SPEAKER 1: It's my pleasure to talk to you folks about a different kind of topic now. We will delve into the world of microorganisms, where patients, technically, are not doing anything wrong, but it's the outside agents. So how do we address the issues that come out of these common viruses.

I have no conflicts of interest to disclose. So these are my objectives. Brief overview of CMV, BK and EBV in kidney transplantation. We'll briefly touch upon the current management strategies. And give you an update about the recent developments in the field.

So why do we care about these viruses, and what is common? There are many viral infections that occur in kidney transplant patients, or many other solid organ transplant patients. But these three viruses share some common features. After a primary infection in the general population, they establish latency. CMV and EBV and lymphocytes and BK virus in the renal tubule cells.

And because of this latency, they are able to be transmitted from donors to recipient, one. And second, if you're a recipient, and if you've never had an infection with any of these viruses in the presence of immunosuppression, you are at risk for infections or other complications. Second, we have a good handle of predicting when these infections will happen, and are able to monitor them in a very systematic way. And, when necessary, implement a preventive and treatment strategy. So these viruses, in a way, share something common.

And so the risk factors, primarily, are either you have no immunity, or you have some immunity because a previous infection, but that immunity is weakened in the presence of immunosuppression. And so the intensity of immunosuppression affects what your risk of getting an infection, or getting a serious infection from these viruses. And so CMV, cytomegalovirus, and Epstein-Barr, the highest risk factor is a recipient who has never been exposed to the infection, but then gets an organ from a donor who has evidence of previous infection. So we call them donor positive to recipient negative.

And so for CMV, it makes up about 20% of all our transplants. EBV, the positive [INAUDIBLE] prevalence in the population is very high. 90% of adults have evidence of previous EBV infection. So the donor recipient mismatch is relatively uncommon. So it makes up for about 7% to 9% of all transplants that happen.

Most infections from these viruses happen in the first one to two years. So that's helpful for us to know because we know went to monitor them and when to implement strategies. So for CMV, the high risk population, the incidence of CMV infection is about 10% to 30%. And PTLD, which is the post transplant lymphoproliferate disorders, one of the most important factors is EBV. This incidence-- the first five years is about 1% to 3%. 80% of these occur in year one. And majority of them are related to the EBV high risk status.

BK. Like I said, the BK virus establishes latency in the renal tubule cells. So in 30% to 40% of patients, we can detect activity of the virus when we screen them on a regular basis. About 10% of patients will show evidence of viremia, which indicates that the replication of the virus is higher than in those patients who have just viuria. And why do we care about this? It's because in about 2% to 5% of patients, because of this multiplication dividers in the allograft, and the secondary immune response to this virus, patients develop what we call is BK nephropathy, which if severe can lead to graph loss.

So for all the three viruses, the clinical features and progression sort of varies, but they all share a similar pattern. For example, for CMV, particularly for primary infections where it's a-- recipient has never had exposure to CMV, but gets a kidney from a donor that had CMV in the past. That is usually when they get an infection. A period of asymptomatic viremia, which then, if progresses, you get the viral prodrome and the viral copies go into the thousands.

And when it's undetected, it can progress to what we call as tissue invasive disease. And usually, the CMV copies in these situations are in the range of much higher than 50,000 per ml, or 100,000, or even higher. We've had patients who, if it's undetectable, come in with viral copies of a million, two million, above the range of detection.

And the tissue invasive disease, most commonly, it's GI issues. GI tissue invasion, but people can get hepatitis, CMV retinitis, we've had CMV nephritis. But the tissue invasive disease is relatively uncommon if you can monitor for that.

EBV, in high-risk patients, also sort of follows this trend of having a period of asymptomatic viremia. They can get viral prodrome, infectious mononucleosis symptoms. And in some patients, selective patients, it can-- because of the constant replication or multiplication of the B cells, they can transform into post transplant lymphomas.

And BK, very similar. Like I said, 40%, 50% get virurias. About 10% get viremia, and as one thing to note, though all of these are asymptomatic for almost 999 100%. And BKV nephropathy, about 2.5%. So why do we care? Because these things affect these viruses. Multiple things that we want patients to benefit in terms of transplantation. So quality of life.

