

Medications for Post-Transplant

Dean Lotito: Welcome everyone. Thanks for joining us here. My name is Dean Lotito, local PKD. Volunteer Massachusetts, and I'll be the hospitality host for this session. You have joined us for medications used after kidney transplantation is the chart in front of us shows. Before we get started. If you have any questions during the presentation, we ask that you type them into the chat box. And we'll address as many questions as possible. We do ask that you keep your microphone muted the entire presentation to ensure good quality over audio for everybody else. So, with that, I'm pleased to turn it over to Rebecca Corey, who will take us to the presentation Rebecca.

Rebecca Corey: Thank you, Dean. Hi, everyone. My name is Rebecca Corey, I am a Clinical Pharmacy specialist in liver, kidney and pancreas transplantation for adult patients at Mayo Clinic in Phoenix, Arizona. It is both a pleasure and an honor to speak to you today about medications used after kidney transplantation. And in 35 minutes, I can't cover every single medication so my focus today will be primarily on the immunosuppressive medications that we use.

I Have no relevant financial relationships with industry to disclose today. All of the immunosuppressive drugs that I will discuss are FDA approved for use in adult kidney transplant recipients. But I would note that not all of the drugs presented are approved in pediatric patients and or liver transplantation in the event that someone would need a combined liver kidney transplantation.

The objectives of my presentation today are several folds. But my primary focus are the first two to review immunosuppressive medications that we use after kidney transplantation identify some of the key adverse effects or side effects that are associated with these medications. And then throughout the presentation, I'll highlight some of the important storage and some things about administration of the medications and drug disposal at the end.

And then I briefly want to discuss at the end - and emphasize the importance of drug interactions and with transplant medications. And of course, some of the potential concerns that the transplant team has with respect to use of dietary and herbal supplements after kidney transplant. So, our immune

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systems are incredibly complex, very fascinating and composed of many different types of cells. And the cells are doing all different functions. All continuously. One key function of our immune system is its ability to protect us from anything that's considered to be a foreign invader.

So, that foreign invader is something that is not self. So that could be a virus or a bacteria trying to infect you. It could be a cell that's turning malignant or cancerous because now that cell is mutated, and it's not a normal cell that's part of you or in the trees case of transplantation, it could be a kidney or an orchid from another person. So, when we transplanted organs, such as a kidney, the natural response of your body's immune system is to attack it because it recognizes markers on that kidney and knows that they're from another person. The only rare exception to this rule is living donor kidney transplant between identical twins.

And indeed, the first successful kidney transplant performed in the United States in 1954 was between identical twin brothers in Boston, Massachusetts, by Dr. Murray and colleagues. And the reason it was in large part of success was because it was between identical twins. And so, rejection was not an issue in that scenario. At that time, we don't did not really have the effective immunosuppressive medications that we have today to prevent rejection. There are various types and severity of rejection that can occur after kidney transplantation. That's beyond the scope of this presentation.

But I do want to mention that the risk of rejection can vary among transplant recipients. And it depends upon multiple factors there's so there's some tests that transplant centers will do while you're waiting on the list for transplant. There's additional testing that is done at the time of transplant. And then sometimes even after transplant, there are tests that may be ordered or are performed to further assess your risk of rejection. So, the transplant center, and the team can adjust your immunosuppression accordingly to give you the best outcomes. So that's why some people may be on different medications than other people.

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Anti-rejection medications get that name because they're against or preventing rejection of your transplanted kidney. They're also called immunosuppressive medications. It's just a different name. But they get that name because the way that they prevent rejection of the transplanted kidney is by suppressing or weakening the body's immune systems.

And so that way, the immune system will recognize the kidney as being not part of you and it will not attack it and damage it and that's what we call rejection. The duration of immunosuppressive therapy after kidney transplantation is for the lifetime of the transplanted kidney as long as it's functioning, we must keep your immune system constantly suppressed.

The strategies can vary. A lot of transplant centers use similar the same medications but there might be some subtle differences in the way that they do things. And after transplant. It's important to note that the type of medication the dose of course, and sometimes even the number of anti-rejection medications that you take can change over time. So, you may start out on three and you ended up on two or vice versa.

And as you get further out from transplant, very important to remember, the risk of rejection is always there. But it does gradually get lower. So, compared to one month after transplant where your risk of rejection is highest, because that kidney is brand new to your body. So that's the time period where the immune system would most likely recognize it as not being your own and try to attack it or reject it, compared to 10 years later, where you're much further out from transplant. So, at that time period, you often don't have to get labs as often and your immunosuppression can be reduced, provided of course that you've had no rejection episodes. If you ever have a rejection episode, everything kind of starts over and becomes more intense again to treat that rejection and keep the immune system in check.

So, there's different types of immunosuppression. My focus today are the maintenance drugs, because those are the drugs that you take long term. But I do want to just briefly mention induction immunosuppression. So, induction is powerful immunosuppression that we just use at the time of your

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transplant, the effects of these medications can last weeks or months. And they're usually given by an injection or an infusion into your vein around the time of transplant, often, with the first dose being given in the operating room when they're doing the transplant surgery. There's a couple of different options that we have, and the choice of agent or medication depends on your particular rejection risk. And then other factors as well.

