It's always a privilege to hang out with adult specialists and I may be the token pediatric focus person today but many of you have had a chance to work with us in the integrated care of children. Clearly there is important areas of challenge for transition of our kids as they become adults and as they enter different challenges of their phase of care and so as we look at our goals really as a community care for children into adulthood and into the entire cycle of life is critical for us and so it's exciting in that context to discuss with you the challenges of the long term care of children after transplant.

I want to look at the long term outcomes, show you a little bit of how we look at issues of late graft dysfunction. I think this will complement some of the challenges that the adults face that will be addressed in your later discussion today. We have introduced in pediatrics additional outcome measures that we call the Ideal Outcome that I'll touch on and conclude with some of the data on retransplantation as you think about the patient that you are facing and what they will look forward to.

Clearly the challenges that have faced our field have evolved over time, and this is Dr. Starzl looking at an early picture of transplantation where the issues related to will my patient survive the operation, will my patient survive the next few weeks or months? And that has fortunately really evolved into different questions that we face. This is Dr. Starzl in less stressful days. My son was asking me yesterday in sort of a playful way so Daddy, are you stressed today? And he kept asking me that repeatedly just I don't know why and I was very stressed by the end of 10 times that he asked me
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that. But this is Dr. Starzl in less stressful days. These are some of our posttransplant kids last summer in our transplant camp. They are both much more brave than their surgeon who would never get on this device. They probably do 10,000 steps just in the morning and enjoy it and this is what our goals are for their care. But the questions that we are asking now of course still include issues of graft survival and patient survival that's still important, but now patients want to know and their families want to know what will my life be like, what will my child's life be like? Will they be able to function, go to school, grow normally? Will they be able to get married, to have children? These are the issues that we want to try to provide outcome data in some meaningful way. And then there are situations in transplant where the transplant does not provide a complete cure but a benefit in terms of medical management and care for some of our metabolic patients, and so we want to understand that benefit and risk profile better.

But first let's start with some of the changes in the disease categories that lead to transplant in children. I think alcohol fortunately does not affect many of our children, perhaps some of the surgeons, but none of the children in this pie chart. Alcohol is not in here, fatty liver disease is a component maybe in a segment of children who are adolescents and may be an evolving area but the main disease categories, this blue pie slice of about 36% which comprises cholestatic liver disease, primarily biliary atresia which remains the most common disease indication for transplant in children, and that's a hint for the upcoming test at the end of the lecture okay.
So this, this is clearly still the most common indication for transplant but it is being challenged by the second most common which is metabolic disease in the orange slice which comprises a variety of many, of even hundreds of different types of diseases some of which have structural liver injury, some of which have normal livers but have enzymatic deficiencies that lead to the indication for transplant, so those are the two big categories.

It's important when you look at the patient after transplant to know what type of graft they received. This is a whole liver graft that we used actually in combination with a kidney for one of our metabolic patients. But in children it is more common to use what we call a technical variant graft and this can be either a living donor graft or we may use the left lateral segment of the liver for a small child, the left lobe for an adolescent or the right lobe as is done in adult transplantation. We may use combinations of these in split liver deceased donor transplants or if the whole liver is available then the whole liver may be used, but it's important to kind of know that there is a different demographic in children where it's most - more likely than adults that they would have received one of these type of grafts. And for example in two different studies you can see that approximately in the United States 50% of the children receive a whole liver and about 50% receive a combination of the technical variant graft, either a living donor or a split liver and this has some impact on late outcomes that we will touch on.

When we look at the first question I want to address outcomes we want to recognize that it is important to begin with critical tier 1 high level patient survival outcomes. This is a schematic that I
like to use because it shows the whole cycle of care. Of course it begins at the very top with patient survival but then there is other components that we've less well described and tier 2 relates to the process of recovery, the ease and speed of recovery complication rates and what patients can expect during that phase of recovery after transplantation. This can be applied to any disease process, we use it in transplantation or you could apply it for fatty liver disease or for other medical and surgical issues. And then tier 3 relates to two questions, the first one being is it likely that my disease would recur or that something would occur to that transplanted graft where the cycle might need to start over again such as in a retransplant because of chronic rejection or because of recurrent disease in hepatitis? What is the likelihood that this cycle could begin again and what are the costs and what is the impact of that happening? And the second tier of that I find very helpful for all of us in transplantation whether adult or pediatric relates to the consequences of the immunosuppression drug therapy that we use and their implications such as hypertension, diabetes, malignancy and other impacts of that immunosuppression. So we want to factor those into our discussions.