So CMV, if they develop severe CMV tissue invasive disease, that affects their quality of life significantly. And similarly, if they get lymphoma. BK dominantly because it's an asymptomatic, quality of life doesn't get affected unless they have advanced kidney dysfunction. So BK, because of that reason, when it's bad it does affect graft survival. EBV in general, if it is treated appropriately, and if you account for patient deaths, EBV per se doesn't, necessarily, by itself cause graft failures. CMV does also increase your risk of graft dysfunction.

The key thing though for most of these viruses is, in particular for CMV and EBV, if they are severe, they will cause patient mortality. I'll show you some data on that. So what are the current management strategies? So what do we do for these people? So I'm just going to summarize it in one slide. What are the potential options, and what works and what doesn't for the individual viruses?

So for CMV, we have a good-- we have multiple antiviral agents that we could use to prophylax patients. I'm not going to go into details about how long we do it, but there is that option. And screening for viremia, the viral copies, is available. And screening is useful because it allows us-- particularly if for some what we call as intermediate risk CMV recipients-- if we don't want to prophylax them, some centers do it. They don't want to prophylax everybody, and they will monitor the CMV on a weekly basis for the first few months. And then, institute antiviral therapy if they're turned positive for the virus.

And we have multiple antiviral drugs available. Immunosuppression modification does help-- either reduction or, in some situation, conversions to a different agent. I'll talk about that. EBV, although many antivirals have been tried because they all belong to similar viral families, none of the antivirals like acyclovir or valganciclovir have been shown to either reduce your risk of lymphoma or some complications from EBV. But they're still used in this high risk population.

We do have a test for viremia detection, but we don't know if it is useful to screen these patients for EBV. And I'll come back to that a little bi later. Immunosuppression modification certainly helps because, like I said, one of the main risk factors for the virus and the B cells to proliferate is the immunosuppression effect. And before chemotherapy became potent with the advent of actoxumab and newer agents, the only treatment that was available was immunosuppression reduction or elimination, which in many patients led to lymphoma remissions. And chemotherapy suddenly works, but not 100% percent effective.

So BK, there is no antiviral BK drug, but we do have a screening strategy. We have a test available both in the urine and blood. And it is useful, and I'll come back to that. And the key management strategy for BK is just reducing immunosuppression primarily because we do not have a drug that works against EBV-- or BKV, sorry.

But still, several challenges exist. For example, CMV, this is key, the drug resistance, particularly to the mainstay, which for us is valganciclovir or ganciclovir. So drug resistance is a problem. And when we have to choose alternate agents, or even for valganciclovir, toxicity, particularly bone marrow toxicity. And for secondary agents, the nephrotoxicity. That's a key concern.

Even though patients-- we have been able to use the prophylaxis with ganciclovir and reduce the risk of primary infection right after transplantation. When we stop it at about six months, they do get infections after that. It's about 10% to 30%, depending on the study you look at. And we don't have a way of saying-- apart from these urologies that we test-- not everybody gets CMV, but we don't have the next step, which is trying to identify how good is their immune system, like a CMV specific immunity test. But I think that field is moving forward.

And like I said, for EBV, we still don't know if monitoring for EBV helps. And second thing we don't know is once people recover from PTLD, what do we do with the long term immunosuppression? The data on that is weak. And we clearly don't have any preventive options like vaccination for EBV.

BK, like I said, the key problem is we don't have a BK specific drug. And for all the three things, one thing to also know is that there is this issue of interlab variability. Because sometimes, we can't just compare test-- so results of the tests that were done within the system, or done at different lab. And so sometimes, when patients are really going through a problematic infection, we may have to have the patients do the test in the same lab so that we can compare the trend and see if they're making progress.

So are we making headway, given all the limitations I talked about? So I've broken down this recent updates into these three viruses. Most of the-- what can I say-- clinically applicable improvements have happened in CMV, so I'll spend a little more time on that. So just sort of drive home the point about the CMV infection matter, does it affect survival. So this is a study from the Australian and New Zealand-- their transplant registry.

So basically, the graph is showing you-- on the top bar is the patients that had either never had viremia, that means no viral copies or very low level. And the bottom two are people that, at any point in their post transplant period, had viremia detected. And so clearly, it affects survival. And this goes all the way up to eight to 10 years. And so the probability of patients surviving-- so only about 60% are alive versus 75%.