The transplant team considers everything when they decide which of the available options to administer for you. In the United States where the 90% of adult and pediatric kidney transplant recipients do receive some type of induction at the time of their transplant. And the most recent annual data report from the scientific registry of transplant recipients that was published this year, noted that 91% of adults and 94% of pediatric patients received induction at the time of their kidney transplant.

So, switching over to the maintenance medications for the most part, with one exception, these are primarily oral medications that you take by mouth there started in the hospital, and then they're continued long term after your kidney transplant surgery to protect that new kidney from rejection. So, these are the drugs that I'm going to focus on today.

There are a lot of names on this slide. If you're post-transplant, hopefully some of them look familiar. If you're pre transplant, there's a lot of complicated long names. And they're divided into different categories or classes based on how they work. So, rather than trying to focus on that, what I want you to understand from this slide is that there are a lot of different options to prevent rejection. And generally, what we do is we combine different drugs from different classes or categories, so that we can control your immune system in different ways avoid overlapping side effects and get the best outcomes for you and your kidney transplant.

So, typically, what happens is we take what's called a primary drug. And when I say primary drug, it's of the two or three that you might be taking that one is the one that is the strongest or most powerful and doing most of the work to control your or suppress your immune system. adjunct or helper

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drugs are also important parts of the regimen, but they're less potent. So sometimes if you have an infection, or some condition, those are the drugs that we might reduce first or temporarily stop during that time period.

So, typically, we take a primary drug, most often to coolness, sometimes cyclosporine, or a drug called Belatacept, combine it with an adjunct or helper drug, usually Mycophenolate. But a smaller subset of patients may end up taking Azathioprine they don't tolerate it. And then when you're a little further out from transplant, some patients may end up taking Sirolimus or Everolimus.

We typically don't use those in the first few weeks after transplant because they can impair the healing of your surgical wounds. So, most transplant centers will wait at least a month. But again, there are exceptions to every rule. And then steroids are an important part of transplant immunosuppressive regimens. So, if you look in the box at the bottom of the screen, the most common initial immunosuppression regimen after kidney transplant in the United States based on the most recent annual data report consisted of two Tacrolimus and Mycophenolate and Prednisone. So, a three-drug regimen and approximately two thirds of adult patients and a little over half of the pediatric patients, about a third of patient's adult or pediatric, were started on just two drugs or a steroid free regimen consisting of Tacrolimus and Mycophenolate.

So, Tacrolimus to start is a primary immunosuppressive drug. It was initially approved for use in organ transplantation in 1994, actually first and liver and very shortly thereafter and kidney transplantation. It's been around for a very long time, but it's still one of the very effective drugs we have at preventing rejection. And so, it's still used today as a main component of most immunosuppressive drug regimens. It's available in several dosage forms, their immediate release capsules that were the original formulation, and of course, they're now available generically. There are also a long-acting capsule formulation and a long-acting tablet formulation that were approved relatively more recently, and they are both for one administration.

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And then just in the last few years. Finally, Granules were approved for oral suspension, and they are available in packets for patients who can't swallow the pills. Prior to the granules, Pharmacies had to compound an oral suspension and not every pharmacy was able to do that. So having these Granules is very good for especially pediatric patients.

So, the dose of Tacrolimus varies widely. I've seen patients on half a milligram twice a day 10 or 12 milligrams twice a day. And I've even had patients with a very big drug interaction evolved to only needed one dose every 10 days. So, everyone takes a different dose, and the dose is adjusted based on the amount or the level that's in your blood. So, when you get lab tests drawn, we measure a level of this medication, and your transplant team uses that result to make sure your dose is where we want it to be.

Again, the capsules and Granules are typically twice daily for most patients, and then the long-acting formulations are usually once a day in the morning. Again, drug interactions or other factors may impact the dosing interval or frequency. So, the transplant team will guide it again, based on that level that's in your blood. That's really what guides the dose and how often you take it.

The statements at the bottom of the screen are very important. Just some statements to keep in mind. This is one of the medications that requires very close monitoring with blood levels to ensure that it's safe and effective. And that's because we need a level high enough to protect your kidney from rejection, but we don't want it too high, because then it can harm the kidney with high levels or cause other side effects. In order for those blood levels that we rely on to adjust the dose to be useful. They have to be accurately drawn. So they're always what we call a trough level. So, they're always in the morning, before you take your dose.

Side effects have Tacrolimus some of them are listed on the slide, you can get a headache from Tacrolimus sometimes if the levels are really high. But keep in mind other things can give you a headache, dehydration, not enough sleep stress. If you have migraine headaches that's completely unrelated to

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Tacrolimus and can be a cause. So, it's important to just keep your transplant team informed if you have a headache that is persistent or won't go away or it's particularly problematic to Tacrolimus can cause some neurologic effects, hand tremors are something that we sometimes see not something to be alarmed about. But definitely let your team know, if you notice your hand shaking when you're writing or about two hours after you take your dose, and the level is the highest if you're on the twice daily capsules.

