012 but you notice the data is 2 years old anyway from there, but this is the latest we have right now. The numbers are staggeringly small, total numbers are in the 120s for the world, this is the international society, not U.S., international. In this country 30 to 40 transplants in a year are in children is a big number, and as you’ll see the numbers we do are very small but we are still an active center.

How do we decide who should be transplanted? We want a recipient that is sick enough to justify the risks of lung transplantation and you’ll see later in this talk that there are a lot of risks of doing this procedure. And you want to ask yourself is the patient likely to benefit from undergoing those risks? And finally are there contraindications that will absolutely or at least in a strongly relative way preclude lung transplantation? So the guidelines we have generally for candidate selection, we want them to be optimally treated for whatever their medical condition is and we want them to have a condition that has a known limited survival. It would be nice to know how long they are going to survive, but we often don’t have that knowledge; and if they have comorbid conditions, diabetes, hypertension, etc. we like that treated. These are old – this is an older slide, they are now transplanting people with lungs who are older than this although I think I’m finally out of that range and I don’t have to worry about that any more, or my wife doesn’t.
If you look at who gets transplanted, these are pediatric lung transplant indications. This is one of two slides, this has the majority of the data. In young children at least one center is doing the majority of patients with surfactant protein B deficiency, or mutation would be a more accurate way to put it; but you can see there are a variety of other things, mainly congenital heart disease and pulmonary hypertension. In the older patients cystic fibrosis is far and away the most common indication for pediatric lung transplantation and has been and probably will remain so for the foreseeable future.

This replaces 3 slides, there are a variety of absolute contraindications including malignancy, advanced organ dysfunction in other major organ systems and a variety of infections. I want to point out this double star here, immunodeficiency we are going to talk about that a little bit later, but it’s considered in most centers to be an absolute contraindication having an immunodeficiency state and also you can see that documented nonadherence in many centers is considered an absolute no go. We have lots of patients who would otherwise be able to get transplanted but just can’t be compliant.

There are a variety of relative contraindications, I put here mechanical ventilation, I should have also put extracorporeal membrane oxygenation or ECMO. That’s considered a relative. We don’t transplant patients who are on ECMO, at least right now. That is going to be changing.

When to refer to our center or when should we list these patients? It was devised a long time ago by my colleagues then at Stanford that there was such a thing as we like to call the transplant window. This is a clinical course of a patient who then declines and you want to be transplanting somebody back here if this is – you don’t have any reference on the timeframe here, but transplanting
somebody back here when they are first diagnosed with an illness may be too early because the benefits of transplant may be outweighed by the chance of survival without transplant, because transplantation has risks and is not – the outcomes in pediatric and adult lung transplantation are not that great, as you’ll see soon enough in this talk. But at the same time if you wait too long the patient may be too sick to undergo the procedure, so there is a window, a time here for you to try and transplant your patient or at least list them.

Now that’s very difficult to know how long you should or when you should do this. In the early days of transplantation the wait for lungs in pediatric patients was about 2 years and a single center study from Toronto Sick Kids suggested that listing somebody when their FEV1 was less than 30% predicted or FEV1 over 30% with a variety of other comorbidities was an appropriate time to list someone because their 50% survival by their studies, by looking at their data was about 2 years. So that was subsequently shown in other centers to be a falsely low estimate of survival, but nonetheless this is what we had to go with when we were first listing these patients back in the early ‘90s, when we did a fair number of transplants I must say.

But if you look at it, you know this is not scientific, this is a theoretic FEV1 course for a theoretical CF patient they start off at age 7 with an FEV1 here and they have this slow decline. Sure, listing them around here might make sense because you know they are still going to be viable and able to take a lung within the next year or so. But here is the same curve on a different child, theoretical child, who is doing fine, gets a bad infection here and then has a steady and very severe decline in FEV1. These curves by the way are the same if you notice. And if you list them here you know they
may not survive to get the transplant. So this is a very inaccurate way of trying to decide who to list we found out.

There are improved guidelines for candidate selection in cystic fibrosis using survival modeling. This uses the Cystic Fibrosis Registry and Dr. Ted Liou, that’s Lil not Lou, Ted Liou who did his adult residency in medicine at Presby whose wife did her pediatric residency here, he’s now – they are both now in Salt Lake City, he used material from the CF Registry and was able to come up with a model that predicted 5 year survival. The problem with using 5 year survival of course is that we usually don’t have 5 years to wait for lungs. But it turned out that Liou’s study was useful when looking at survival following transplant and I’m going to talk about that later on in the talk.