Now, a few limitations when we look at these things. It's hard to know if the viremia happened because some patients are at risk of rejection. They got treated. They got more immunosuppression. But we have to take that into context. But this one, I thought, is more interesting. It's a much more recent data from 2015. This was from the UK database.

They basically asked the question, we know their CMV serologies are donor positive, recipient negative, and all these four different combinations, which are highlighted at the top. And we know the highest risk is for people that are donor positive and recipient negative. And basically, they just group these four things, and looked at the patient's survival. Irrespective of what happened to them, infections, rejections. And what, then, clearly stands out though is that if you were a donor positive and recipient negative, you followed a different trajectory. So the D plus R minus, which is sort of the dark, it's not very visible.

So the best group in terms of survival are donors negative to recipient negative. That means neither the donor had evidence of previous infection nor the recipient had any evidence of previous infection. Because the risk of CMV is not zero, because you can acquire primary CMV just from the community. But in general, those are the patients that do well.

So I would refer you people to this consensus statement that came out very recently. This is a third consensus guideline. It's 100 plus page document if you want to know anything about CMV in all organ transplants. It's very useful, and goes into full detail.

So a few of the updates that I want to briefly talk about. If you've noticed in the CM lab results these days, they don't necessarily-- there's a copies per ml, but they now make sure that the end result is often reported as international units per ml. So the WHO has taken this lead with two standardized testing results for CMV. And so every lab has to go through the standardization process, and report and have the positive negative controls, and ultimately results should be provided in this international units per ml. So this reduces the variability.

But there's still variability that comes out because of the way they process the specimen, the PCR, but it's better. We should also know that, generally, the test is looking for DNA copies and not necessarily whole viruses, so they often report it as DNAemia. The whole blood levels of the virals or the DNA is much higher than the plasma. So if a patient is on treatment or has viremia, it's good to make sure it's done in one way, either blood or plasma.

We should know that the lower limit of quantification, that's the lowest level we can detect, is about 200 international units. And unless patient has any symptoms, even though they say it's detected, but it says less than 200, generally, it's not been shown to be clinically relevant. So what does this mean for clinical practice? That results are not fully compatible despite this improvement in standardization. And it is preferable to measure in either plasma or blood consistently.

And I think before, we would always wait for two negative tests before we stop therapy once the patient has improve. But at least the new recommendation suggests that if everything is going according to plan, you don't necessarily have to wait for two negative viral results. But you should certainly follow it up with a repeat test in a week to make sure it remains negative.

So I talked about this. Do we have a test that tells us if the patients-- because CMV immunity is not just antibodies. Because that's what we check when we check the serologies, but CMV-- so the ability to get rid of the virus depends on your T cells. But we don't have a test that's commonly available to see if somebody's lymphocytes, when it sees a CMV virus, can reactivate and can eliminate the infection.

So the rationale of these tests is to see if, somehow, we can demonstrate CMV specific T cell immunity, and in that way, we can predict who is going to get the viral infection, who will have a relapse when you stop the drug. The concept is very similar to the quantifier on TB test that I'm sure most, or many of you would have already taken. It exposes the lymphocytes to a certain CMV antigen, and then basically, measures the-- the most measures cytokines that the cell would produce to kill the virus. Most common is interferon gamma, but you have other cytokines you can measure.

So there are a number of commercially available products that have been tested. The most one of them is the QuantiFERON-CMV, and the other one is the ELISPOT. And the other one is called the ICS. Basically, it just stains for these cytokines. All the original studies initially focused on trying to predict. And if we use the test in patients who have some immunity, or patients who are stopping prophylaxis, we'll test them. See if they're developing immunity. Can we predict who is going to get infections? Is going to get a bad disease.

The most recent studies, though, are trying to focus on, OK, if we know the result of the test, and then we tailor the prophylaxis whether you want to put the patient or not, or how long you want to keep the prophylaxis on, does it change management? So the most recent studies that are coming out are now in the second phase trying to see, should I know what the test showed, but can we modify? Because these drugs, the antiviral prophylactic drugs, they are good, but they do come with cost. They do come where toxicities, and so you cannot give them indefinitely.