A lot of times if we adjust the dose and target a slightly lower level, the tremors do get better go away. And again, there's options if they don't. neuropathy is something that can occur with Tacrolimus diabetes can also cause neuropathy, that's often tingling or numbness in your hands or feet. So, if you have diabetes, the best thing you can do is try and keep your blood sugars under the best control possible to prevent neuropathy from occurring or progressing. And there are also medications that can be used to treat it or manage it.

Seizures are very rare complication to Tacrolimus. We do sometimes see them. We do transplant patients with seizure disorders, that doesn't mean they can't receive to Tacrolimus. But we're definitely more cautious and we make sure that we do our best diligence to make sure all the anti-seizure drugs are on board and at full doses to make sure that we can get the best outcomes.

But Tacrolimus can still be used with some precautions. In the long term, it can increase blood pressure, and sometimes blood sugars even causing new diabetes after transplant. Again, there's some things you can do maintaining healthy weight and diet can help.

And again, if you have diabetes, we have a diabetes or endocrinology team that can help manage that in the long term. magnesium and potassium are what we call electrolytes. And when you get lab tests drawn, those are always measured. And the key is that we want them in the normal range. If they get too high or too low, they can cause your heart to beat abnormally, and other problems as well. So, sometimes if your potassium tends to be on the high

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side, we might, it might require an additional medication to keep it low, or you might have to restrict high potassium foods in your diet.

And magnesium supplements are often used after transplant, *[Inaudible]* *[0:35:51]* you see hair thinning, sometimes Prograf can cause hair thinning. But there are other conditions too. So, we always want to make sure that you don't have another reason for that, such as thyroid dysfunction, or a deficiency of something such as zinc or iron that may contribute contributing or malnutrition. Also, if you don't eat enough protein in your diet, or your very low weight that can contribute as well. You see kid decreased kidney function, I'm sure this is raising a lot of eyebrows.

So, kind of explain that this drug has been around for a long time. So, we know a lot about it. We know that, especially if the levels get high, it can harm the kidney. And so that's one reason why we watch them so closely. But the take home message is that it's a benefit to your kidney because your immune system would destroy that kidney much faster than the drug. So, everything's about benefit risks. And that benefit of preventing rejection is extremely important after transplant. And that's why we use it in kidney transplant patients because it outweighs any of those risks. You're also followed by kidney doctors and so I can assure you they're paying close attention to your kidney, and they often will be able to figure out if it's not working properly what the causes.

You see infection and skin cancer that's related to overall immunosuppression not specifically this drug. Very briefly storage and administration. You want to swallow the pill whole for any drug you ever take. Don't ever cut or crush or chew it without checking with the pharmacy to make sure that that's okay because these capsules are intended to stay intact. And the long-acting versions also cannot be cut or crushed.

You want to always take all of your transplant medications, including this one consistently at the same times every day, with or without food. And that consistency is key. If you always take it on an empty stomach, keep doing that, if you always take it with food keep doing that.

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And again, I want to emphasize that the blood levels, it's very important that they're timed appropriately. The Granules, except for someone who needs to use those to Tacrolimus is a drug that tends to adhere to plastic. So ideally, if they can be mixed in glass with the water using a metal spoon instead of plastic, that's the best scenario. But if that's not available, you just don't want to leave it in that plastic cup, you know, have it in the cup and administer it right away so that it doesn't sit in there and some of the dose gets lost.

Cyclosporine is another primary immunosuppressant drug; it was initially approved in the early 1980s. So, it was the first revolutionary drug that came out. And the company that made it came up with a formulation that 1995 called cyclosporine modified, which had better absorption. So, that's the formulation that we use primarily today, this drug works exactly the same as to Tacrolimus to weaken your immune system. And it's still used as a main component of many immunosuppressive drug regimens. But primarily is an alternative for patients who have intolerance to Tacrolimus.

The dose of Cyclosporine varies widely. Again, just Tacrolimus you'll see a lot of commonalities with some of these drugs, the dose is based on the level in your blood. And so that level is used to adjust the dose to have you in the target range for your transplant team wants your level at whatever time period it is after transplant.

So, initially we target higher levels and then later on with target lower levels, just like to Tacrolimus we need these blood levels drawn accurately, they're very important to ensure safe and effective use. And it also has many drug interactions, which keeps the pharmacist busy. So, when you compare these drugs side by side, there's a lot of words on this slide. But I want to focus on just some of the unique differences between them, they both work exactly the same way.

They both can affect the kidney function. So, that's something to keep in mind. But again, their benefit of preventing rejection outweighs that, because that's very important in the immune system has a much greater risk, especially right after transplant.

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Tacrolimus tends to be more likely to cause high blood sugars and diabetes in the long term. And it tends to have more neurologic side effects. But on the other hand, cyclosporine tends to be more likely to cause hypertension, high cholesterol. Another important distinction I mentioned Tacrolimus can cause hair thinning cyclosporine can cause excessive hair growth, or it's called hirsutism. And that's usually on your face, unfortunately, not on your head.

So again, if you stopped one drug and started another you sometimes you trade one side effect for a new one. As far as storage of cyclosporine. Again, a lot of words on this slide, but I just want to point out again consistency taking it the same way every day is important. It can be diluted, because sometimes it has a funny odor to it. It can be diluted with orange juice or apple juice, but you want to check with a pharmacy because that may vary among different products, you never want to use grapefruit juice because that interacts with a lot of our anti-rejection drugs.

