[MUSIC PLAYING]

**JAIDEEP BEHARI:** And we'll talk a little bit about national organ allocation policies for deceased donor transplants. For second and third year fellows, this may not be new information. But for first year fellows, some of you may or may not know this information.

Then we'll talk about some patient selection issues. It's always a challenge to know when to refer a patient, when not to refer a patient, what the special situations are, circumstances are, in terms of patient selection, and then just some salient features of medical management of liver transplant patients since some of the management is different because of immunosuppression.

So talking about organ allocation policies for deceased donor transplants, the overall regulation is by a federal agency called the Department of Health and Human Services. And within the HHS, there is an agency called the Health Resources Services and Administration, or the HRSA, and within that a bureau which regulates all organ transplants in the US.

And the way this is organized is that the actual regulation of organs and transplants is regulated by an agency which is called the United Network for Organ Sharing. And this is a public-private partnership. So there's clearly a very important federal government role. And UNOS runs the organ procurement and transplant network, which is called the OPTN. So you'll hear these words sometimes at selection conference, UNOS or OPTN. And so you sort of have a background on what these mean.

And the regulation of organ transplants was really formalized under a national organ transplant act, which is an act of Congress in 1984. And then there was a final rule published in 2000, which set up the regulatory framework for organ transplants.

And currently there are 11 regions in the country, which are called UNOS regions. And these are all color coded. We are right here in Pennsylvania. And the original purpose was to increase access to decrease costs associated with organ transplants and to minimize travel time across the country and decrease organ preservation time, since they do have implications for outcomes.

And this is our Region 2, which includes Pennsylvania, West Virginia, Maryland, Delaware, New Jersey, and DC. So there's five organ procurement organizations here. I'll talk about that in a minute. There are 35 transplant centers. So this is a very busy and competitive region. I'm sorry, this should be 2016. There were 1,000 liver transplants. And as of July 13, there over 2,000 patients who are awaiting liver transplants within our region. So when you are evaluating a patient in the hospital or seeing a patient in the liver clinic or in selection conference, this kind of gives you an idea of how many patients there are out there who are still awaiting liver transplants.

However a problem with those 11 UNOS regions is that there is a pretty substantial disparity in terms of wait times and MELD scores at transplant. And this just gives you this variation. And there are some parts of the country, for example, down here in the south, where the median MELD scores are less than 22.

But those a few who've been on the floors or at selection conference know that we can only dream about that here in Pittsburgh. And we are averaging MELDs of 26 to 28. But certain blood types like O have to be in the 30s sometimes to have a realistic chance of getting an offer. And there are some other regions, such as California, where the wait times are even longer and the median MELD scores are 30 or higher. So that's a real problem in terms of wait times across the country.

So because of that, there's been some moves to decrease the number of regions from 11 down to either 8 or 4. This has not been formalized yet. It's still being considered. And if there were eight regions, this is what the map would look like.

There's also a proposal to have just four districts instead of 11 regions, which is supposed to decrease the unequal distribution in terms of organ allocations. And the proposal, of course, is that this is what exists to the left. And if you go from 11 regions down to 4 districts, then there is a little bit reduction in disparity in wait times across the country.

So within a region there is an organ procurement organization. And here in green is the OPO that serves our area. So Allegheny County is right there. And so this is mainly Western Pennsylvania as well as West Virginia. And our OPO is called the Center for Oregon Recovery and Education, or CORE. And if you are around the ICUs here, sometimes you'll see cars with the CORE sign carrying organs for transplant, not just livers, but other organs too.

And this is a pretty large territory. It includes 150 hospitals, 6 million people. And these are the five transplant centers, which are mainly in the Pittsburgh area, as well as Charleston, West Virginia. So these are the hospitals where CORE will go for recovery of organs when a donor is available.

And there's usually a algorithm that's followed when organs are available. And for liver transplants, there is a score assignment, which goes by status 1A, which I'll talk about then in just a second. And there are some patients who are listed for transplant, but they are inactive for a variety of reasons. A common reason for that would be the patient is too sick. They may have an active infection. Perhaps they're in the hospital for some other non-liver related complication. And these are patients who are inactivated for a brief amount of time.

Following that is a calculated MELD sodium score. I won't talk about the MELD sodium score since a lot of you're very familiar with it.