All these assays-- a couple at least, Quanti-FERON and ELISPOT are approved by the European agency for use in Europe. They are not currently approved by FDA here for use. Although there is a test that the transplant ID team does use. It is performed by this viral core company that we've had some of our patients where we've tested them for this. So I think it can be done in an off-label manner.

So this was one of those studies that I said is now in the second phase, trying to see-- OK, we'll do the test when the patients stop. So the first picture just tells you the value of the interferon on the y-axis. They tested when the patient is topping the prophylaxis. And as you can see, all these red dots are patients that show some-- the T cells are able to recognize the CMV. And the black dots are patients that have absolutely no-- they don't have any response. Just a negative Quanti-FERON.

What they do for these red dots is they say, well, I think you have enough immunity that we don't have to put you on any prophylaxis. And that in figure 2 is the blue dot. So as you can see, patients that remain free from CMV is pretty good. I think in this study, only one out of the 20 odd patients they had developed an infection.

Whereas, in the other group, were all black dots here. They were put on prophylaxis despite that almost half of them did get a relapse of new CMV infection. So it's a proof of concept that it may soon be something that we will use in some of our patients to see if we need to prolong the prophylaxis or do other things.

So resistant CMV. So briefly, just so that we all know what the orientation of these drugs, so this is the CMV virus. It has this the core, the nucleus of a DNA. So the DNA, technically, is synthesized as one long strand that has these multiple components, which you can see in the orange. And so all the orange DNA are the same, and they'll be spliced into different DNA pieces and new viral copies will be assembled.

So most of the drug that we use target this mechanism, which the virus uses to replicate or synthesize the DNA, and package it into new viral copies. So not to go into too much detail, so if this is these-- at the bottom, purple shows you where the DNA is synthesized. That's the DNA polymerase. Let's see. I'm going to try to use a pointer.

OK, so the most common drugs that we use are ganciclovir, which has to be first converted into this-- it has to be phosphorylated three times. And then, it access a competitive inhibitor for this nucleotide, which is what is necessary. The polymerase links together these multiple nucleotide pieces to make the DNA. So the ganciclovir just acts as a competitive inhibitor so that the new DNA isn't made.

The are two agents that we use in resistance, or one is the foscarnet and the cidofovir. So foscarnet, it doesn't need to be phosphorylated by this UL 97, but it does act on this DNA polymerase, which is coded by this UL 54 gene. But it's a different side than the ganciclovir, so the resistance is often not-- you don't get resistance, often simultaneously, to both ganciclovir and cidofovir and foscarnet. Cidofovir, again, doesn't need to be phosphorylated by the UL 97, but it does get phosphorylated. Ultimately, it works on the same side that ganciclovir or the valganciclovir works.

So there is a potential that if you see mutations in UL 54, it may be simultaneously resistant to both cidofovir and ganciclovir. So often, the first drug that ID folks go to, if there is ganciclovir resistance is foscarnet. So what's the incidence of CMV drug resistance? It's about 5% in our high risk patient population. And the question always comes up, when do you test for CMV resistance?

So I think it's good to know when not to test. If a patient just presents with very high viremias, or very severe CMV disease, that doesn't necessarily indicate that they're resistant. If there is a breakthrough infection, if they were already on treatment or on prophylaxis, and then they have a severe CMV or there's a breakthrough CMV, then you have to suspect resistance. If a patient is on full dose therapy for at least two weeks, and you don't see a log reduction, then you should start considering whether CMV resistance should be tested for.

Generally, the median time when the viral copies reached half their presentation level was about 20 plus days. So it takes time for CMV to improve. So like I said, the traditional approach, the first resistance it looks for is the UL 97. That's what phosphorates the ganciclovir. If there is a mutation, there are two options. One is if it's a weak mutation, we can use a high dose of the valganciclovir, which we do sometimes. If not, we go to the foscarnet, which I showed in the previous slide.

If there is resistance to foscarnet, then we have to go back to cidofovir unless there is resistance to cidofovir as well. But then, that's when we run into issues. Now, the important thing to note though is this foscarnet and cidofovir have a lot of nephrotoxicity, and so that limits how much we can give and how long we can give these drugs. Certainly, we reduce immunosuppression in patients with moderate to severe disease.