So, grapefruit and grapefruit juice should always be avoided. And just like Tacrolimus it can adhere to plastic, so glass is preferred. And if you are on the gel caps are the pills of cyclosporine. They're come in these foil blister packs, and those are designed to protect the pills from exposure, so it's better to keep them in those blister packs until you need to take them.

Mycophnolate is an adjunct or helper immunosuppressive drug. It's available in two different formulations. The first one, Mycophnolate was approved in 1995. It's available in a couple of different dosage forms. And then a little bit later, about 10 years, nine years later, Mycophnolate sodium was approved. And it's the same exact active drug, but it's available in an enteric coated delayed release tablet.

So, a little bit different. They're both twice a day. And we don't have to routinely monitor levels of these medications, but they can be checked. If the transplant team has concerns that you have more side effects, and they want to make sure your levels not too high. And other scenarios make sure it's not too low.

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The side effects of Mycophenolate many of them are dose related. Nausea and diarrhea are very problematic. I probably should have bolded those on the screen, but every patient is different. So, we tell you to take it with food and minimize that. And there are some different things we can try to aim to prove that if that is a problem for you. One side effect or risk that's not related to the dose, just the drug itself is that these medications can cause fetal harm if administered during pregnancy.

So, it's very important for young female patients to be aware of that, because they would need to be off of these medications and on a more safer regimen for at least six weeks before trying to become pregnant due to the risk of congenital malformations and miscarriage. The transplant pregnancy registry is an organization that's a very useful resource for both patients and healthcare providers and I listed the website on the slide.

So, as far as administration storage of either microphone or a product taking with them with food can help reduce nausea. So, we always recommend that as a transplant center, and it does not affect the overall effectiveness of the medications to any significant extent. And again, we don't have to check blood levels. But we can if we need to.

The Mycophenolate capsules are relatively large. But again, you don't want to open or crush or cut any medication without checking with the pharmacy. These are meant to stay intact. So, if you have trouble swallowing them, there are some tricks that we can try or we can do transplant team can order the suspension for you, which is a liquid that you just have to measure out. But it's much easier to swallow

Azathioprine is an old drug. But it's still used for a lot of autoimmune conditions such as some inflammatory bowel disease conditions, and other diseases where the immune system is wrapped up. We still also use it in transplant. It's been around since the 1960s. And right now, it tends to be an agent. That's an alternative for patients who don't tolerate either of the Mycophenolate formulations. Or in scenarios where a young female transplant

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patient wants to become pregnant because it has a better track record with respect to that, and safety.

It has some side effects, sometimes liver test abnormalities, but we can monitor for that and nausea. And sometimes it can affect other lab tests such as your white blood cell count. There are some drug interactions. But again, that's not for you to worry about. That's for us to manage. So, your job is really just telling your transplant team all the drugs are taking. And if there's an interaction, the transplant team will address it.

Corticosteroids or just steroids for short, are also helper drugs again, just like he's a diaphragm they've been around since the 1960s. And they still remain a very important part of immunosuppressive regimens and used for many other conditions as well, including asthma, autoimmune conditions, and so forth. Around the time of your transplant, and sometimes to treat rejection, we give high doses of steroids by injection in the operating room and easily the first few days after transplant.

And then people if you're going to stay on steroids will often switch to oral steroids either Prednisone or Prednisone liquid. For people who take prednisone long term. Most often your dose is tapered, meaning it's gradually reduced over time. And so, your transplant team would often give you a chart that shows you how to lower that dose gradually. And then usually the dose that you maintained in the long term is a low dose. One thing to keep in mind is that if you're on prednisone or a steroid for a long time, you should never use abruptly stop it because your body gets used to having it around. And so, it stops making a hormone called cortisol, which is produced by your adrenal glands that sit on top of your kidney. Cortisol is a hormone that's used in stressful situations.

And so, if your body is used to having prednisone around, which kind of replaces it, it's not making that hormone. So, if you abruptly stop it, the body can respond, and your blood pressure will drop, and other problems can occur. Side effects of steroids are often annoying to many patients, I've only met one patient in over 20 years that liked prednisone, everybody else pretty

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much wants to be off of it or lower the dose. And I can understand that. But I do want to mention is that if you need it for rejection or for the type of kidney disease you have, it's useful medication. And as your dose gets lower, a lot of the side effects should improve or get better. So, keep that in mind.

After transplant, everyone pretty much has high blood sugars in the hospital because we get really big doses of injection steroids. And if you have diabetes, can be hard to control your blood sugars initially. But as the doses get lower, and everything gets stable, it should be a little bit easier to control blood sugars. The high doses can also cause some mood swings, so they can make people very emotional. Don't let that bother you. But if you notice that it's most likely your medications and it should get better, and of course inform the transplant team.

Over time, steroids tend to make people eat more so you can gain weight gradually. We often tell people to weigh themselves every day after transplant to keep track of your weight, you gain three or five pounds in one day that's not from your prednisone or eating too much. That's usually due to fluid. And that's something that team wants to know right away so they can address it and see what's causing it.