And then there are some situations where there is an exception score, where we don't use the native MELD sodium. But these patients are given priority based upon their underlying liver problem.

But the highest priority is that for status 1A. And that includes patients who have acute liver failure. So this is a catastrophic liver problem that leads to liver failure in a very short amount of time in the absence of any underlying chronic liver disorder. And usually, we are seeing these days commonly drug induced liver injury. Rarely, we'll see acute hepatitis B and other reasons. But really drug induced liver injury is a very common problem that you'll see frequently, acetaminophen or other drugs, such as antibiotics.

It's also status 1A if a patient undergoes a liver transplant, but there's primary non-function of the liver graft within seven days, because that's associated with a very high risk of mortality. And after a transplant, if the patient develops hepatic artery thrombosis, which can cause very significant injury to the bile ducts and allograft loss. And that qualifies as status 1A.

And then an exception to the chronic disease rule is an acute decompensation of a patient with Wilson's disease. So sometimes these patients may have some underlying chronic disorder but develop an acute decompensation. And all of this these patients would qualify as status 1A, which is the highest priority for transplant.

In 2002, the MELD system, the Model for End-stage Liver Disease score was adopted. And prior to that we were using wait times as well as the Child score system. But starting from 2002, the MELD score was adopted.

And, of course, the driving force for this was to give the organs since they are limited to those who needed the most. And that's why the MELD system was developed. Now, some of you may know this that the MELD system was originally developed to determine prognosis and outcomes after TIPS and then was subsequently adopted for liver transplants.

And in 2016 sodium was added to the MELD score. And so now we're using a MELD sodium system, because if you have a low sodium score even with a relatively low MELD, the MELD sodium is high, because it's associated with a high mortality.

And this is a very important paper from 2008, which showed that low serum sodium was associated with a high risk of death. And you'll find most of these patients have refractory ascites with or without SBP or other complications. And these are patients who have a high risk of death despite having a low MELD score, leaving aside sodium. So by incorporating sodium now, we can capture these patients who have refractory ascites and are at high risk, higher risk for mortality without a transplant.

The other important change was a Share 35 policy, which was adopted recently, just a few years ago. And according to this policy, within the region, when an organ becomes available, it's offered to a patient that's listed with a MELD score of greater than 35, before it's given to our own local candidates with a MELD score of under 35. And this is, again, an effort to decrease the wait times and make sure that the person who needs the liver the most gets it.

And here are some analysis based on SRTR data showing that the mortality once the Share 35 rule was adopted decreased, suggesting that this was having the intended effect. It does mean sometimes that when an organ becomes available locally, a center outside of this region gets it because of the Share 35 policy. That also works to our patients advantage if they are listed with a high MELD score, because then the organs come in from other centers. And this has been adopted several years ago and all of us follow it right now.

There also some situations where patients don't have a very high MELD sodium score, but they are given special points, which are called MELD exception points. And these situations include certain cases of cholangiocarcinoma, not in every case, but certain situations where patients do meet certain criteria. The most common reason is hepatocellular carcinoma where the lesion is T2-- and we'll talk about the Milan criteria in just a bit-- and in cases where post-transplant there's hepatic artery thrombosis but the patient does not meet criteria for status 1A, which is in the first seven days.

Hepatopulmonary syndrome meeting certain criteria also gets, or can qualify, for MELD exception points. Portopulmonary hypertension and other cardiopulmonary complication, cirrhosis and portal hypertension, some metabolic and genetic diseases can also qualify. Typically on the adult side, we see a few of these cases. But you'll see a lot of hepatocellular carcinoma getting MELD exception points.

So the Milan criteria was initially proposed in 1996. And this was a landmark paper, which suggested that if patients with hepatocellular carcinoma fulfill certain criteria, their outcomes after transplant were actually very good and comparable to those patients who did not have HCC. So this meant that liver transplant was actually a great option for patients who had cirrhosis with liver cancer, primary liver cancer. And this is called the Milan criteria.

And so these patients have to be stage T2, which is defined as one lesion greater than two centimeters or less than 5, or three lesion all of them have to be less than 3 centimeters. So they have to be between 1 and 3 with no microvascular invasion. And there should be no extrahepatic spread or metastases. So here's an example of a patient that has a T2 lesion on contrast enhanced imaging.