So who do we – how do we go about the evaluation process? First of all we get sent information about patients. We have to look at their underlying disease, ask if there are obvious contraindications and try and assess how sick they are and whether they should be coming to us for evaluation. We bring patients here for outpatient evaluation. We used to do it as an inpatient but it’s better we think to do this as an outpatient. It takes about 3 days and the most important part of this as far as I’m concerned is they made the team headed by our transplant coordinators, I’ll cite them out later in this talk, but the transplant coordinator is underlined because they are the keys to this program and make it run. They follow the patients, they know the patients and they teach the patients and families the ins and outs of transplantation. For that matter they teach me the ins and outs of transplantation also. They also meet the rest of the team, and also including psychology and
social work. They have to understand the process of transplantation. And once we accept these people, and I have to say most of the people we wind up evaluating we try as hard as we can to list.

You have to realize how this organ allocation works. We have to allocate organs which are a scarce, rare and probably priceless commodity and this was setup fortunately in 1984 with the National Organ Transplant Act that stated that we had to have an organ procurement and transplantation network in this country. And two years later this work was undertaken by UNOS, the United Network for Organ Sharing, divided the country into 11 geographic regions. This is a private nonprofit company, organization. They work with transplant centers, they have input from all the transplant centers in the country. I happen to be on one of their committees that helps decide whether people can get a higher score as you’ll hear about soon in this talk. They operate this organ procurement and transplantation network under the contract of the federal government.

So prior to 2005 organs were allocated in a simple fashion. We had the patient’s blood type, we had the candidate’s size, we’d get the donor size and whoever was at the top of the list based on blood type was offered the organs first. Now that meant that people could be seen and considered for lung transplant 5 or 10 years before they really needed a transplant and just rise to the top of the list which was kind of a way of gaming the system, and it also meant that people who became sick later were at the bottom of the list and might have been more deserving or needing a transplant more than the people at the top of the list. This was imperfect but it’s how it worked. Organs were assigned to those locally nearest the donor center, the OPO means Organ Procurement Organizations which
work with local hospitals to procure organs. And then if there is nobody locally at increasing distances from the donor center.

But after 2005 realizing that this was inherently a not fair system for many of our patients after a lot of work by many, many statisticians and clinicians they devised a (inaudible) UNOS, a Lung Allocation Score or LAS. This was assigned to patient’s greater than or equal to 12 years of age and it gives each patient a wait list urgency. It tries to decide their predicted survival over the next year and a posttransplant survival prediction. These are hard to come by, as you might imagine, and they take a lot of higher math that I don’t understand and both of these are used to calculate what we call raw score leading to an actual lung allocation score. The wait list urgency is weighted if you will more than the posttransplant survival, so people who need the lungs more will tend to get them.

The LAS goes from 0 to 100 and there is a lot of data that goes into this that we must collect. How far they can walk, their New York Health Association Class of Activity, whether they have diabetes, whether they are on mechanical ventilation, whether or not they are on oxygen and if so how much and some of their pulmonary function testing or other organ function as well as PC O2 and if they have a cardiac cath, we like that data also. This data that’s available must be updated every 6 months, or coordinators make sure this happens and the score goes from 0 to 100, 100 is the sickest, 0 is the healthiest. Having said that we have at least one patient right now who has been waiting for lungs, his lung allocation score is 96, that’s about as close as you can get to being well – he’s very, very sick. And he’s been waiting for well over a month and we have gotten calls but the lungs are just not good enough, and we’ll talk about that later in this talk.
Well other recent changes are – to clarify, they want to clarify that pediatric donor lungs are now preferentially directed to pediatric recipients. So peds patients get pediatric lungs first, they essentially trump the adults. Adolescent lung candidates however who are under this LAS score a lot of our adolescents are really small. We have CF patients who are 15 who are the size of 8 year olds so they are competing with 8 year old kids or 9 year old kids and they are too small to get adult lungs, so they may have an LAS score but it doesn’t always help them.

