[MUSIC PLAYING]

CHETHAN PUTTARAJAPPA: I gave this talk last year as well, just a few updates. But the goal is to-- I'm going to talk about surveillance of three viruses that we do after transplantation. You've heard about cancers after transplantation from Dr. Harry as a consequence of being immunosuppressed.

So infections are the other realm that we see, where it also affects how patients do after transplantation. And although they get infections of different varieties-- viral, bacterial-- some are amenable for sort of being monitored and maybe implement some strategies to limit the bad consequences. So I'm going to talk about these three different things.

Interestingly, they all cause three different set of complications. The cytomegalovirus is problematic just because of it's primarily viral sort of systemic infection, just getting like a viral infection. The BK virus is problematic, because it affects your graft survival. And then the EBV sort of causes the Post-Transplant Lymphoproliferative Disorder, that PTLD, that Dr. Harry touched about.

So my objectives are to go through these three different viruses and talk about the burden, and the significance of these viruses in kidney transplantation, and the rationale for why we monitor them, and some of the limitations with what we do, per se. So just to put it into perspective as to where these three things fall, I mean, there are a number of viruses that our patients get, but essentially we know about the herpes viruses.

There's a whole family of them-- the herpes simplex virus 1, 2, the chicken pox virus. They're all of the same family of viruses. But I'm going to talk about the cytomegalovirus virus and then the Epstein-Barr virus and then the polyomaviruses of which the BK is one of them.

The common thing about all these viruses are that they can establish latency after the-- so once you get a primary infection, they can remain inside the host in sort of different cells in the body. For all the herpes viruses, most of them-- as you know, the herpes virus 1, the chicken pox virus, they're all neurotropic viruses. They are inside the nerves. And so when you're under stress, you get the breakout of the herpes infections. Or sometimes, you get zoster when you get old, and also in immunosuppressed systems.

The cytomegalovirus and EBV, they establish latency inside the hematopoietic cells system, like the precursors of the blood cells. And then the BK establishes latency in the genitourinary tract. And that is why it causes graft dysfunction after transplantation.

So there are some prerequisites for implementing any screening or surveillance program. You should have some sort of a gap between when the disease starts to happen and when clinical symptoms manifest. And then you should have a good test to detect these infections and should have some strategy to do something about these things. Otherwise, there's no point monitoring them. And then often, they have to be cost-effective.

So I'm just going to go through those concepts for these three different viruses. CMV, as I said, is one of the herpes DNA viruses. In immunocompetent individuals, you get a primary infection. It's almost like mono. You get fevers. Most of infections happen in childhood or adolescence. And then the virus establishes latency in the T cells, T lymphocytes.

In general, the prevalence of the infection in the community is about 60% to 80%. So 60% to 80% of adults can show evidence of a previous infection with CMV. And then it's sort of higher in countries with lower socioeconomic status. And transmission is airborne, all different ways.

So one thing about the reason I mentioned the latency of these viruses is because they can cause two different types of problems. One, they can be transmitted from the donor to the recipient-- that's one problem-- and cause primary infections in somebody that's never been exposed to the virus. And two, if the recipient already has had exposure to these viruses, they can become reactivated. And so that's the second part of the problem.

So CMV, in some special situations, where like in the congenital CMV, as you've heard, it can cause a lot of problems as part of the TORCH viruses. The HIV population is where first the immunocompromised patients started to have a lot of CMV-related infection. And then we noticed it when patients started to get immunosuppression as part of transplantation.

So in general, as I said, 60% of the population has some evidence of previous CMV infection. And the converse is, 40% don't. So you can mix and match that positive and negative and get a different combination of donors and recipients at the time of transplantation. You can start with donor-negative and recipient-negative, which is the lowest risk, because neither will they get any reactivation, neither will they have a primary infection transmitted from the donor.

And then the opposite spectrum would be somebody that has no immunity-- the D+, R-. The recipient has no immunity to the virus, but the donor has been exposed to the virus. So these cells are dormant in the lymphocytes. And when you transplant them, there's a risk of primary infection, which can be quite bad.

So the CMV in a kidney transplant patient can manifest different. Like I said, it can be a primary infection, if it comes from the donor, or it can be reactivation. In general, in most patients that where it reactivates, it often is not that bad. So the highest risk is in those patients that have no immunity but get it as part of their transplantation from a CMV-positive donor.