There are also some situations where a patient may not fulfill the Milan criteria but may still qualify. And one example of that is what's called the UCSF criteria, which is a little bit more liberal. And this proposes that one lesion less than 6.5 centimeters, three lesions each less than 4.5, instead of 3, and the total tumor burden of less than 8 centimeters would also qualify. And here, patients that fulfill the UCSF criteria have reasonable outcomes.

So if someone has a lesion that meets UCSF criteria, we sometimes down stage those patients. And they can then be listed. So this is an example of a slightly liberal policy, although most regions will use Milan criteria, but some regions do use UCSF criteria.

The other changes that have been implemented in terms of the organ allocation rules were the changes to HCC MELD exception policy. And one of the major changes now is that before a patient can get MELD exception points for HCC, there's a six month waiting period.

So once the patient meets criteria, Milan criteria, and is listed, they do not get the MELD exception points right away, but they are initially listed for six months on their native MELD sodium score, which may be low, for example, a patient that has child's class A cirrhosis, very low sodium of 7, 8, 9, but has a T2 lesion would be listed at their native MELD score and have to wait six months. So this is a time when we frequently would refer patients for local regional therapy, so that that tumor does not grow in size and become more advanced than T2 within those six months.

But once those six months are over, then the patient gets a MELD exception upgrade to 28 points at six months. And then goes up by 10% every three months, with a cap at 34. So this is just under that Share 35 rule. And this was an effort to decrease an increase in the number of HCC that was out of proportion. There were some concerns that patients who had HCC were getting preferential organ allocation compared to those very sick patients who were listed with a native MELD sodium score that was really high. So this was an attempt to bring some parity back into that system. And we've been following this rule for a couple of years now.

So sometimes if you see a patient at selection conference that otherwise meets criteria, we have to wait for six months before they get the exception. And it does mean that we have to pay some attention to local regional therapy for those patients.

So there is a algorithm then that's generally followed for patients who are on the wait list. Typically, status 1A is right on top. And it follows a MELD in descending order. But typically when the MELD score, MELD sodium score is less than 15, because those organs go to other regions, it's very uncommon to have a patient get transplanted with a MELD sodium score of less than 15.

So therefore, if you have a patient that is otherwise clinically very sick and you think you that the patient needs a transplant a live donor transplant is a very good option. And here is very recent data from the *American Journal o Transplant* looking at an analysis until 2016. And living donor transplants is a very, very small number. In 2015, there were only 359 live donor transplants in the country.

In Pittsburgh, this number has increased dramatically over the last few years. And part of the reason for that is because we have a relatively high wait times with high median MELD scores for transplant. So many of our patients die waiting for transplant. And this is a very good option. So for any patient that you're considering for a liver transplant, it's always a good option to consider live donor transplant for those patients.

Moving on to patient selection, a couple of questions that you should ask is when and if liver transplant is indicated for these patients and can the patient undergo transplant with an acceptable outcome. So these really are two important questions to consider.

And one of the things that you will hear a lot is when is when is it appropriate to refer a patient for a liver transplantation. And this was a very important paper from a few years ago showing that there is a survival advantage to liver transplantation above a MELD score-- and this was in MELD sodium-- but a MELD score of 15, although the crossover probably happens somewhere between 12 and 15.

But this is an important region, because beyond that, a higher MELD score will give you a survival advantage. So when you have a patient with cirrhosis that you're seeing either in the hospital who has never been referred for transplant or in the clinic that you're evaluating, it's always a good idea to ask yourself, is this an appropriate time? Is this a patient that has a MELD score that's around 15 or higher that may benefit from a referral? Or it's a patient that has a low MELD score, but is rapidly increasing so that the patient may cross that threshold in the near future.

So it's always a good idea to consider that, because as you know, it does take some time to put patients to the evaluation process because there's a huge amount of insurance approvals, medical and surgical evaluation that's necessary for patients before they are listed. So this is an important threshold to keep in mind, of course not an absolute threshold, but just sort of a mental benchmark for you to keep in mind.

The other common question that's asked especially in our current population which is now increasingly NAFLD and NASH related cirrhosis with very effective treatments available for hepatitis C is how patients who have a high BMI do compared to people who have normal BMIs. And this is a paper from 2009 showing that patients who had a BMI of 40 or higher than 40 did slightly worse than patients who had BMIs between 18 and 40. But they actually did better than those who were really underweight. And this may have been because patients are either frail or malnourished and who may have other serious illnesses. So certainly not an absolute contraindication, but just something to keep in mind, because we are seeing increasing number of patients who have obesity as well as cirrhosis.