When patients finally get the call and get lungs we bring them here and we send a donor team to the donor hospital. The surgical approach for these patients is a bilateral sequential lung transplant. In the old days we did a block, both lungs with a tracheal anastomosis were put in, now we do individual lungs. It’s done with a transverse inframammary thoracic incision, I’ll show you a picture of that. We do not reimplant the bronchial arteries here, they have been done elsewhere but it doesn’t improve the outcome. The lung harvesting is done by flushing the lungs with a hypothermic pulmonary artery flush of a large volume, it’s a low potassium dextran glucose solution and they are brought back essentially on ice or very cold before they are implanted.

This is what it looks like, the incision is here, this is a big surgery, folks, and you spread open the, the chest this way. We like to call this a clamshell, or this is like the hood of the car and you can look down and see the engine and here is the engine and here are the carburetors using the analogy. So it gives you a good view for the surgery.
This is a patient right before and right after lung transplantation, you can see that they have lots of tubes, lots of lines, you can’t see these and they have – they are fully lined as it were and they wind up in the CICU, most of our patients are extubated to BiPAP and our CICU has now become very, very skilled in handling these patients. I’ll mention that fact later on when you see some of our data of how we are doing. But you have to understand that lung transplantation is a treatment, it’s not a cure and it is not a panacea.

These words by Albert Trulock from Washington St. Louis is one of the really great I think adult pulmonologists who has pioneered transplantation written in 1997 and they are absolutely true now, it’s a treatment, it’s not a cure and it certainly doesn’t cure everything. The surgery that’s done it’s technically challenging but that’s not the difficult problem, it’s the recovery posttransplantation, it’s the life after transplant, that’s the real test of the patient, the family and us. These patients require a lifelong immunosuppression as far as we can tell, that requires lifelong compliance and we deal with patients with cystic fibrosis and other diseases who are not used to being compliant and that is a source of a great deal of gnashing of teeth and also patient loss I have to say because we’ve had noncompliant patients following transplantation who have in fact not done well. There is the constant risk of complications, rejection, infection and a whole variety of other complications. I’m going to go through some of those but not all of them.

So let’s start with rejection and the difficulties of the immune system. Well it’s not difficult, it’s for me it’s impossible but the immune system can be defined as you see as a system of biological structures and processes within an organism protecting it from disease resulting from specific
pathogens. But the immune system identifies an allograft such as a lung transplant as foreign and thus a potential pathogen. So our task, the task of transplant science and transplant physicians like myself is to try and control the immune system in a way that will preserve the graft but not abrogate or lose the ability of the patient to protect him or herself against true pathogens, and this is a very fine line to walk and we don’t have, as you’ll see, we have advanced in the number of tools and medications we have but we are far from perfect in this, in this area.

I’m going to give you a brief overview of graft rejection. In the old view of graft rejection T cell dependent adaptive immunity was felt to be the key and possibly only immune response that was important and all we had to do was control T cell function or decrease our T cells that we were trying to get rid of the graft and we would be home free. That turns out not to be the case. The newer view is that there’s a combination of innate and acquired immunity, there are pattern recognition receptors that detect pathogen associated molecular patterns, PAMPs, but these can also detect and bind to damage associated or cellular damage associated molecular patterns or DAMPs. And DAMPs these can result from just the mere tissue and organ harvesting or brain death itself releases these markers of injury that could be recognized early in transplantation. These can lead to a local inflammatory cascade that affects the graft and thereby releases more shall we say more antigens or potential antigens that can drive the immune response and perpetuate it.

There are a whole variety of other effectors but they include the complement system itself which can directly damage cells and the development of antibodies to mismatched HLA, HLA being the if you will the main major histocompatibility complex in mice or the human leukocyte antigens here that
we like – we would like to match for say bone marrow transplants, but these are – we do not match our lungs, we do not do pre-matches of our lungs usually with the donors.

Well back to T cells, there is a 3 signal concept of T cell activation. This is a bit complicated and I’ll show you a picture of what this looks like a couple of times. First there is a priming signal where the interaction of the T cell and T cell receptor with the donor HLA or MHC antigens that are presented by antigen presenting cells, these are cells that are professional presenters of antigen and they present this to a T cell in order to start its activation. The second signal is costimulation which is the interaction of two epitopes between the T cell and the antigen presenting cell in two sites, and I’m going to show you these in a minute. And as a result of both of these there is a transduction signal that responds to an increase in calcium in the cell, activating calcineurin and increasing nuclear factor of activated T cells and NF kappa B which themselves go to the nucleus and go to specific promotors and DNA leading to the increase of transcription and mostly, most importantly it seems leading to the increased production and release of IL2. IL2 has both paracrine and autocrine effects, it can self-stimulate the cell that releases it, increasing its activity and can stimulate other cells to become cytotoxic lymphocytes if necessary.