The good news is that overall pediatric outcomes really have been reported to be well even looking at the early history. This is relatively recent UNOS data looking at the very excellent 80% living donor outcomes beyond 7 years for patient survival, almost 80% for deceased donor grafts. This is UNOS data. And long term both from Pittsburgh and from UCLA have demonstrated 20 year outcomes that are quite, quite spectacular when you look at the patient population and the eras in which they began in early '90s or late '80s, in the UCLA group from '84 through '98, over 20 year outcomes, and Pittsburgh from '89 to '92, 77% patient survival. This is the Pittsburgh data and just
refer your attention up to the upper right hand corner - upper left hand corner of the slide where the pediatric outcomes up to 20 years were 77%, almost 80% in this very early cohort under tacrolimus immunosuppression so that's the good news. These long term data really give us a snapshot of what we can expect when we do a transplant and we, we've seen improvements in these outcomes even more so in the recent era. But they are still challenged. You can see in the lower side that most of the mortality did occur in the first year, plus transplant there still is impact that we are working on in the subsequent years where there is isolated patient or graft loss that we'll touch on in the later part of the talk.

In our own series over the last 23 years of 615 patients at Children's for all diseases, metabolic, cholestatic, malignancy and all comers our patient survival has been 85% at the 15 to 20 year mark, and then 75% graft survival at that same interval for our patient cohort. So that's an overall snapshot. We'd like to give you a little bit more of the details of what the rest of the issues are. This is a good schematic I think of taking a picture on a recent trip just showing the multiple interactions. Of course the liver is the most important organ there that's highlighted there but they have everyone, all the systems and all the specialists working together to care for and study this challenging population after transplant. And those challenges really revolve both around surgical management and recognition of complications, medical issues, it's a very much a multidisciplinary field when we address care for children because so many subspecialty care and expertise is required. There is infectious disease control management, PTLD, renal insufficiency and other issues that we look at.
The second critical issue is the management of immunosuppression and we'll talk about some tools that have emerged in that. We don't have time to talk about two other important areas which are neurodevelopmental issues for children as they grow, and then the issue of nonadherence particularly in our adolescent population and in that transition period to the adult clinic where much of the nonadherence issues come forward. But that's an area of much study as well.

The way that I look at and our clinicians look at allograft dysfunction in the late term is summarized in this slide because there are many components that often overlay and interact with each other. They can include technical issues, understanding if there any immune issues in the patient population, infection. Recurrent disease is really the least common issue that we deal with in pediatrics, it's a bigger component in adult transplantation but in children recurrent disease is the smallest contributor among the various variables that we take care of. Because of the issue of those technical variant grafts there is challenges in understanding how those livers remodel, grow, what happens to those bile ducts and the hepatic parenchyma, fibrosis over the long term, that's a new area of study and then the issue that I mentioned of nonadherence.

So let's look at some of the first bubble, the technical management. After transplant - we focus very much as surgeons on technical excellence in the early conduct of the transplant procedure but there are ways that we can optimize technical and mechanical issues late after transplant and that's why we believe that surgical involvement in the posttransplant care is very critical. For example this is a young girl who suffered a hepatic arterial thrombosis that was satisfactorily taken care of in the early
posttransplant period but she presented 3 years after transplant relatively asymptomatic with a minimal ALT elevation of 47, slightly elevated and chronically elevated GGT in the 50 to 100 range, it was 92 when we saw her in clinic. We got an ultrasound as is our protocol, she had no symptoms and otherwise was doing well, thriving as a young girl. But the ultrasound did note some biliary dilatation and we proceeded with a percutaneous cholangiogram, again this illustrates a lot of the interaction with our medical and radiologic colleagues who help us in the management and you can demonstrate that clearly there was an abnormal appearing bile duct that we believed would lead to later long term sequelae. This was not dealt with even though the liver function was relatively normal. And it was so significant that despite percutaneous accessing of the left and right ducts we actually couldn't navigate into the biliary system, into the rear systems that she had essentially a near complete biliary obstruction in this asymptomatic period about 3 years after transplant.