And this is a histogram just showing you the distribution that most patients are sort of in the middle of the range. But you will frequently see patients who are at the extremes of these range. So when you see a patient that has obesity versus a patient that's underweight, really these are the patients who may actually do better than the seriously or severely underweight patients.

Ages is another common question that you may be faced with. We do have an aging population, especially here in our region. So there is no absolute cut off. However, the older the patient, the higher the risk of post-operative complications as well as for operative complications but typically patients who are older tend to do worse than patients who are younger, but there is no absolute cutoff.

So we've had patients in the recent past listed who were in their mid 70s. And the oldest patient that I had was 73 at the time of transplant, who's now 79 five years post-transplant and doing really well.

The other common things to keep in mind is that there is an increased risk of post-transplant vascular complications with smoking. So when patients undergo behavioral evaluation during their transplant work up, we insist that the patient stop smoking. You definitely have to ask about marijuana use-- some patients me consider that separately from smoking-- and tobacco use, etc.

Another common question that will come up is this question of a six-month sobriety rule for alcohol use. And as such, we do not actually have a six-month rule, although Dr. Demartini's research, who's a transplant psychiatrist here, suggests that the longer the period of abstinence from alcohol, the less likely the patient is to relapse post-transplant. So it's important to ensure as long a period of sobriety as you can manage.

The problem, of course, is that these patients are very sick. And sometimes there's very limited opportunity for patients to undergo rehab formally. So it's a difficult problem.

But this is an interesting paper from 2011, where very selected patients with alcoholic hepatitis were offered transplantation. And they had much better outcomes at 24 months compared to those patients who did not undergo transplants. So we all know that alcoholic hepatitis is associated with very high mortality risk. And so this is just like the Milan criteria paper from several years ago, this was truly an important paradigm changing paper. And there's several other trials going on now trying to figure out what the best population is within this high risk group of alcoholic hepatitis patients who would benefit from a transplant, but then would not have a higher risk of a relapse in terms of alcohol use post-transplant.

And we are also very interested in this question here, especially since Dr. Bataller is now our chief of hepatology, who's an expert at alcoholic liver disease. So this is something that will get a lot of attention in the near future.

So patients that are being evaluated for transplant will frequently have a prior history of other extra hepatic cancers. And several years ago, we put together this sort of guidelines, which is our UPMC guidelines, which give you some idea of how long patients need to wait after their treatment for an extrahepatic cancer before they can be considered for a transplant. And common ones being colon, breast. And here, depending on the stage, it could be two years or five years. And then there's some other common cancers which are listed here.

But this is a decision that's based on a case by case basis. Every patient is very carefully considered. And it does not mean that it's an automatic disqualification. So that's something to keep in mind in case you see a patient with a prior history of an extra hepatic malignancy.

We also now have some guidelines and a protocol for ABO incompatible liver transplantation. So if you ever face a situation where patients have a relative or an acquaintance that is willing to be a live donor for them, but there is a question of ABO incompatibility, we do have a protocol for that. And in appropriate situations, that can be considered. We recently had a patient that underwent ABO incompatible transplant. So again, something to keep in mind if you get asked these questions, especially by patients or their relatives.

So moving onto medical management of the transplant patient once they've undergone transplant. This graph is a really important one, again based on SRTR data up until 2016. And this was just recently published.

It's important to know that patients who are re-transplanted do much worse than patients after they first transplant. And there's a variety of reasons for this. Surgically, it's a more difficult surgery. They have more problems at the time or afterwards. Many of these patients have kidney dysfunction related to their immunosuppression use or a recurrence of their original disease.

And so it's important to do the best you can to keep the organ functioning well. And so it's important to take good care of not just the allograft but also the other medical issues.

So when you're seeing the patient in the transplant clinic, it's usually helpful to systematically approach all of these issues. And I've listed some of the points that most of us would look at for the patient in the transplant clinic.

You definitely have to think about allograft function. So some of the common questions that we'd ask in clinic with these patients is, are the liver injury test OK? Is the liver synthetic function OK? Do any imaging studies suggested that the allograft is showing signs of cirrhosis of portohypertension. So it's an important thing to keep in mind. And there isn't any single goal test, but you really have to look at all of these factors to decide how the allograft is functioning.