This is a diagram, this is the T cell here, this is the antigen presenting cell, this is signal 1 with the antigen here being presented to the T cell receptor, these are the costimulatory molecules. This is the IL2 that is acting in an autocrine fashion with signal 3 increasing the cell cycle. These are the nuclear factors that will go to the nucleus and increase your mRNA and if you notice a lot of these things are labeled. We have other receptors here. You are going to see this same slide very soon
showing you where these – our immunosuppressive agents actually work and I’m not going to go into all of the molecular biology of how they work because to be honest I’m not sure how they all do work, but they – this is where they function.

But the effector mechanism of graft rejection itself involves a both allograft independent and allograft dependent mechanisms. So an allograft you can organ ischemia and you get a nonspecific or not allograft dependent, a nonspecific inflammatory response. This as I said can magnify the recognition of the graft as foreign with a release of these DAMPs if you will. You also have cytotoxic T lymphocytes that recognize the foreign cells at which they are directed and then react directly with them injecting granzymes into these target cells that trigger apoptosis leading to death of the cells. This all sounds very simple and very obvious but for me it’s not.

If you look at a short history of immunosuppressive agents they date back to 1949 with the discovery of Cortisol by Hench who was awarded the Nobel Prize in Medicine for his work. Actually not in rheumatoid arthritis as I recall but a whole variety of other medications, the ones we use are outlined in red, we use corticosteroids, Tacrolimus and Mycophenolate and I’ll show you in a moment that they act in different places. We also use biologics, antithymocyte globulins derived from horse or from rabbit can be used to knockout T cells or knockout just literally this is a nuclear war option if you will to knockout T cells and we often will use this for induction to decrease the likelihood of rejection early in the course. But there are more specific anti – there are more specific monoclonal antibodies that can be used. We do not use OKT3 that knocks everything out. We do use Basiliximab on your handout it’s misspelled but this is a correct spelling of it. Our colleagues in
adult pulmonary at Presby use Alemtuzumab which is called Campath and they’ve had some success with this, but a high rate of infectious complications.

Going back to that first slide I’ll just point out Cyclosporin and Tacrolimus work on calcin, ethical in urine end of things. This Basiliximab works here and we have other specific monoclonals like OKT3. The others, this is where anti-CD52 works and you can see Azathioprine, Mycophenolate work to inhibit nucleotide synthesis. There are other newer agents that work on Sirolimus or Rapamycin and Everolimus work on a target or Rapamycin. We won’t go into why Rapamycin is named Rapamycin, that’s another talk. So you can see that there are specific sites for these drugs to act and one would think that by using a combination we would have an easy time and be able to prevent rejection, that sometimes is and sometimes is not the case. We use here Thymoglobulin, we use Basiliximab in very selected cases, we do not use Campath. This is our long term management strategy, it’s based on Tacrolimus, rarely Cyclosporin, it used to be Cyclosporin. We use Tacrolimus as our primary immunosuppressive with Corticosteroids and Mycophenolate. There were times where we have to decrease our immunosuppression because of complications and we are going to talk about one of those in a few minutes.

Well lung transplantation means trading one disease for another disease, except in the case of our cystic fibrosis patients, our most common recipients of lungs, where one trades only one part of one disease for an entire second disease. The second disease being immunosuppression and the effects of immunosuppressives and all of the potential complications of lung transplantation and certainly complications are the rule rather than the exception. And the lessons that I and my colleagues have
learned and been taught to us at great expense by our patients, many of whom have paid the as they say the ultimate price of teaching us what we did wrong or teaching us what we should have done right if we put it that way.