So most commonly, patients can manifest with what we call CMV syndrome. It's just a viral syndrome, who can have fever, diarrhea. They can have leukopenia. But then if it is really bad, you can have severe tissue invasive disease. You can have anything from enteritis, pneumonitis, hepatitis, nephritis. Lots of different things have been described.

The numerous bad consequences from having a severe CMV infection, you can have high morbidity, increased hospitalizations. It also upregulates your immune system, because the immune system is trying to fight the infection. And as a consequence then, you have a higher increased risk of rejections.

And also, we decrease the immunosuppression sometimes when you have a bad infection. So both the things contribute to higher rejections after a CMV episode. And then overall, there is like a pretty large study-- a couple of them, that show that after you get a bad CMV infection, there is a risk for inferior patient and graft survival.

So in general, what is the approach for CMV in these high risk, where the donor is positive and the recipient is negative? So once you determine their CMV status at transplantation, we use a very effective-- oops. So we use a very effective antiviral medication valganciclovir for six months-- this is sort of standard for most of these high-risk patients-- which has reduced the incidence of CMV from 70%. Before these drugs came on the market, CMV would sort of affect 70% of patients.

Now, it has gone down, during the prophylaxis, less than 10%. But there is still the problem of-- whoops-- once you finish the prophylaxis beyond six months, patients can get what is called late CMV, which can still happen in about 10% to 30% of patients. And the consequences are the same.

So when we looked at our own experience, that's what we found, that for the first six months, there were some breakthrough infections. But after you stopped the prophylaxis-- So this is sort of freedom from CMV. As you go for the first year, by week 50, almost 40% to 50% were having infections, despite having good antiviral prophylaxis.

So the reason I'm mentioning this as part of the surveillance is, what do you do for patients when they stop the prophylaxis at six months? One option is do nothing, just wait till they manifest symptoms and then treat them with effective drugs, or prolong the prophylaxis up to a year, which is what they do for lung transplant patients. We don't do that for kidney. Well, the third option is monitor them for a CMV virus copies in the blood and see if you can treat them ahead of time, before it becomes really bad.

So these are the prerequisites, like I said, I'll go over for all the three viruses. The CMV fits this picture, because there is a lag period between when the virus copies appear in blood and when the symptoms actually manifest. Usually, patients start having the virus prodromal symptoms when the virus copies are maybe in 20,000, 30,000, 40,000 copies.

And so you can detect the virus with a very good test early on. And we have good antiviral medications that you can use. So I think it sort of fits that picture.

There have been some studies that looked at whether that thing will work or not. And then they reported mixed results. But I think the problem with many of those studies was, once they stop prophylaxis, I don't think they monitored long enough.

And then the threshold at which they started to treat the patients with antiviral medications were sort of like, I think, high. Like, they were using a cutoff of wait till the copies are 35,000. And then I think sometimes patients became symptomatic before that, and also how they describe the efficacy of this strategy. So I don't think-- it's sort of been proven that they don't work.

So for example, I'll give you this case. This is one of our patients from a few years ago. We used to, at that point, once the patient has finished six months of prophylaxis, monitor them once a month, just because to strike a balance between avoiding too much monitoring versus also not detecting these infections at the right period. We used to give six months of prophylaxis.

This is a patient that finished six months of the valganciclovir. And then we used to monitor seven, eight, nine months. And the patient had negative the PCR test, but then at month 10 presented with very severe CMV disease, pneumonitis, is ICU stay, lots of complications, stayed in the rehab for like months together. So that can happen.

So when we looked at our own data during that period, this is what we found, that during the prophylaxis-- like on the x-axis is the weeks-- we still got some infection, when the patient was taking the drugs. But once they stopped the drugs-- let's see if I can use the monitor. Oh, there we go.

So during the prophylaxis-- most of these breakthrough infections, we figured out later on was because they were being underdosed for the medications, many of them. So we've sort of corrected that. But once they stopped the prophylaxis, we found that at least-- when we were doing surveillance like at monthly interval, most of the virus copy levels at which we found the infections were pretty low, like 100 to 1,000.

But then there were still some that presented with a million copies of the virus. But once we stopped the prophylax-- like monitoring them at nine, subsequent infections that happened-- most of these got admitted-- were all like very high copies of the virus. And so we figured, maybe we could do this better.

And so what do we know about the CMV virus? It multiplies very fast. So this is sort of days. And this is sort of doubling of the CMV in log. So it goes from 10 to 100 to 1,000 very quickly.

It's estimated it can double its copies between every one to four days. So it's very fast. So the screening that we've been doing every month, probably it's not very sufficient. Because if you have a negative test today and you start developing the infection tomorrow, you'll be like really high virus copies before you're due for the next test.