There's this new thing about patients who take mTOR inhibitors for immunosuppression, the sirolimus or the everolimus. We don't use it that commonly here. Just multiple studies have shown that these patients, for a variety of reasons, have less CMV. Rather that's because of the intensity of immunosuppression or a completely different sort of mechanism.

So I just want to update you on two drugs that are currently available-- being tested. One is the maribavir and then the letermovir. And then, we'll briefly touch upon the adoptive T cell therapies. So I showed you the vital DNA complex. So the letermovir acts on this [INAUDIBLE] complex, that breaks this DNA and packs them into new individual viral particles. And the maribavir is the inhibitor of this UL 97, which phosphorylates the ganciclovir. We don't know, technically, what the function of this genus in the virus per se, but the drug works on that.

But I think, and the newer drugs will likely have selective indications for use. They're going to replace valganciclovir or ganciclovir. So briefly, letermovir, like I said, currently it's only approved for CME prophylaxis in hematopoietic stem cell transplants. That's it's only indication. We have used it off-label in resistant CMV. The good thing, though, it's not nephrotoxic like cidofovir or foscarnet. It doesn't have myelosuppression like valganciclovir.

One of the chief concerns is, though, that it has a very low genetic barrier to resistance. And so that means that resistance can occur more commonly than with valganciclovir or the other drugs. It doesn't work against herpes simplex or other herpes viruses, so you have to use an acyclovir drug in addition to the [INAUDIBLE]. We are participating in this trial, looking at-- so currently there's a trial going on comparing it with valganciclovir for CMV high risk patients as a primary prophylactic agent. I think this idea is also probably be out in 2021.

So maribavir had a lot of initial disappointing studies. And then, they found out that it worked in some patients with resistant CMV, so now there's a ongoing trial that we are participating in that's looking at its use in resistant CMV. So if somebody has resistance to valganciclovir, we can enroll them. So they get about eight weeks of maribavir or placebo, and they get the usual care. Again, resistance is because of mutations at UL 97. And again, it also doesn't have any nephrotoxicity or bone marrow suppression, so mostly it's metallic taste.

So briefly, immunotherapy, I think, is going to be something that would become more and more common, or at least available for some of these bad complicated resistant CMVs, or even in the future PTLDs that are related to EBV. So in a nutshell, what is adopted T cell? It basically, just is-- the concept is infusing T cells that have the capacity to fight the virus. Because the recipients, we think, don't have the immune capacity to fight the CMV virus.

Now, where do you get the T cells from? It could be either derived from the recipient themselves, or you can have a third party donor, take the T cells, you stimulate them with this CMV. There's a process for that, you produces these T cells, and then you just infuse it back into the recipient with the hope that it's able to do what the patient's immune system does not or cannot do.

The reported cases in kidney transplant are rare. I found one case put in 2015 about a kidney transplant patient that got that. Our trust ID folks helped us out with one of our patients here who had everything that I talked about in resistant CMV. Basically, this was a 49-year-old male. He had a high CMV status. He developed CMV after stopping prophylaxis. And he went through the whole gamut. He got high dose ganciclovir. He was in the maribavir trial. He got the foscarnets, cidofovir. And basically, the CMV kept waxing, waning, and the copies were generally very high, 400,000, 500,000.

So Dr. [INAUDIBLE] from [INAUDIBLE] helped us out quite a bit with this. She worked with the company that makes this donor lymphocytes, got the FDA and IRB approval, and patient received three infusions of these adoptive T cells. And he improved quite remarkably with this. His viral copies of the DNA went down to about 400,000 to 1,000 over three months. And I think, recently, he's cleared the infection.

So this was one of those things where everybody got together, and we got a lot of help in trying to help a patient who was really running out of options. So that was a successful use of this newer technology. Quickly. So in summary though, CMV, there's been a lot of development in terms of newer drugs coming, particularly with therapies for resistant CMV and testing for CMV. BK, unfortunately, though I can just put disclaimer that there's no new drug to talk about. I briefly mentioned the drugs that have been failed. And go through some of these. So outcomes data that we have in the past few years.