You'll also see that in our clinics, we have patients transplanted 10, 15, 20 years ago. And sometimes it's very difficult to tell for patients who are transplanted many years ago what the status of their allograft is. And so sometimes we'll get biopsies if a patient hasn't been seen in clinic for 5 or 10 years and is coming back to establish care, especially if you're concerned that they've had persistently elevated liver injury tests for a long period of time, but no specific intervention.

It's always important to very carefully look at their immunosuppression doses levels, look at immunosuppression history, see how they did before. It's important because the most commonly used immunosuppressive agents, such as Prograf and Cyclosporine, can cause kidney injury. So frequently five, six years down the road, especially given our population, which has been transplanted many years ago, it's always a question of trying to optimize immunosuppression so you can decrease the risk of extrahepatic complications from long-term immunosuppression use.

Recurrent disease is quite frequent. Hepatitis C was a major problem for us. It's become less of a problem now because all the very effective antivirals work very well post-transplant, or many of them do. So we have very nice protocols as well as clinical studies now, so that hepatitis C can be effectively treated post-transplant.

Hepatitis B can be effectively treated. It's become less common to be to have transplants for hep B because we treat many of these patients pre-transplant now with antiviral therapy.

PSC, PBC, autoimmune hepatitis, all of these diseases can recur post-transplant. So it's important to ask whether the patient may have recurrent disease, especially if the patient has elevated liver enzymes post-transplant. And hepatocellular carcinoma is also an important recurrent disease that can take place post-transplant.

In terms of transplant-related complications, rejection is always a big concern. Biliary, vascular complications can happen, not just immediately post-transplant, but many years down the road, infectious complications because of immunosuppression. And with long-term post-transplant situations, especially with increasing BMIs and body weights in our populations, metabolic complications post-transplant, diabetes, et cetera, and cardiovascular complications has become increasingly important. And then pay some attention to health maintenance issues including all appropriate vaccinations, cancer screenings, such as colonoscopies, and some attention to metabolic health such as diabetes.

So if you see a patient that comes to clinic for evaluation and has elevated liver injury tests, there is no single test that you can do to know what's going on. So you have to really think about several possibilities. It's always a good idea to repeat liver injury tests, because you can get mild transient elevations, which subsides. So you don't want to put the patient through a lot of unnecessary testing if you can avoid it. So it's always a good idea to repeat it. Typically, if it's a mild elevation, we'll have our patients undergo blood work in a week or two weeks, depending on the situation.

I typically will start with an ultrasound with dopplers. If a patient has completely normal renal function, you may consider other contrast enhanced imaging studies. But typically, an ultrasound with doppler is a very good initial test.

There, you're paying attention to any bile duct dilation, for biliary complication. And you're also paying special attention to both the hepatic artery as well as the portal vein, and in some situations, even the hepatic venous outflow. So this is really important. And especially if a patient has a problem with the hepatic artery, you have to intervene very quickly, because those patients can develop very dramatic biliary complications and ischemic cholangiopathy.

And depending on the results of the ultrasound, you can consider, depending on how close the patient is to the transplant and how severe the problem is, either go to angiography or sometimes even a surgical re-exploration. And in places where there's hepatic artery thrombosis, immediately post-transplant these patients can sometimes require retransplantation.

We will sometimes consider liver biopsy if you have high liver enzymes with completely normal imaging studies, because we're always concerned about antibody mediated rejection or cellular rejection. So that's always a concern.

And in some situations where there is a concern for recurrence and you're not very sure about the diagnosis, especially in the setting of autoimmune diseases, recurrence of PSC, et cetera, when you're not sure based on imaging studies where the patient has recurrence or another problem.

The role for FibroScan is still unclear. As you know, we do have a FibroScan, which is a noninvasive way of measuring liver fibrosis. But how it correlates with the transplant liver fibrosis is less clear. We've had a few cases where there is poor correlation. So I am not routinely using a FibroScan scan. And there's not a whole lot of data available right now for use of FibroScan in the post-transplant setting.

There's also some other non-invasive tests available. You could consider MR elastography. We do have that here at Presby. But again the rule has been not well defined compared to the pre-transplant setting.