So we figured, OK, maybe we should monitored more frequently. But we have a number of other things to consider-- one, obviously, the virus kinetics-- but then how feasible that is, the burden to the patients, the cost, and the coordinators that do these tests. And what is our goal? Is it to prevent all symptomatic disease or just sort of hospitalization and some sort of severe disease that comes with it?

So what do we do currently here? So we-- I'm not presenting you the results of this. So we did some like modeling to figure out, what is the cost of doing every test every week, and how many infections do you prevent?

And we sort of came to this analysis that maybe doing every two weeks is probably the most cost-effective. And this is what we are doing at this point in time, is monitor every two weeks per se. And we treat most viremias when they go beyond 1,000 copies, which is still pretty early.

But then, does it work? I think we've been doing this for a year. I don't have the results of that. But I think anecdotally I can say most of the CMV-related hospitalizations that have happened in the hospital, at least the ones I've kept track, have always been either patients that were some sort of noncompliance with either monitoring or the way they were taking that medication.

So I think we should just-- I'm planning to look at this at some point. But that's where the real proof would be if we're doing the right thing. But that's what we do.

But there are some pitfalls in the way we are doing this, per se. It's like I said, if patients are noncompliant, it may not fully work. But I still think, based on our model analysis, even if they're half compliant, it'll still be better than not monitoring them at all, per se.

And then there are other issues with how we do this testing. Because the CMV test, if you do it in a peripheral lab, we don't get the results that often. So there are a lot of issues with monitoring the CMV viremias in many of our sort of rural population.

And then the other third issue-- this is true for all screening techniques-- is if you find something, are you sure that that was going to give you problems in the future? So this is the controversy with many prostate cancer screening, that you may find disease that may not necessarily do anything to the patient outcome. So if you find very low level copies, do you always have to treat them, per se. I think, but in these patients that have no immunity, we at least have an option to maybe wait and repeat the test a week later and see if it is progressively increasing. So I still think it is useful to screen these patients.

And then the last thing is that we stopped our protocols, say we'll stop at one year, that's just mostly an arbitrary cutoff. But we've had patients that present-- like, we had two in the last few months, they stopped the tests at 12 months. At 13th month, they got [INAUDIBLE], they were infected and in the hospital. But we can't necessarily-- so that's sort of limitations.

Just briefly on, what do we do for these-- you know, I talked about the different sort of combination of donor and recipient thing. So this is low risk. The donor is negative, recipient negative. We don't monitor. They don't get any prophylaxis for CMV.

This intermediate risk group, we still prophylax them for three months with valganciclovir. And then we don't monitor these patients once we start prophylaxis, because they have some intrinsic immunity from being exposed to the virus in the past. And even there are some patients who will get disease, but the frequency is very low. So we don't track them. And sometimes, when we find the viral copies, they don't necessarily progress, like the patients that have no immunity at all.

So in summary, what we found is that late onset cytomegalovirus infection is still a problem, despite having very good antiviral prophylactic agents. And clear strategies to manage this infection is still lacking. So at least we think doing surveillance every two weeks with the PCR test may be more cost-effective.

One thing I did not mention here for some of these patients who have some immunity is there are groups that are looking at ways of measuring viral-specific immunity. Just like how we do QuantiFERON for TB, you can do a QuantiFERON for CMV and sort of divide patients into those that, even though they have antibody positive, their cells are not effective at fighting the infections, versus those that, even though their IgG antibody is positive, they're CMV-specific QuantiFERON is negative, telling us that they are at much higher risk for infections in the long run. And so you can monitor them a little closer or extend the prophylaxis. But that is still not prime time. I think we still need more data. Let's see.

Questions on CMV? All right, I guess we'll leave the questions till the end. So I'm just going to shift gear and talk about BK-- so the second of the three viruses that I'm going to talk about. So BK, as I said, causes different kinds of problems.

So this is also a virus that establishes latent-- oops, sorry. So infection is very common in the population. But unlike CMV, patients don't know that they have BK virus infection. Most of them are asymptomatic. And then it localizes and establishes latency in the genitourinary space.

So when the kidney is transplanted, the BK comes with the donor kidney. Immunocompetent people, you can check their urine. And they can shed the virus in about 5% of the population.