Despite unsuccessful percutaneous drainage we were later to do a sequential combined operative approach where we opened the biliary limb through the Roux limb, accessed the system and then with our radiology colleagues achieved internal/external drainage and then balloon dilatation of this to help this liver be maintained and healthy into the next years. We believe now the catheters are removed and her liver function is normal, minimal fibrosis on biopsy so this may extend her graft life a significant period of time, but it's an example of some of the challenges we don't have good standardization yet in terms of what tests we should monitor, when we should do these and what we should do when we find abnormalities.
The medical challenges that we face really center on immunosuppression, and this is just a slide from our SRTR Annual Report to demonstrate the general state of immunosuppression of children. A couple of take home messages. As you know Tacrolimus is the main immunosuppressant here, it was replaced with Cyclosporin. Steroid use has been decreasing but still used at transplant about 80% of cases. We use the steroid free protocol in about 50% of our patients. Steroid use at one year has decreased but it's still about 40% of the pediatric population in the United States and this may be an area to work on in terms of minimization of steroids in an appropriate way.

The challenge though of this is that there are differing issues in children. Dr. Soltys from our group used pediatric studies of pediatric transplantation data to report that the majority of cognitive late mortality in children once they are doing well at one year when you look at what happens to them after that year is really related to over-immunosuppression, so you can see that a third or the patients die from sepsis, multiple system organ failure or PTLD in this cohort here.

In contrast when you ask why patients lost their graft after they were doing well for one year you could see that a third of the patients lost their graft to chronic rejections. You see you have a dichotomy that exists still where there is at either end of the ball shaped curve there area patients that may have over-immunosuppression and are having infection as well as evidence of under-immunosuppression in another cohort where there is evidence of immune injury. And then there is 80% of the patients that are doing perfectly well right in the middle, but how do you help identify those at either spectrum and how do you walk that tightrope?
Clinically the noninvasive measures that we have right now are generally - the invasive measures that we use are limited to liver biopsy and careful clinical monitoring. We have with the work of Rick Casindian and our colleagues at the hospital and the SDI have developed an FDA approved biomarker that is not available and this has been used both in liver and intestine and in kidney patients to help prevent rejection risk and it's a CD154 HLA type of exam that tries to estimate donor risk, so this is in the slide here you can see that this patient with a higher antidonor response to HLA of the donor as compared to third party is at higher risk for rejection as opposed to this patient who has a response that's much suppressed at the donor as compared to a third party. This would be a patient that could be reduced at an earlier time point in terms of their immunosuppression. And these type of tools may be helpful in walking that tightrope and in helping patients who need less to be on reduced immunosuppression and the contrary for those who need more.

But the goal is to optimize long term graft health and I want to highlight two of the challenging studies and issues that have come up. One is the area of fibrosis in long term grafts and the second is donor specific antibody that has been tested in long term pediatric grafts. This is data that has come from biopsies that are done in children, some with normal or near normal liver function that does demonstrate varying patterns of fibrosis late after transplant. And this is an area of controversy and where working groups are developing standardization for when we should do these biopsies and there is no accepted standard practice now but I wanted to highlight some of those - the issues at least for your awareness.
This is sort of a schematic of a very focal perivenular fibrosis to more of a clearly established fibrosis that can occur sometimes in the context of normal liver function. And what has been demonstrated is that in children as in adults to some degree although it's cleaner in children because there is less confounders of hepatitic disease or other autoimmune disease, this is happening in typically non-autoimmune and non-viral disease posttransplant courses. You can see that fibrosis does increase over time and this is one of the challenges that we are instructing our families and following with our patients now. So most studies have shown that this is increasing over time. Some of this is in Cyclosporin data and needs to be replicated under Tacrolimus and more current immunosuppression.

And we've also seen that that fibrosis may be correlated with the presence of what's called donor specific antibodies for those of you who are not familiar with that where we look at the patients who develop higher grades of fibrosis have a higher presence of donor specific antibody against - directed against the donor and how this may influence our therapeutic algorithms such as adding immunosuppression or modifying immunosuppression to avoid that donor specific antibody.