Stomach irritation or ulcers can occur when you're on steroids. And so, a lot of times if you're on prednisone, the first month or so, you may be on an anti-ulcer drug to protect your stomach from stomach acid during that time period. Or if you have a history of heartburn, you may stay on it too for the long term.

Osteoporosis or weak bones is related to how much prednisone you take and how long you take it. Kidney Disease also can cause osteoporosis. So, that's important to keep in mind. Because you need to have regular bone density tests in order to make sure if your bones are getting weak that you can be referred to a specialist to manage them long term. There's a lot of medication off options to do that.

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And lastly, sometimes people can get cataracts again, you want to be followed by an eye doctor and the cosmetic changes they can sometimes make your cheeks puffy and that's usually when you're on the higher doses. Once you're down to a low dose that that shouldn't be as big of a problem for Azathioprine and Prednisone. Their storage is just room temperature and basically for both medications taking with food is very important to help reduce nausea and stomach irritation.

And last but not least, the last two oral medications are Sirolimus and Everolimus. These are adjunct immunosuppressive drugs or helper drugs. And they're often used in combination with a low dose of two Tacrolimus or Cyclosporine. The first one that became available was Sirolimus it was FDA approved in 1999 first as an oral solution that apparently didn't taste good, because I heard a lot of complaints from patients.

But then they came out with tablets, which obviously don't have a taste. It's once a day and infused with cyclosporine, there is a drug interaction, so we have to separate it but the pharmacy or the transplant team will tell you that Everolimus was more recently approved, and it's a derivative of cyclosporine, but it's a little bit shorter acting, so it's given twice a day, it's actually approved for use in kidney and liver transplantation.

And interestingly, in much higher doses under a different brand name, it's actually used to treat various cancers such as renal cell carcinoma, which is a type of kidney cancer, or breast cancer and other cancers as well. Just like to Tacrolimus and cyclosporine, we have to monitor these two medications with blood levels very closely. And that's what we use to guide the dose. And that ensures safe and effective use. And again, these blood levels are drawn in the morning before you take your dose. And that timing is very important. And they also do have many drug interactions.

As far as side effects, these have some unique side effects, they can increase your cholesterol and compared to cyclosporine, they're much more problematic. And they can increase triglycerides quite dramatically in your blood. So, most patients end up needing medications to control this after they

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start these, one of these two immunosuppressive drugs. They also as I mentioned before, can delay wound healing. So, a lot of times people need a really big surgery after transplant, such as a heart surgery or something else a hernia repair, we may stop these drugs or switch them to a different drug to allow that wound to heal.

And so, we'll do it several weeks before the surgery and then wait till this wound has healed before restarting them. They are more kidney friendly than Tacrolimus and cyclosporine. But they can sometimes cause protein in the urine. And if you get too much protein that can hurt the kidneys. So, that's something that we monitor.

As far as taking these medications, consistency, just like Tacrolimus and cyclosporine is key always taken the same way with or without food and trying to be on time as closely as you can. The last immunosuppressive drug is the only one that's not oral, it's an IV or an infusion into your vein that you would get in an infusion center after transplant, Belatacept was approved in 2011 for use in kidney transplant recipients and it's considered a primary immunosuppressive drug.

So, it would kind of replace either to Tacrolimus or cyclosporine. And a regimen that also includes Mycophenolate and prednisone. It's a weight-based dose and you'd have scheduled infusions initially they're more frequent when it started. And then eventually, once you're on what's called a maintenance dose, you would only have to get it every four weeks. As far as precautions with this drug, there's one big risk of and that's in people who've never been exposed to a virus called Epstein-Barr virus.

And in that patient population, we just do not use this drug. There's a lot of gray areas in transplant, but this is not one of them. And so that's something that every Transplant Center will adhere to. And it's not approved or used in liver transplant. So sometimes when we have a combined liver kidney transplant recipient, the kidney team may want to use this drug, but the liver team often will say no. So that's kind of reserved for kidney only patients.

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The infusion is generally well tolerated. Some of the side effects are listed here that are listed in the labeling. But really the biggest risk that we worry about is that it's called post-transplant lymphoproliferative disease, very long name, it's a type of lymphoma, that's more likely if patients have not been exposed to that virus, I mentioned called EBV. And the group of patients we don't use this drug. So that minimizes the risk, obviously tremendously, by just avoiding it.

So again, with respect to side effects. One thing I want to mention everybody's different. Your transplant team is listening to you so keep them informed to hear problems. But there's a lot of things we consider when someone has a side effect. You know, first of all the severity of it. Other possible etiologies of the side effects. So, you might have diarrhea, it might be due to your Mycophnolate but there's a lot of other things that can also cause diarrhea, so we have to do detective work. And you play an important part of that to try and figure out what might be causing it.

Your rejection risk plays a role you start one drugs started up stop one drugs started another there's time period, we might be a little bit higher risk of rejection because the new drug isn't therapeutic yet. And then also if we change something, we want to see if that improved your side effect. And then again, I mentioned before, if you stop one drug and start a new drug, you might stop one side effect and then get a new one. So, there's a lot of factors that we consider when we're making changes with immunosuppression.