So in immunosuppressed patients, it can be a problem. For example, in stem cell transplant patients, it causes very bad what we call as hemorrhagic cystitis, because like I said, it is in the genitourinary space. So patients can get very inflamed urinary bladder symptoms. Often, it's very difficult to manage. In many of them-- so 50% to 90% manifest virurias in the first couple of months.

For solid organs, like in the kidney mostly, the manifestations-- at least the way we pick it up-- for the most part, it's very asymptomatic. Rarely do kidney transplant patients have any symptoms from BK. But we do know that you can detect it in the urine, as the first sign. And we can [INAUDIBLE] BK viruria, for the viremia.

We can detect it in the blood when it's really bad. And because most of the time the virus is multiplying in the kidney and the urinary space. And it can in severe cases cause what we call as BK nephropathy, which can lead to inflammation scarring and graft failure. It has also been implicated in stricture of the ureter and some other non-renal pathology, which I'm not going to go into.

So this is sort of the incidence of-- so percentage of BK in kidney transplantation. We screen all the kidney transplant patients for BK. 30% to 40% have evidence of viruria, and most often happens within the first few months, more than 90% of them within the first two years. 5% to 10% of these will be severe enough that they progress to viremia, where we can detect copies in the blood. And then if you do biopsy them, in 2% to 5% of patient population, it can cause severe BK nephropathy and graft loss.

So the timing, this is viruria, purple, viremia, creatinine bump, and then biopsy. So usually, like I said, the first few months, you detect it in the urine and the blood. And then often at some point, the creatinine starts going up. And generally, it's followed by a biopsy.

Not every patient that has BK either in the urine or blood needs to be biopsied. That's not our protocol. We only usually biopsy patients that have a concomitant creatinine elevation.

So you can classify the BK in different waves, per se. This is the most recent classification. But essentially, it's just based on how severe is the involvement of the kidney by the virus and what is the degree of scarring that is happening as a result of infection.

This is the most recent classification, just came out last year. Dr. [INAUDIBLE], who's one of our pathologists, is part of it as well. Basically, as you go from class I to class III, you have an increase in the number of kidney tubules that are affected by the BK. You can detect it with special stains. I'm going to just show you some pictures.

And then the immune system reacts to the virus in the kidney. And you have increase in inflammation as you go from class I to class III. And inflammation then ultimately leads to scarring, which is what causes the ultimate graft demise.

So like I said, class I-- I would just ignore the readings-- but class I, class II, class III-- this is just like microscopy on the top. These are special stains for BK. And as you can see, in the early stages, there's not a whole lot of inflammation. Like, you can look at this blown-up picture here. You can just see good kidney tubules, not a whole lot of these blue cells, which are inflammatory cells.

But when you stain for special BK virus copies, you can actually find them in the kidney cells. But as the severity increases, the degree of inflammation goes up and the degree of the involvement of the cells by the infection goes up. Over time though, you can see this good, nice-looking kidney tubules are replaced by sort of destroyed tubules, a lot scar tissue. And in fact, even though you're detecting less BK on the special stains, the damage has already been done. And that's what leads to the graft failure.

So again, it meets all these requirements, like I said, for screening, because there is a definite delay between when the viral copies start to manifest and when the disease happens. And we have a very good test to pick up this infection, both in the urine and blood, and some sort of a management strategy to deal with it, per se.

So what do we do? We monitor for the BK in urine and in the blood starting like maybe at month one, two, three. Like I said, most BK happens first six months, 12 months, probably the first two years. So we monitor very frequently in the first year and a little less frequently in the second year. We stop routine monitoring after a year two.

That doesn't mean BK doesn't happen. We just had a patient who was in Florida vacationing. And at 40 years, they found like millions of copies of BK in the blood. So it can happen-- rare, but it can happen.

Other programs may do it slightly differently. Like I said, you can detect the virus first in the urine. And most of those patients end up sort of having resolution of the viral copies in the urine. And not all of them progress. Only like 10% progress viremias, and only 5% ultimately graft failure. Some programs just check only blood, per se, and just ignore the urine-- so different ways of doing it.

So there are no specific antiviral medications to BK. Many have been tried-- antivirals, antibiotics. None of them have worked. But we do know that part of the reactivation has to do with the immune suppression. And so the mainstay at least that most programs use, they sort of judiciously minimize immunosuppression.

Once you detect the BK at whatever month after transplantation, the monitoring is quite frequent-- maybe every two weeks, maybe every four weeks, depending on the peak level and how fast the virus-- what the viral copies have been multiplying at and also the kidney function. The risk, obviously, of minimizing immunosuppression in any of these situations is you don't want to do it too aggressively and then risk the graft going into rejection, because that's been reported.