One of the things that I think was recent is classifying BK nephropathy. Dr. [INAUDIBLE], who's our pathologist here, is critically involved in these BK studies. So we have a new classification. The reference is down there. This was in 2017. So as I said, BK virus multiplies in the renal tubules, and that elicits inflammation. The immune system tries to get rid of the BK. And so the classification, basically, takes into consideration how severe is the BK multiplication, which we can stain using a special BK stain, as you can see here, the dark brown ones.

And then, it looks at how much is the inflammation, and how much the scar tissue. So as these things increase in intensity, your BK nephropathy classification goes from class 1, class 2, class 3. So as you can see, this is class 2. Here, you can see the intact tubules, but there's not much inflammation. Here, there's a lot of lymphocytes. There's some tubular destruction, and you can see more cells staining for the BK compared to the stage 1.

And when you go to stage 3, you may not necessarily have a lot of BK staining, but it's primarily dependent on how much scar tissue you have. The chronicity or the interstitial fibrosis. So compared to the fairly intact tubules in the left lower corner, you can see that there are very few tubules missing. Now, why does this matter? I think because if you diagnose different category at the time you make the diagnosis, it predicts what you're creatine is going to be at about 24 months.

So the bottom one is the BKV stage 1, BKV stage 2, and the beginning stage 3. Clearly, over a period of two years, you're looking at a creatine change anywhere up to four milligram per deciliters. So the mild and moderate BK tends to do OK. This is not surprising in a BK nephropathy stage 3 pretty much has advanced fibrosis. But it's helpful to know what thier trajectory will be.

So what is the current management? We screen patients. The options are to screen either in urine or blood. We do both here in UPMC. And the main strategy is reducing immunosuppression. Because that's only thing that's been, as of now, shown to work in reducing the morbidity and graft loss that comes with BK. Occasionally, we switch patients from tacrolimus to cyclosporine. That's done on a patient to patient basis.

We monitor patients every two to four weeks once we have some viremia detected. And the key thing to know, though, is that you can't do this too fast, the reduction immunosuppression, because there's a risk of rejection, or de novo donor-specific antibody development, which is about [INAUDIBLE] to 5%, depending on how aggressively. So the key thing is to not lose the graft from severe rejection. So we have to be careful about that. We don't always biopsy patients for BK viremia. We only do it if there's, say, elevated creatinine or suspicion for some other pathology.

So how long does it take for the BK to improve, even after you institute immunosuppression reduction? Sort of like months. This is days from when the immunosuppression was reduced. So we just have to be patient. It takes weeks, and we've had patients that continue to have low level viremias or even moderate decrease of virurias for years. But at least we want to make sure that there is a large reduction in the first few weeks, so we have to follow them very carefully and give it enough time to, at least, not-- we should at least aim to achieve a log reductions of 2 to 3, 4 log reduction over the first two to three months.

But then, there are several challenges, and I talked about this. There is no approved BK specific drug, and there's no promising drug on the horizon, which is sort of disappointing. There've been many drugs that have been tried. We've used it in the past. Cidofovir, leflunomide, fluorophenyl, they've all failed. People were optimistic about this oral formulation of cidofovir, CMX 001, but because of a negative trial they had in hematopoetic stem cell where they were looking at it for CMV, they've shelved all their other studies for other viruses.

And we still don't know what is the optimal method to reduce immunosuppression. Do we stop the anti metabolite, which is the mycophenolate, do we reduce the calcineurin inhibitors, do we do both? Every center has their own management protocol, and we don't know which is better. And so there is this issue of lack of standardization. So I think in people with very high viremias and virurias, we prefer to do them in one lab if possible.

And we still don't know if a patient that have persistent low level viremias for years, or moderate virurias for years, what their long term outcome-- I'm talking about 5 or 10 years, we don't know. We don't have data on that. So I talked about this. What is the risk of developing de novo DSA? So this study, this was [INAUDIBLE], this single center study. They looked at patients. They, basically, grouped them into those that never had BK viremia, and then those that had ever had BK positive, that group. And then, persistent BK they defined it as about four months or BK viremia.

So you can see the percentage of people that developed DSA is about 15% if you never have BK. If you have any BK viremia, it's about 20%. It goes up to 25 if you have persistent BK. Either this is because of immunosuppression reduction, or there is some-- because of this immune inflammation in the kidney, does it expose the antigens to the immune system, and there is this cross-talk and the immune system starts making antibodies? So it's probably a combination of both.