So, very quick summary. With immunosuppressive drugs, we use various combinations. Duration is lifetime as long as your kidney transplant is function, we have to keep your immune system suppressed. We do know that side effects can occur. There's no perfect drug, but a lot of them can be managed and there's also a lot of options that we can choose. I consider myself a fixer, a lot of the things that I do with the transplant team is helping manage a lot of the drug interactions and the side effects in addition to the doses of medications. And you never want to stop taking any of these drugs unless you've discussed it with your transplant team, because that could be dangerous for you and your kidney. So always have a discussion. So briefly

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want to talk for the last few minutes about some drugs that we use to prevent infection, and then drug interactions. So, in addition,

Dean Lotito: Rebecca, we're getting close to the end of time, we're going to have time for questions, just letting you know.

Rebecca Corey: Okay, I'll speed up. So, I don't have time today to talk about all the other drugs that you take. But you often will take drugs for osteoporosis, diabetes, if applicable, blood pressure medications, and so on. The key thing to remember is at the bottom of the screen, not just your transplant team, but you want to be followed by a primary care physician, dentist and other specialist providers after transplant, so they can help focus on these conditions for your best outcomes. preventing infection is also important.

There are some things that you can do to prevent infection. A lot of the things on this slide are common sense things like hand washing, or gel sanitizer. If you don't have a sink with soap and water available. You don't want to swim in small lakes or streams, because that can be a source of infection. And then of course, there are food safety precautions drinking water, I do want to emphasize don't get rid of your pets, pets give us great joy.

But there are certain precautions that you can take to help minimize any risks that you might get. So, if you have a cat, don't clean the litter box, someone else will have to do that for you, for example. And then you want to avoid live vaccines always after transplant because you're immunosuppressed. And there might be precautions if you have a grandchild or a child that's getting a live vaccine that we can give you in that scenario. There are also medications that you take to prevent reject infection after transplant. I don't have time today to discuss all of them. But these medications are often taken for time periods where you're at the highest risk for that particular infection.

So, the approach can vary depending on the type of organ you've received, and other factors where you live in the country. And then the transplant center protocols and preferences. We often involve infectious disease doctors to help us because they're experts in this field. These are some of the infections

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where you might take medications don't get overwhelmed by this. But this is something that we would determine at the time of transplant, and you would be educated only on what's relevant for you after transplant, and you would get that education before leaving the hospital.

And last but not least, I just want to emphasize, without getting into too much detail that transplant medications have a lot of drug interactions. Some of them are minor, we don't have to require any intervention. But some can be quite dangerous if not identified and managed appropriately. They can increase blood levels of transplant medications causing more side effects or toxicity. And in contrast, they can also reduce blood levels which may lead to transplant rejection, there are so many that I wouldn't have time to talk about them.

So, your only job would be to inform your transplant team before taking any new medications. Prescription over the counter or dietary herbal supplements. This slide just has some of them, I do want to just emphasize protease inhibitors, you don't need to know what those are, but one of them ritonavir is included in a medication that's used to treat COVID infection. So, one of our fears of among transplant centers is that patients would take this because it's one of the medications that would be very problematic with your transplant drugs, and it would make them toxic very quickly.

And so, it's always important to check with your transplant team before taking any new medications. Herbal supplements are not regulated as strictly as prescription or over the counter drugs so well, some of them can be beneficial. We do allow transplant patients to take them some of them do nothing. You just wasted your money, but at least it didn't harm you. And our concern though is some can cause harm. And I've seen firsthand or herbal supplements that can cause liver failure to the point where someone needed a transplant. That's the extreme scenario. But it's very important to remember that although these are considered natural products, they sometimes have effects like drugs, so they may interact with your transplant medications.

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They could potentially cause liver heart or kidney toxicity. Some of them can interfere with lab tests, and some may even have contaminants. So, if you want to take any herbals or dietary supplements, please check with your transplant team first so they can be reviewed for safety. Final tips, miss dose, the pharmacy will advise you on that. So, to allow for questions I'll kind of skip over that. But those are just general rules, and they apply to transplant medications as well.

One thing at the top always has an adequate supply on hand. It's you don't want to run out of any of these medications. So, if you're traveling take extra with you and always have at least a 10-day supply on hand so you don't run into problems. As far as storing. I mentioned a lot of this already. But if you have to discard older expired medications, there's a couple of different options. So, you can drop them off at a drug takeback site which only happens a few times a year.

Some medications actually the FDA recommends flushing them down the toilet and there's on their website. There's a list of those medications because even one dose could be harmful if taken by accident, and they're subject to misuse and abuse. Some medication not on the flush list, there's some general things you can do, you can buy specialized drug deactivation or disposal systems, our pharmacy gives those out to patients at no charge, where you can order them off the internet, and they're relatively inexpensive.

And another option is just to mix them in a coffee can with coffee grounds or dirt, something that's unappealing tightly close the lid and discard them in your trash. And of course, if you have an empty prescription bottle, remove your identifying information. That's just a better-looking version of it. So, I'm finished. I thank you for your attention. And I want to thank the polycystic kidney disease foundation for giving me this opportunity. They do a lot of great funding of research and supporting research, and they're advocates to advanced therapies and cures using the patient voice. So, thank you. And I'll take any questions you might have.