In terms of immunosuppression, we are typically using some induction agents in the transplant period followed by a bunch of maintenance agents. On the medical side, you will typically face the maintenance agents more frequently than you well some of these induction agents, which are given at the time of surgery. And the maintenance agents are typically what the patients will stay on long term for immunosuppression.

And of these, really the most important workhorses are Tacrolimus or Prograf. Sometimes we'll use Cyclosporine for patients who are unable to tolerate Tacrol. We also use in the appropriate situations, Everolimus, Mycophenolate mofetil And the others are very rarely used these days.

So the typical agents post-transplant, immediately prednisone, Tacrol and MMF. And then sometimes we'll use Everolimus for patients who have Prograf or Cyclosporine induced kidney injury to decrease the risk of nephrotoxicity of CNI agents.

Very common consult if you're on the inpatient service is how do you manage immunosuppression levels. Just as a rough guide is if the patient is immediately post-transplant, we're aiming for somewhere around 8 to 10. Up to a year, we're aiming for 6 to 8. But most of our patients by the time you get consults for these patients who are beyond a year, we're aiming for somewhere between 4 and 6.

So it's helpful to remember, up to a year, you could say less than 10, and then somewhere around 5, so 4 to 6 beyond that time. Now this is, of course, depending on which other immunosuppressive agent the patient is on. So if someone is on prednisone, if they're on cellcept or Everolimus, then you can get away with lower Tacrolimus dose. It's always helpful to have some sense of what their original disease was because if a patient had autoimmune hepatitis, it's always a good idea to keep them in a small prednisone dose indefinitely. If someone has had multiple prior episodes of rejection, then you probably want to keep these levels on the higher side with more than one agent sometimes.

So this is just a rough guide. But it gives you for an uncomplicated patient who's presenting with a non-liver related issue to the hospital, you can follow this as a rough guide for immunosuppression levels. And we'll typically test these levels maybe every three or four days. A trough level in the morning before they get their morning dose, and then you can give the appropriate advice to the service that's consulting you.

However, it's important to keep in mind that acutely as well as chronically, Tacrolimus does have many potential side effects that you need to keep in mind. It can cause hyperkalemia. Hypomagnesium is an important one. So you'll see and notice that most of our patients require long-term magnesium replacement.

And that sometimes becomes a problem because the patients are on magnesium replacement therapy, but you are being called for a consult on the inpatient side for diarrhea. So that's a common problem to keep in mind because it could be contributed to by high doses of magnesium. So sometimes you have to play around with these doses and even hold it briefly in the appropriate setting.

There's also a significant metabolic toxicity associated with CNIs. Tacrolimus can cause hyperglycemia, hyperlipidemia. Nephrotoxicity is an important one. So many of our patients over many years can have progressive liver injury requiring dialysis or even kidney transplants. So that's an important side effect to keep in mind.

And if you see a patient early on that has kidney dysfunction, we do consider lowering the dose of Tacrol and adding a second agent, such as cellcept, which is Mycophenolate or one of the others. And Everolimus and MMF are potential second agents that can be added.

Post-transplants, especially with high doses, neurotoxicity is a common complication to keep in mind. Patient can have seizure-like activity and other neurotoxic effects and can develop tremors without other severe toxic effects for a long term. So these are some important side effects to keep in mind, if you do see patients in follow-up.

In terms of which immunosuppression you use post-transplant, an important consideration is renal dysfunction. You'll notice many of our patients now with NASH related cirrhosis, because many of them have diabetes, they will go into transplant with kidney dysfunction. And so it's common to have patients be on dialysis for a few weeks post-transplant or have very slow renal function recovery post-transplant.

And so it's important to keep in mind what the renal function is. And based upon whether they have no renal dysfunction or whether they have renal insufficiency, we usually follow a couple of different pathways. And in patients who do have renal insufficiency, the goal there is really to try to minimize the dose of Tracrolimus and add a second agent, either Mycrophenolate or Everolimus as a second agent, whereas those patients who have normal kidney function, then to continue Tacrolimus monotherapy long term becomes a potential option.

And usually at 60 days, we are assessing the need for Everolimus. So if a patient within that immediate post-transplant period is on cellcept, then we can consider Everolimus if the patient can tolerate it. And then we usually do not discontinue Tacrolimus, but if you can continue Tacrolimus is probably a good idea, and then add Everolimus to decrease its dose.