I want to conclude with talking about the outcome measures that we look at by showing you some granularity from split data at the 5 and 10 year mark. This is our multicenter consortium. In this first on the left hand side this is 5 year survival patients, about 500 patients, looking at the laboratory abnormalities that when they presented at the clinic. You can see that's very uncommon for a
patient, a child to come at the clinic after transplant and be jaundiced, bilirubins are normal. But if you look at more subtle abnormalities of ALT, AST or particularly GGT you can see variations in up to 30 to 40% of this cohort population at least. And so this is an important factor.

Secondly, in terms of their immunosuppressant use at the 5 year anniversary about 65% were just on monotherapy which would be considered a goal of our care. But there were 25% on double therapy and 11% on triple drug therapy at the 5 year mark, and so clearly those are the component of patients that may benefit from additional optimization. And then this study was followed up by a 10 year study to give you a picture or a snapshot of what to expect at the 10 year mark and again colleagues from the studies in pediatric transplant demonstrated about a 10% incidence of an abnormal GFR PTLD rate over that period although the morbidity - mortality had decreased significantly using current therapy but the incidence remains at about 5% in this cohort. And then abnormal cholesterol metabolism and BMI in another proportion of patients, so this is what we are looking at in our current 10 year and 15 year outcome survivors.

So using this data the consensus panels and experts in the clinical team developed a starting point for additional outcome criteria that we call the ideal outcome criteria and again this is just expert based but included both allograft criteria such as a normal ALT and normal bilirubin, albumen and GGT, no chronic rejection, no retransplant and monotherapy immunosuppression. So if you want to ask the question how do I know if my graft is doing well this was a beginning point to what we defined as that, and then that they would not have immunosuppressant related morbidities, those tier 3
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morbidities including no PTLD, no diabetes, normal growth, no renal dysfunction or hypertension. And so when you looked at the graft these were the results of looking, at least in this small initial 10 year cohort, the patients that had met all prior criteria for a normal liver and then thinking outside the liver those that had no evidence of immunosuppressant related morbidities, no PTLD, no renal dysfunction, normal growth and no diabetes as well as no Prednisone use, no antihypertension use or seizure medications. You can see that when you add all those 13 criteria it really elevates the bar but it is more representative of what we want for our outcomes when we say how well can I expect my child to do? These are not unreasonable or excessively high standards, they would be what any parent would think would be a reasonable goal. Now only in this study only about a third of the patients met every one of these criteria, so you can see that even in these patients coming at 10 years with normal liver function you look at the proportion that have this ideal outcome we still have a ways to go in terms of getting that for the majority of our patients.

And then to conclude, patients want to know you know how long can I keep this graft? We've had an experience and most of the United States data has demonstrated that retransplantation in children is not that common. Currently you know well less than 15% of children require retransplant. This is different than cardiac or renal transplantation. But the data still is evolving, we need to monitor it over time. On the right hand side of this slide is the half life for pediatric liver transplant. There was a blip in this cohort of the mid-2001-2002 but overall the half life has varied and stayed stable between 10 to 20 years. This is still we believe will increase and improve but we don't have true long term half life data for what to expect at 30, 40 or 50 years after transplant. In our own
retransplant experience we've demonstrated very good retransplant outcomes in children when that is needed, again less than 15% of children need that but since 2000 the retransplant survival at Children's has been 78%, and this was recently submitted for publication. So the expectations for those who do require retransplantation currently is good but the data needs to be gathered at the long term follow-up mark.

So in summary the challenges for us are great in this area. I think they are unique challenges typically after transplantation because of the disease mix and the challenges of transition. But the focus is looking both at an outcome that includes allograft health so the best and normal allograft health possible. Challenges to that include immunosuppression, over and under-immunosuppression, but then avoiding these and really working on optimizing these other parts of the best outcomes such as no complications of immunosuppression, normal growth, normal functional health and good self-management as they transition to adult care. And clearly there is work ahead of us but we are all part of that community together as we transition to (inaudible) so it's a privilege to work with you.