There are innumerable surgical and medical complications, these are just a few. The graft might not work despite good harvesting, all patients will suffer some degree of alveolar damage secondary to ischemia and reperfusion, they are working on ways to try and minimize that and I’ll talk about that later in this talk. Anastomoses in children – in adults are difficult but in children anastomosing pulmonary veins, pulmonary arteries and bronchi are difficult especially in small children. So you can have complications including dehiscence, frantic vocal paresis and gastroparesis are common. Acute rejection is what everybody might seem to fear but as I’ll show you soon this is relatively easily treated, it’s infections that kill our patients early. We have toxicity of immunosuppressives and all of these agents we use have toxicities. These are just a few of them. And because of the corticosteroids and other problems with Tacrolimus, increased risk of diabetes is not uncommon. We just admitted a young fellow last night who was suffering from diabetes that we essentially diagnosed after his biopsy. Acute cellular rejection is determined by transbronchial biopsy or open lung biopsy if necessary, it’s a perivascular phenomenon, keep that in mind because “chronic rejection” is an airway phenomenon and whether it’s truly chronic rejection I’m not sure but certainly acute rejection is perivascular. Lymphocytic infiltration and its treatment is with high dose steroids and it’s very effectively treated in this fashion. This is what it looks like, you have – there is a blood vessel here and these are lymphocytes. You can see that the alveolar septi are nice and crisp and clean, this is really localized to blood vessels. Other complications include hyperlipidemia from
our drugs, posttransplant lymphoproliferative disease which is a disorder, a B cell driven lymphoma, it’s EBV related and finally obliterative bronchiolitis and other malignancies. And these two I’ll touch on now.

We have a patient who is about 5 months after her lungs, she got her mother’s kidney because she had some renal dysfunction going into her lung transplant and there was – this was missed by the initial reading, this little density here but a few months later she comes back to clinic and I think nobody misses it now, and this is what it looks like on a CT scan, this was biopsied and proved to be PTLD or posttransplant proliferative disorder. She was treated by immuno, by reducing immunosuppression, she did not receive any treatment and this is her 4 months later and she is now about 5 years, about 5 years out without signs of disease. We keep running her immunosuppressive agents on the low side. Other patients require more vigorous treatment of PTLD with anti-CD20 antibody or Rituximab, and that also is fairly actually remarkably effective when we have a monoclonal or type of PTLD. We are struggling with this right now in the intensive care unit with one of our recipients who is about 6 years out from his heart-lung transplant.

But obliterative bronchiolitis is really the problem in lung transplantation. This is the thorn in the side of transplantation, a riddle wrapped in a mystery inside of an enigma. Everybody know where that’s from? Hands up anybody who knows who said that. Anybody? Good. Do you want to say? Churchill said that when he was discussing what would Russia do prior to World War II. Don’t ask me about the Soviet Union, it’s a riddle wrapped in a mystery inside of an enigma. Well so is obliterative bronchiolitis. It affects the airways not the blood vessels, it’s been called chronic
rejection. I’m not sure that’s really the case, it is difficult to diagnose on biopsy. You often have to
go to an open lung biopsy, so instead of calling saying patients have obliterative bronchiolitis we
watch a fall in their pulmonary function and we assign them a bronchiolitis obliterans syndrome
number. A higher number means their lung function has fallen more severely. This does not
respond well to steroids or for that matter any of the therapy and it really is the cause of the loss, the
death of many of our patients far out - you know after a year or more after transplant.

This is what it looks like if you get a biopsy that happens to catch this fibromyxoid collection of
cells. This here is the smooth muscle around the small airway and this is completely occluding this.
If this happened to all the airways the patients would be dead but it’s more a spotty phenomenon
which is why it’s hard to diagnose and why we rely on pulmonary function to give us a definition of
bronchiolitis obliterans syndrome. And indeed most patients will wind up having it. This is freedom
from bronchiolitis obliterans and as you can see by 5 years out from transplant at least half the
patients have been given a diagnosis of bronchiolitis obliterans syndrome. It seems to be leveling
out but we are not sure that really happens.

So we don’t know the underlying cause of this problem. There are a lot of factors that have been
associated with it, primary graft dysfunction, CMV mismatch and CMV pneumonitis, CMV
mismatch when the donor is CMV positive and has seen CMV, and the recipient has never seen
CMV, is CMV naïve and they can develop a CMV pneumonitis or build up antibodies to CMV.
Respiratory, common respiratory viral illnesses, gastroesophageal reflux, multiple episodes of acute
rejection and finally the development of donor specific, donor HLA specific antibodies by the
recipient. What we don’t know is how we put all of these together to come up with a reason for having bronchiolitis obliterans in the first place.