On the other hand, if patients have a difficult time tolerating Everolimus for a variety of reasons, you can get mouth sores, sometimes very severe dislipodemia, because it's an ENDOR inhibitor, then you can consider cellcept. So these are just some options, not that you have to memorize this or know this by heart on a regular basis, but just something to keep in mind if you're ever consulted about a patient that has kidney dysfunction to know that there are options available for you to play around with immunosuppression.

When you are switching to a second agent or adding a second agent and decreasing the dose of Tracrolimus, it's always a good idea to check after four days and then check again in a week. Continue checking at least weekly for a few weeks and then monthly. And we usually would expect the patient to get blood work at least three or four times a year to make sure that their levels remain stable.

We usually have patients check some blood work, including CDC. It's important to check their lipid profile, because it can dramatically affect their lipid profile. And it can also cause protein uria. So we always keep an eye on the urine profile.

Other potential complications to remember with Everolimus is oral ulcers. It can cause anemia. It can cause interstitial pneumonitis. And these are relatively uncommon, but you still need to keep them in mind because given our very large population, post-transplant population, you'll see some of these patients in the hospital. So these are just some things to keep in mind if you see a patient that comes in with a problem that has been on Everolimus immunosuppression.

We always try to minimize steroid exposure as much as possible. So we have a couple of steroid tapering regimens. Depending on the underlying situation, typically by the time the surgeons hand over care to hepatologists, most patients are off prednisone by then. In the setting of autoimmune hepatitis, though, you probably want to keep the patient at a low dose indefinitely.

You can get episodes of rejection. There are some patients who have primary non-function or hyper-acute rejection. These patients typically end up getting re-transplanted.

There's also acute cellular rejection. Those patients are typically treated with a prednisone bolus. You can also give OKT3 or adjust their maintenance therapy depending on how severe the rejection is.

You also need to be aware of a phenomenon that's been recognized in liver transplant only recently. And that's called antibody mediated rejection. So if you're reading a liver biopsy where the report says that there is no acute cellular rejection, but the C4d the staining is pending, you have to wait for that report, because what that means is that the pathologist is looking for donor specific antibodies, which can give rise to antibody mediated rejection.

So this is an important problem. In severe cases of antibody mediated rejection, we've had patients undergo plasma exchange in house. There's some literature on the use of Retuximab and higher immunosuppression, including steroids use. So it's something to keep in mind. You may face a situation where the biopsy shows no ACR, but the patient actually has AMR.

And AMR can also present with subtle findings, such as biliary injury. And so you have to just maintain a high degree of suspicion for other reasons why the patient may have rejection, but it's not ACR.

Some patients may present after many years with ductopenia, or the vanishing bile duct syndrome. So if you have a patient with cholestatic enzyme elevation chronically, it's typically a patient that has been on sub-optimal dose of immunosuppression or has been non-compliant for whatever reason, and so having ductopenia and cholestatic enzyme elevation can sometimes raise concern for chronic rejection, which is a difficult problem to solve. And we typically will react to that by increasing their maintenance immunosuppression.

If a patient does have a rejection, we do have a protocol. The treatment is based upon how severe the rejection is, which is graded based on a liver biopsy. So whether the patient has severe, moderate, or mild cellular rejection. If it's a mild rejection, we will typically adjust the Prograft dose, recheck labs and then follow based upon that.

This can change based upon their baseline kidney function. So if someone has underlying kidney dysfunction, instead of increasing the FK level, you may choose to add prednisone or one of the other immunosuppression drugs.

On the other hand, if the patient has moderate to severe cellular rejection, we typically will treat with either intravenous Solu-Medrol or sometimes with high doses of oral prednisone. Recheck the labs and then continue.

If the patient does not respond, sometimes we have had to re-biopsy the patient within a few days with very severe cases of rejection. So certainly if you face a situation where the patient has severe rejection and has not responded with improvement in liver enzymes and you've ruled out vascular and biliary problems, do not hesitate to consider a liver biopsy at that point, because it may affect your management, depending on what the second biopsy shows.

I talked about antibody mediated rejection before. Here's just a paper showing what C4d staining looks like. If you have an opportunity to come to our Tuesday afternoon papology conference, we frequently will have allograft biopsies showing positive C4d staining. In the last couple of weeks, we've had cases with C4d staining, suggesting antibody mediated rejection. And there's a bunch of treatment options, including a protocol that we follow, based on how severe the injury is. So something important to keep in mind in terms of rejection.