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Dean Lotito: All right, we do have quite a few questions, although we'll do our best to get to them all here says it's still important to take the Tacrolimus 12 hours apart if you take it twice a day, because I know my when I had some people said I take it morning and night somebody will say take it two hours apart when my doctor's orders. So, what's the real guidelines there?

Rebecca Corey: Yes, so great question. The most important thing is consistency, we want it 12 hours apart, but even in the hospital, nurses may have several patients, you have a little bit of wiggle room, you know, if it's due at eight am and eight pm. And it's 8:30. You know, that's okay, what you don't want to do is start having really erratic times, you know, one morning you sleep in till 11 am. And then you went out to movie you forgotten. Now it's 1 am, or you take it too early.

So, you want to try and be as consistent as you can 12 hours apart most of the time. I also with the lab timing, you know, we want the labs drawn before the dose. But let's say you get stuck in traffic, and you get to the laboratory late and they draw your blood, and you were supposed to take your Prograf for your two Tacrolimus sorry, I use the brand name here to columnist at eight am. But you don't get to the lab till nine am and get the blood drawn first and then take the morning dose and then get back on track.

So, consistency is key. But we are humans. So, there's a little bit of wiggle room but you what you don't want to be is all different times because then it's not going to be consistent blood levels. I hope that makes sense. And then with food, always with food or without food consistency, again, is key, they're a little more gets absorbed if it's on an empty stomach, but some people prefer to take it with food, and I find it's a lot easier to eat than not to eat. And so that helps prevent any nausea that some of your transplant medications can cause.

Dean Lotito: All right. You mentioned to can prednisone, prednisolone. So, someone asked her prednisolone causes bone loss like prednisone?

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Rebecca Corey: Good question. They're actually kind of one in the same. If you take prednisone, your liver converts it to prednisolone. So, they're, they're both kind of pretty identical with respect to side effects, just different forms of kind of the same drug. And prednisolone is used in a liquid. So, some people might take that if they can't swallow pills. You also can crush prednisone tablets. So, that's an option as well, you know, put them in applesauce or something. But they're both equally the same with osteoporosis, one would not be better or worse than the other.

Dean Lotito: Do immunosuppressant drugs suppress red blood cell production?

Rebecca Corey: Some of them do. mycophenolate, can sometimes cause anemia. There's a lot of things that can cause anemia or low red blood cells, though, if you have iron deficiency that can cause it. There are some conditions that can cause it. So, the important thing, kidney disease also contributes to anemia as well. So, if you have anemia, sometimes after the transplant, the red blood cell counts, the hemoglobin might be low for a while, but it usually eventually comes back to normal. And if it doesn't, the transplant team can do some investigations to see why it's well, such as checking to see if your iron is low and so on. Some of the medications can contribute for sure. But whether the team changes them is a big question because anytime you change drugs, you have to find another alternative and a lot of them can cause anemia, Sirolimus or Everolimus as well.

Dean Lotito: All right, someone asked if the long acting to Tacrolimus preparation has less associated with a side effect of tremors or numbness than the standard dose?

Rebecca Corey: Oh, good question. We do actually sometimes, because tremors - you tend to see them most often, you know, two hours after the dose of the immediate release of the twice daily capsules, because that's when the level is highest. The long acting to Tacrolimus formulations have more of a steady gradual blood levels throughout the day. And so sometimes for people with tremors we will try those formulations if their insurance will pay for it. Sometimes we get success sometimes it doesn't help, but it's certainly worth a try. And that's definitely one of the strategies that we use if people have tremors and

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we've lowered the Tacrolimus dose as much as we can. We don't want to go any lower. We might switch to the long-acting formulation to see if that improves, it and sometimes it does.

Dean Lotito: All right. How important is it separating [Unclear] [1:01:58] from magnesium by two hours? What of the issues if you don't actually, I was told it was separating it from calcium?

Rebecca Corey: Yeah, the package insert it specifically mentions may like Maalox like magnesium or aluminum containing acids. Because in there's different theories, whether it binds to them or just lowering the stomach acid contributes to the interaction. So, the general recommendation is try to keep them two hours apart. Now with calcium, that's tricky, because sometimes the transplant team will tell you take your calcium with meals specifically, or they'll take you tell you to take it in between meals for specific reason, and you want to follow those instructions to get the best benefit from the calcium. And calcium is very similar to magnesium. But if you're taking it in the morning, sometimes it's not possible to separate medications.

So, if at ideally possible, separate from aluminum and magnesium, specifically by two hours, but again, let's say you have taken your magnesium supplement it at seven pm your Mycophnolate, let's do at eight pm, one hour is still reasonable two hours or more is ideal. Again, sometimes you have to have a little bit of wiggle room with these medications. And if there's a concern, they can always check a level to see if it's therapeutic. For the medications. If you find that you have to do that often or you're on a calcium supplement, you have a concern, they can check a level for Mycophnolate to make sure that it's in the range we want it.

Dean Lotito: What is the lowest dose of prednisone available?

Rebecca Corey: Good question. The lowest strength tablet is one milligram. Most patients who are on prednisone long term, or the typical dose is five milligrams daily. Some patients I've seen on two and a half milligrams daily, some were in the middle. And sometimes if we stop another drug, everything's about

balancing. So, if we have to stop Mycophnolate for a patient because maybe they have a virus infection or something else.