And I think we are still trying to figure that out; however David Wilkes and his associates at Indiana University have found some interesting data suggesting that we can uncover hidden or potential antigens secondary to organ harvesting or these other problems. And these include collagen type V, which is in small amounts and is relatively protected and not seen usually in the lung or kappa alpha 1-Tubulin found in epithelial cells. With the harvesting of lungs or other damage to lungs these materials can be either uncovered or released and then they can be recognized as foreign. There is a role for IL-17 and possibly TH-17 cells in perpetuating this airway damage and this is outlined on the slide recently from Weber and Wilkes where these cells – the antigen presenting cell can pickup these antigens if you will and then present them and you wind up having autoantibodies. So they are questioning whether chronic rejection as we are calling it or obliterative bronchiolitis is actually the result of an autoantibody built up in response to damage to the underlying – to the organ itself. And this makes a lot of sense, there is early data to suggest that in a rat model if you feed the rat small amounts of collagen V you decrease the risk for chronic rejection. So feeding this material induces some degree of tolerance.

How are we doing with this whole thing? Well this is looking at over time at pediatric lung transplants the early years were relatively dismal but if you’ll also notice the numbers we did were relatively small. And we’ve gotten better, we have gotten better at taking care of our patients in that first year. We have fewer problems in the postoperative period because we are getting better at our
surgical technique. We have surgeons who have been trained in lung transplantation and are getting better at it. We have ICUs that know how to take care of these patients, we have infectious disease colleagues that can identify those patients who should or should not be on specific regimens to decrease the likelihood that they are going to get CMV for example or other opportunistic infections. But notice over time that these curves, these survival curves are parallel and this parallel if you will decline is secondary to obliterative bronchiolitis. We still do not have a good way to prevent it, identify it or treat it and that’s why this remains the thorn in the side of our efforts.

Well this is – these are the results of the lung transplant program here at Children’s. We have a total of 81 patients, much smaller than the obviously the national but still respectable. This is all comers and this is in years down here and it looks pretty abysmal but actually the 5 year survival everybody is pretty close to 4 ½ years. And that doesn’t look, you know that’s in keeping with what we saw earlier. However, when we look at the period from 2004 to 2013, the last 9 years, we see that we seem to be doing better. Now I would initially looking at this I would attribute this to the fact that I helped recruit Victor Morrell here as our CT surgeon, and then he went ahead and recruited Pete Wearden here as a second CT surgeon and they are both as I like to tell people I will take our CT surgeons, our pediatric CT surgeons against anybody’s anywhere anytime and they are remarkable.

However I would like to give the credit only to them but in reality what this reflects I think are multiple factors. One, our CT ICU which is dedicated to caring for these patients has developed protocols to take care of them in immediate posttransplant period, they’ve become much more comfortable with that. Everybody for example now gets the BiPAP, they have better ways of
deciding who gets extubated. They are on top of all of their potential complications so they get them through that crucial initial phase. Second of all we have had a long pretty steady group of physicians and most importantly transplant coordinators who are the heart of this program. We know which patients we should list, we are better at deciding who should get lungs and what lungs to accept. We are very, very, very picky about which lungs we accept and because of that our numbers, the numbers of patients we do is not that high, but we’d like to say that well what we lack in the numbers we make up in the survival of our patients. No, it’s not perfect but we still are making strides in the right direction. But it’s the stability of the team. I know myself and Jonathan Spahr do most of the transplant care for these patients, certainly in the immediate transplant program period. From the pulmonary standpoint we have a team of cardiologists who do nothing but – not nothing but – but do primarily transplant work. Not – they do a lot more than that they’ll tell me. And of course then our coordinators, and we have a cadre a small cadre of infectious disease specialists who come to our meetings. We have weekly meetings about all these patients and I think that’s what has helped account for improvement over the last 9 years. We still have a long ways to go, but clearly we are better.

So let’s talk about – I promised you there would be some conundrums and controversies and let’s talk about those. This paper came out in 2007 from Ted Liou I talked about earlier who used the CF Registry data to come up with a 5 year survival and he published this paper with some colleagues on lung transplantation and survival in children with CF. This Cox, David R. Cox is to those who know him is Sir David Cox and when you think about Cox proportional hazards that’s who this is, so
I had the opportunity meet Sir David at a meeting called by Ted Liou in response to this paper. We’ll talk about that in just a minute.