I would, again, refer you to this consensus paper that came out very recently written by Dr. [INAUDIBLE] and Dr. Hirsch. Again, goes into detail. Updates until now, and the future outlook. Briefly, I want to talk to you about IVIG, the immunoglobulin for BK. Because this comes up once in a while. There have been small observational studies that have shown that, yeah, it works when we use IVIG for BK. And this is a paper [INAUDIBLE] from Dr. [INAUDIBLE].

Basically, they showed that commercially available IVIG does have BK neutralizing properties. It can neutralize it. The problem is it's costly. Well, of course, we don't have studies. But then, mechanistically, we know that kidney transplant recipients already have a lot of BKV antibodies. So whether they're specific to the donors BK or not, but that's one limitation. So will additional IVIG help? That's a question. And it doesn't affect the intracellular BK. And the half life is only about three weeks. So you may have to give repeated infusions.

But there's still some interest in looking at if IVIG can help as an add-on therapy. So again, Dr. [INAUDIBLE] is participating as its IPI for this. This is the phase when our CD is trying to look at two doses of IVIG when patients have viremia on top of immunosuppression reduction versus placebo. This is a phase one just to see what happens. So we just have to see what the results come back as.

So the last five minutes, I'll just briefly update you on a couple of things on EBV related PTLD. EBV, like I said, it establishes latency in the B cells. So it has receptors that would help it attach to the B cell. The DNA is integrated into B cell DNA. There is an initial phase where there is-- this is called a lytic phase. There's a lot of patients get this kissing disease or glandular syndrome. There's a lot of active proliferation of the virus.

But then after that, it goes into this latent mode where there is a very low level of B cell production. So there is no separate viral multiplication, is just that the B cells that have the viral DNA just keep replicating at a constant rate. Intermittently, in situations of stress or illness, you may be able to detect some EBV because there's that little bit of increase in multiplication. But then, it goes back to this constant low level B cell proliferation.

And PTLD related to EBV, like I said, is a curse in patients who have no immunity to EBV, and then they get a donor that has had exposure to EBV. And so along with the donor kidney or other organ comes these lymphocytes that have the EBV. And because of lack of immunity and immunosuppression, they proliferate aggressively. PTLD, like I said, the incidence is about 1% to 3% or five years. But these EBV mismatch related PTLD, 80% of them occur in the year one.

And this is a nice review, again, from 2018. Dr. Haberman was here giving grand rounds for us just a few months ago. So it nicely summarizes the whole process with EBV and PTLD. So like I said, the risk for PTLD has to do either with a EBV infection, plus or minus lack of immunity, or there are some PTLDs that are not related to EBV at all, and they just have to do with some sort of genetic aberration. Just like lymphomas that occur after transplant, the risk is just higher because the immune system is unable to get rid of these mutations.

Either way, if it's EBV related, you will see this elevation in the viral copies. If it's a primary infection, patients should start having some EBV copies in the blood that goes up into thousands, generally, before they get PTLD. So you have this potential to survey them, and look for EBV during this phase.

Certainly, we will look for clinical symptoms. Fevers, lymph nodes, weight loss, diarrhea, bloody stools. And then, you make a diagnosis, and then you classify them. There's a WHO classification. We, obviously, work with the hematology oncology folks. We have specific oncologies that help us out with our patients. They get a PET scan, they get stage, and they get treated.

Most commonly, everybody gets immunosuppression reduction. That is the RIS, reduction immunosuppression. And then you consider chemotherapy, which is either with a [INAUDIBLE] or [INAUDIBLE], which is the standard lymphoma therapy. And we leave that to the-- obviously, the oncologist. Follow-up. Even though they go into remission, we have a high index of suspicion. They follow up with oncologists. There is periodic PET scans. They may, at some point, lose their grafts. And they do come back for re-transplant. And it is possible to re-transplant them. And we've done a fair number of these, and it doesn't necessarily increase the risk of PTLD with the second transplant. We just have to worry about the intensity of immunosuppression.