I will not go into this in great detail because the treatment post-transplant is more or less similar. Do keep in mind that HCC can recur. So we do have a protocol for surveillance post-transplant. We have very effective antivirals now for post-transplant, similarly for hep B. And these treatments are essentially the same as pre-transplant.

A very common problem now is post-transplant NASH. We do not have very good treatment options yet. Certainly lifestyle modification and avoidance of weight gain and minimize prednisone are important therapeutic goals here.

PBC is treated with URSO. Really no effective treatment for recurrent PSC. And always be on the lookout for recurrence of alcohol abuse post-transplant, which is not an uncommon problem.

In terms of biliary complication, you can get early problems. They can be anastomotic leak stricture. We don't use T tubes as frequently here now anymore. But this used to be a problem in the past. Late complications will typically involve anastomotic stricture. So those of you who've been on the pancreatic or biliary service will frequently get called for patients who have developed anastomotic strictures, sometimes even years after a transplant, presenting with cholestatic enzyme elevation.

In terms of vascular complications, we talked a little bit about hepatic artery thrombosis. We've had a few cases now where the HAT happened 10 years, 15 years post-transplant. So always keep that in mind. And at least if you get an ultrasound with dopplers here at Presby, you get a fairly decent read in terms of vascular patency, so looking at hepatic vein stenosis or thrombosis, hepatic artery thrombosis, and portal vein thrombosis. And of the three, hepatic artery thrombosis is the least well-tolerated because it gives rise to ischemic cholangiopathy.

In terms of infections, based on whether it's early, little later, or more than six months out, there's a different epidemiology of these infections. And typically after six months, most of the infections are community acquired. And therefore, based on how close the patient is to the transplant, you have to think about different agents. And we have a very good transplant infectious disease service. So if you ever face a situation where you're unsure about what's going on with a patient, it's a good idea to considered rare infections.

We do have a protocol for CMV infection. So based upon the donor and recipient status, if both are negative, it's a low risk. If the donor is positive, but the recipient is negative, it's high risk. And then there are these two intermediate situations.

So based upon where the patient is in terms of the donor recipient CMV status, they have different risk and are treated differently by the infectious disease service post-transplant. So this is something to keep in mind. If the patient, for example, it has a D plus or minus status presenting with high liver enzymes, always a good idea to consider CMV PCR for CMV recurrence or dN 01 infection post-transplant.

Always important to keep in mind that some of these anti-viral therapies can cause other problems. So keep that in mind. They do have many drug interactions. So this is just something to keep in mind post-transplant. Most of these patients within a few months are taken off of these anti-fungal therapies.

Never forget the metabolic syndrome for post-transplant patients. The farther out you go, the more weight patients gain. There's some data to suggest that most of the weight gain takes place in the first one year or so post-transplant because the patients are feeling better. Their appetite is better. And so much of the damage gets done early on.

But then they do develop diabetes, increased risk of cardiovascular problems, and obesity with time. So this is an important thing to keep in mind. These definitely do not have very good interventions available at this time. And, of course, cardiovascular complications is a big concern with diabetes and obesity.

Also, important to keep in mind that there is an increased risk of cancer. So continue colonoscopy. Also, a common cancer is skin cancer. So at least in our clinics, we are now recommending annual skin cancer screening. We make a referral from dermatology.

There are live vaccines that you should not be allowing your patients to get post-transplant since they're immunosuppressed. But there are many vaccines which are inactive or recombinant vaccine, which are very safe and in fact, highly recommended so. In the appropriate setting, make sure that the patients get all the appropriate vaccinations. Sometimes they may require a higher dose or more frequent dozing since are immunosuppressed.

The immunosuppressive drugs, prednisone and the CNIs can sometimes also cause osteoporosis. So starting within one or two years post-transplant, always a good idea to get a baseline DEXA scan and get patients appropriately treated or prophylaxed depending on their situation.

So to quickly summarize, we talked a little bit about organ allocation and how it's administered by UNOS. There is a MELD sodium based organ allocation algorithm. But there's also MELD exception criteria. It's important to select these patients carefully in the appropriate setting. Definitely think about live donor liver transplants and have a systematic approach when you see patients either in the hospital or in the clinic for their long-term post-transplant care. So I'm going to stop there and take any questions.