This paper looked at CF Registry over a 10 year period and looked at all the patients listed and those transplanted did a proportional hazards modeling of data and they looked at the 5 year projected survival for all these patients based on the data in the CF Registry. And they estimated that survival and they looked at how these patients who were transplanted did relative to their estimated survival. They tried to estimate quality of life but they really couldn’t do that, and here is what they said. This is quoted from the paper. Our analyses estimated clearly improved survival for only 5 of 514 patients on the waiting list for lung transplantation. Prolongation of life by means of lung transplantation should not be expected in children with cystic fibrosis. And they offered 3 options. Continue to offer lung transplantation to patients with a possible improved quality of life maybe but possible or probable they thought shortened survival. And indeed the quality of life of these patients once they get transplanted is remarkable. I’ll show you a little bit about that soon. The second option was to stop all lung transplants for cystic fibrosis period. But more than 36% of the patients who couldn’t, didn’t have enough data for which they could actually determine the benefit, so that would ignore that large number of patients who were you know clearly not helped or clearly helped. So that would not be we thought fair. Or do a prospective randomized controlled trial, a lung transplantation for CF in the pediatric population. This was actually offered in the paper. As you can imagine doing a double – doing a randomized controlled trial of such a procedure would be daunting at best.
And as you could imagine there was a raft of protest that arose from lung transplant physicians and surgeons around the country. I kept my mouth quiet but I went to the meetings. Ted Liou was smart enough to listen to this, the protests against some of the faults in the data and there were faults in the study that they did and he called a meeting and a lot of us met and came up with the idea that we should one, continue transplantation but come up with better ideas of ways that we can improve our selection of our candidates. By the way anybody know what this plan painting is? Anybody know this painting? Any – hands up? Jericho the Raft of the Medusa, it’s in the Louvre, anybody been to the Louvre you’ve probably seen it. This is a protest painting by the way. This is a protest painting, it’s a political painting.

All right, everybody has heard about the recent case of a patient to the east of us in Philadelphia. These are from the web so you don’t have to worry, these are in public domain. The pictures I have in June of 2003 the parents of a 10 year old patient with end stage lung disease from cystic fibrosis sued to allow her to be considered to use – for adult lungs using the lung allocation score. Remember it’s only available for kids over 12. The suit was granted in a court. She received adult lungs about 5 days after this went into effect as she was listed with a high lung allocation score. She suffered from a unilateral diaphragmatic paresis and acute graft dysfunction and failure. She had to get another transplant from an adult donor 3 days later, this is in the public domain, she is now trached and vented but she is as they say still here. It’s a shame that this had to be decided in the courts, I’ll say that from the outset, and a lot of my colleagues in lung transplantation are echoing that same sentiment.
Some of the questions that were raised, here is one as this is from someone from the Southwest Transplant Alliance, who would have gotten that lung if this little girl didn’t have a law suit? And if the patient, she that is the potential recipient is that potential recipient therefore not going to survive? And if that person is not necessarily the age of a child but is somebody’s child then who will that family sue and who will they sue? Just one question. So this girl got an adult lung that meant that an adult donor – adult recipient didn’t get a lung. In this case she got two lungs.

The other question I would ask is if pediatric patients can sue to get adult lungs can small adults then sue to get pediatric lungs? As you saw very few pediatric patients are transplanted, we are outnumbered by the adults over well over 10 to 1, 20 to 1 in terms of transplants. But this could decrease an already diminished number of available pediatric lungs. So this is another - and I haven’t heard of this happening but I won’t be surprised if it does.

The other problem is that adult – if pediatric patients who are small take adult lungs, often those lungs have to be cut down and that – they reduce the size, and reducing the size of those lungs takes extra time in the operating room that’s more ischemic time. It also reduces the peripheral lung tissue. What we don’t know is if this is going to increase the morbidity of transplant or shorten the survival of the graft but I would offer that any extra time outside the body that the lungs are sitting around being worked on is time taken away from their further survival.

So those are just some of the questions raised. However UNOS revised, succumbed to this or gave into this or whatever they had to do because this was a suit that stood and they stated that candidates
aged 11 or younger could be considered for offers from adult and adolescent donors based on the lung allocation score. I serve on the committee for UNOS that has to go through every one of these appeals and my workload about tripled in going through these. The pediatric candidate they noted will also retain his or her priority for pediatric donors, so they were not going to let pediatric lungs go to adult donors yet.