We might, the team - everything's about balancing, they might add in a little dose of prednisone for that person, it might be five milligrams or 10 milligrams. But the short answer is the lowest strength tablet is one milligram and the dose is whatever the transplant center feels is the lowest dose that you can be on to balance side effects, but not have rejection of the kidney or recurrence of your kidney disease. If it's something autoimmune related, which fortunately, polycystic kidney disease is not, but there are other diseases that can recur.

Dean Lotito: Alright, we've got four minutes left a few more questions. Can you talk about the JC virus with Belatacept?

Rebecca Corey: Yes. So, with Belatacept, we have noticed that that Epstein-Barr virus, is a virus that it can cause mono in patients, and it can also cause post-transplant lymphoproliferative disease and Belatacept definitely increases the risk of that and people who have not been exposed to it prior to transplant. And so, we avoid that it also tends to - we've seen a lot more other virus infections, including Cytomegalovirus, JC virus and others.

So, it tends to be more problematic with respect to the viruses than some of the other transplant medications. But that's again, something that is about risks and benefits and balancing. So, the transplant team would have to decide if the benefits of that drug outweigh any risks of viral infections in you. And then of course, close monitoring.

We also noticed that in patients who are transplant recipients who received the COVID vaccine, the patients, this was data from Johns Hopkins, we had a surgeon that came here and presented it and it was very interesting. They didn't respond to the vaccine as well if they were on Belatacept compared to some other immunosuppressive regimens and Mycophnolate it also because the different immunosuppressive drugs have different effects on different

immune cells. And so that's how they have these subtle differences in risk of viral infections in response to vaccines and so forth.

Dean Lotito: How common is EB exposure?

Rebecca Corey: By the time we're adults, a lot of these they're in a big family called herpes viruses. And by the time we're adults, most of us have been exposed to a lot of these viruses throughout our life or childhoods. For example, Cytomegalovirus very common virus by the time we're adults, two thirds of us have been exposed. And the way we know is we check lab tests, and you have antibodies to it. Same with Epstein-Barr Virus. By the time we're adults, most people are exposed as children, teenagers College, we have antibodies against it.

And so that's what indicates our exposure to the virus is just like Varicella Zoster virus, a lot of people get chickenpox as a child. And so, you have exposure, and you have those antibodies, indicating that you had exposure earlier. These viruses do have all in common that they kind of remain latent or dormant in your body. And when your immune system is suppressed, such as after transplant, some of them can reactivate. And so that's why sometimes we will give specific medications to prevent them, or we might do lab tests to monitor for these viruses. So, if for some reason they reappear, we can address it in the most appropriate way for that particular virus.

Dean Lotito: Right, we're just about a time. Someone did ask me this any current research on interaction over the counter stuff with transplant drugs, I'm going to cancel that and in half a minute.

Rebecca Corey: With over-the-counter drugs, since drugs over the counter and prescription have to be approved by the FDA, they go through a lot of rigorous testing, and they have to look into drug interaction testing, it's kind of a requirement, so we have more information about them. The downside of supplements is that they don't have to go through that rigorous testing.

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So, there's a lot of unknowns with respect to drug interactions. I have a few good references that I use, and some of them have information about drug interactions. But sometimes, people learned the hard way, there was herbal supplement used for depression called St John's-wort. And it drastically lowers immunosuppressive drugs.

And this is probably 20 years ago, but people had really low levels, and they didn't realize that it interacted now we know. But that was something people learned kind of the hard way. And we've discovered that, you know, oral CBD oil that people like to use can increase some of the immunosuppressive drugs Turmeric if you have a little bit in your food to season it, that's usually fine. But the supplements with much higher, more concentrated amounts can increase some of the immunosuppressive drug levels.

So, I have some references. But with the herbal supplements, there's a lot of unknowns with drug interactions, because they don't have to do that same level of testing that that prescription over the counter medications do.

Rebecca Corey: There's a question about for Segal, it does help post-transplant and what for Segal is I assume you do?

Dean Lotito: Oh, we do have some patients on that medication. And again, it's benefit risk if your endocrinologist thinks that for Segal is the best medication for you to control your diabetes, I know our heart team uses it. So, again, it's one of those situations where you see your primary care doctor, your endocrinologist, let them kind of decide what the best drug is for you and then check with your transplant team to see if there's any precautions or drug interactions that we need to address or keep an eye on for you.

Dean Lotito: All right. So, one more question came in. Do some patients take progress with space dosing versus daily?

Rebecca Corey: A I don't know if I understood exactly, but space dosing most people take Tacrolimus twice daily. But if they're on their long-acting formulations, there's two different versions then they only take it once a day and usually in

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the morning because we want to get those blood levels. If that didn't answer it, let me know.

Dean Lotito: Alright, well, we're out of time. I want to thank you very much the people commenting they really appreciate the presentation, as did I, we're hoping the slides become available. I believe the foundation will allow that at some later time, because there's so much useful information. But thank you, Rebecca, and thank you everyone for joining. Appreciate it.

Rebecca Corey: All right, thanks.

Dean Lotito: Bye.

Rebecca Corey: Have a great day everyone.

[The End] [1:09:59]