So does PTLD-- so I mentioned this. It does sort of affect patient survival. And these are two different studies looking at PTLD and patient survival. So at about 14 years, only 30% of patients are alive with PTLD compared to 60%. It's almost like half if you have PTLD. And there are some risk factors. If you're old. Relatively, that means if you're about 50, 60. And if it's lymphoma that's in the bone marrow or CNS lymphoma, they have worse prognosis. And most PTLDs are B cell PTLDs, but they're a small proportion with a T cell, and they do significantly worse.

So like I said, you have the potential to screen for it. We have a test. And many centers do screen the high risk population with periodic, in the first few months, for EBV virus. And the thought being that if you detect a significant level of viral viremia, you could give them pre-emptive rituximab, and hope that that reduces the risk of progressing to full blown lymphoma.

It'll also allow you to, maybe, evaluate for signs and symptoms of PTLD, which are sometimes non-specific. But there are some issues though. Like I said, there are some PTLDs that don't have any EBV. So having EBV viremia is not always required, particularly for late PTLDs. And for early PTLDs, not everybody that has viremia progresses to PTLD because there are many of these patients that have thousands of copies of EBV, but they don't necessarily have other symptoms of PTLD. So we have to be careful. And reducing immunosuppression just because they have viremia could be tricky, and so that's a concern.

And then also, the thresholds at which people treat with rituximab is also unclear. Many centers use either a 50,000 per ml-- I think the non-kidney field is a little more aggressive because the risk of PTLD is much higher, like the lung transplant, the bowel transplant, a heart transplant. So they are aggressive in giving patients rituximab if their copies go to 50,000 or 100,000.

And again, just like in CMV, adoptive T cell therapy with EBV specific lymphocytes has been used, and the very first case was 1995 in hematopoietic stem cell transplant. There are several reports of using solid organ transplants as well. But it's limited to salvage therapy. And then I'll come to why. But basically, again, you get the T cells either from the recipients themselves or a third party derived cells. And basically, you go through the same process of making them enriched for EBV specific and then infuse them.

But I think part of the problem is, because patients continuously need immunosuppression, these cells may not be as effective in getting rid of the lymphoma. So there have been some interesting developments. People have developed the cytotoxic T lymphocytes that are resistant to calcineurins because they modify the targets for [INAUDIBLE] and cyclosporine, so that these cells, necessarily, are not affected by [INAUDIBLE] or cyclosporines. So you can, at least, increase the efficacy of these cells in targeting the lymphoma.

In the interest of time, I'm going to go through this. But the review that I mentioned in 2018 talks about additional chemotherapy agents that are available or upcoming. Many of our patients are on this because the primary-- the first language is rituximab or [INAUDIBLE] doesn't work for everybody. So lastly, why don't we have a vaccine? So a nice article. If people are interested, look at Nature. And I think Dr. Harry is going to invite Dr. [INAUDIBLE] for grand rounds next year. He's an Australian that works a lot on adoptive T cells, and he had several interesting points to make as well.

So basically, it's been a challenge to develop EBV for several reasons. Like I said, one of the reasons is because after the primary infection, it's very latent. It's very quiet, and just at a very low level of multiplication. So it doesn't have too many antigens that the immune system can target.

Second, to prove that the vaccine protects against EBV related cancers is difficult because cancers that occur because of EBV like nasopharyngeal tumors or lymphomas take decades to manifest. And so to study the efficacy is very difficult. But I think PTLD might offer us what the article talks about because we know the predictable patterns, and PTLD occurs very early of transplantation. So that may be a group of patients where I think that's what the group is interested in trying to study the vaccine. Patients, kids, particularly young adults, or children who don't have immunity to EBV, to see if the vaccine will reduce their risk of getting EBV related PTLDs. So it's an interesting article that I would suggest. It remains simply clinical trial.

So in summary, I think CMV, EBV, and BK, they are important causes that affect allograft and patient survival. There have been a lot of improvements in the management of resistance CMV. For the BK, the therapeutic options are none, other than reducing immunosuppression. So that's a field that is lagging behind. And in general, the adoptive T cell therapy, which is still not the first line of therapy, but I think it is showing promise in, certainly, CMV and EBV related PTLD. And we may use more of that in the future. So with that, thank you for your attention. I'll answer questions, if there are any.

[APPLAUSE]