But this is unfortunate as some of you may know, I think it’s choice.gov, or choice.net, some site that seeks people to send their voice to government on matters like this was inundated and the legislatures, both the House of Representatives and Senators were inundated with appeals from a variety of places for this to be considered, for kids – for little kids to be on the LAS score. One of my colleagues in transplantation wondered if all those people who took the time to fill those forms out also filled out a donor card. And he didn’t say it as a joke, but the real problem we have is if you think about it we don’t have enough donors, that’s the problem. We’ve got plenty of people who want lungs and hearts and livers, we don’t have enough donors.

And this shows you in a microcosm what that means. These are data from Children’s. On the far left of each of these groups of the number of patients we list, this is in a calendar year. So you see the numbers are not high. Next to them the numbers we transplant. So already the numbers of listed patients exceeds the number of transplanted patients. The third bar are those who die waiting for lungs in a calendar year. They are not always the same patients, and the died after transplant in a calendar year. So the numbers of patients we are asked to see to receive lungs exceeds the number of donor calls we get with good lungs. And that’s a problem.
So where are we going with this? I’m going to talk about the donor lungs in a minute but remember earlier I said that immunodeficiency has been considered an absolute contraindication of lung transplantation. Is it possible to transplant these patients? In other words that would add more work to us but is it possible to give them lungs? Secondly, 70 to 80% of donor lungs that are offered are unacceptable for transplantation. Their oxygenation is poor, they have infections, they have contusions, other things that make them unacceptable. Is there a way to improve this?

Well let’s talk first about congenital immunodeficiencies. We are now undertaking a project here spearheaded by Paul Szaboics of our Bone Marrow Transplant, he’s done this at Duke and we are going to start doing this here. We will identify candidates with immunodeficiency, list them and identify donors with 3 of 6 HLA matches that are the same size. We’ll send a team out to procure those donor lungs and a separate team headed by Dr. Szaboics to aspirate bone marrow from these patients and also to obtain a vertebral – the block of vertebrae to isolate bone marrow. We’ll transplant the lungs here and separately the marrow will be depleted of CD-3 and CD-19 positive T cells and save 6 weeks to 6 months after the lung transplant, assuming that all goes relatively well. The patients will undergo low intensity marrow ablation and they will be infused with the donor derived T cell depleted marrow which if it engrafts will eliminate essentially we think a lot of the risk for graft failure and for rejection, certainly acute rejection. He’s done this in several patients at Duke and at least one of them is now at least 3 or 4 years out, is on no immunosuppressive agents and is in college. So this is where we are going to be going with this. We have this in line, we already have at least one patient listed.
Second of all how can we save lungs that are bad? Lungs that are bad don’t get taken, but there is now an ex vivo lung perfusion system that’s available, lungs can be perfused and ventilated, pumped with a Steen solution which is acellular and deoxygenated through a membrane oxygenator. You pass the gas through this that’s 86% nitrogen and it becomes deoxygenated and then you can tell if the lungs are functioning as a god gas exchange organ because this is being ventilated with oxygen. So this is a way of or of saving lungs, letting them heal. These lungs can be bronchosceded and materials infused into them. This is what it looks like, one of these setups. Presby now has one of these and we are hoping to be able to tag along with them and get lungs that would otherwise be discarded, healing them in vivo, in ex vivo as it were, and being able to transplant them. This has been done in several occasions in several patients in other centers.

This is a team effort that I’m doing, I want to call out our transplant coordinators, Kathy and Pam Berman and Alice Maksin, these people run this program and make it work. The rest of us are hangers onto these guys. These people work really hard, they take the calls, they are up at night going through that with little remuneration in my opinion. We have a lot of other people to thank. I have a lot of acknowledgements but I’m not going to go through all these but I will tell you that without Jonathan Spahr I would left this job a long time ago. And those of you who think that transplantation shouldn’t be done in children with CF this is Mattie who is – this is about 6 months after her lung transplant. She’s – don’t worry she doesn’t do this all the time, she’s actually trained as a ballerina, so she knows how to do this and she’s now in college about 4 years later. And if you
want the slides there is my email or just come in and I’ll give them to you. Thanks a lot for your attention.