5%, 15% is the risk of rejection when you wean immunosuppression down. And many people say you lose the graft more often from a bad rejection, because you cut down the immunosuppression too much. So that's something we need to be cautious about. We generally biopsy the patients only in the presence of creatinine elevation. Occasionally, we do switch them from tacrolimus to cyclosporine on a case-by-case basis when the viral copies are really resistant and the patient is having a pretty aggressive manifestation.

So this is when Dr. Harry and Dr. [INAUDIBLE] were in Wisconsin. So just sort of depicting how long it takes for-- and Dr. [INAUDIBLE] is here, so I'm going to put a shameless plug-- how long it takes from the first time you detect the BK, even if you make all the reductions, immunosuppression, date from first BK detection to-- so weeks to months.

So the point of putting this up for us is, when we make changes to immunosuppression, we don't make too many rapid changes on a weekly basis. We make a change, often 20% to 30% reduction in immunosuppression, and sort of just wait to see-- just be patient and wait for like log reductions over weeks to months, because we want to avoid rejections-- bad projections.

So in summary, BK activation is very common-- 30%, 40%; 5% graft loss. Still, there is no anti-BK drug. Part of the problem is it's sort of like an orphan disease. It affects a sort of small percentage of-- like, the graft loss is 2% to 5%. And most of the patients have no prob-- like, general community or other organ transplants don't have much problem with BK. So the drug development has been a little bit difficult.

But we do know that routinely doing surveillance and carefully managing immunosuppression can benefit patients. And most of them at least notice some resolution over time.

Last few slides on EBV, it's the third virus I'm going to talk about. Like I said, this is also one of the herpes viruses. It establishes latency in the B cells. You get primary infection, which we all know infectious mononucleosis happens in the young adolescent age. By the time people reach adulthood, 90% have evidence of EBV infection. And so only 10% have no evidence of EBV at the time they get transplanted.

So like Dr. Harry said, PTLD can come in different sort of flavors, where you start from just a mono-like syndrome-- you get fever, lymph nodes-- to a full-blown lymphoma, like the full spectrum. The EBV-positive PTLDs usually occur in the first year, because it always occurs, most of times, in patients-- Just like the CMV, you have the D+ and R-, where the donor had evidence of EBV infection. And the 10% of the recipient population who has never been exposed to EBV, they have a very high likelihood-- nine out of 10 organs that they get-- either from living or cadaver-- are going to be EBV-positive. So it's very highly likely that those patients that have EBV-negative serologies will get an organ from an EBV-positive serology.

And so the lymphoma incidence is 1% to 3% at five years. And 80% of these is within first year. And most of them are related to EBV. And like I said, EBV D+, R- is the biggest risk. And because children-- and like I said, by the time you reach adulthood, 90% have developed immunity. And so children are the ones that haven't yet.

So the highest prevalence of EBV-negative serologies is in children. And many of the children get organs from adults. So they have the highest risk of D+, R-. And obviously, the intensity of immunosuppression matters. If they give very strong T cell-depleting agents, like thymoglobulin or alemtuzumab, the risk is higher.

This is from the same review paper that Dr. Harry mentioned. So it basically goes through, once you have an EBV infection, it infects the B cells. And it sort of drives the B cell proliferation. And the B cells express some of these viral-specific molecules. But then the immune system is good in most of us, that it sort of recognizes these B cells that have EBV infection and just sort of gets rid of them.

But then if you add a patient who has end-stage kidney-- like organ disease gets transplanted and you add immunosuppression, maybe episodes of rejection, that sort of check that you have on these infected B cells is removed. And over time, the B cells multiply. And at some point, one of them gets into what we call a chronic proliferation, just out of bounds, just becomes neoplastic.

And Dr. Harry went over this classification. Like I said, you go from being just like polymorphic, just like different kinds of cells multiplying, to like one type of clone. And as you go from being polymorphic to monomorphic, the association with EBV goes down. Most lymphomas that happen in the first year are EBV related. Half of the lymphomas that happen many years out of transplant are not EBV related.

So well, then, the obvious question is, OK, can we just monitor for the virus and pick up these lymphomas before they become lymphomas? We do monitor them, and many programs do. We monitor EBV in the first year, only in these patients who are, again, donor is positive for the EBV IgG and the recipient is negative.

If you detect the viral copies, that doesn't mean they have lymphoma. I'll come to that. EBV viremia is neither sort of sufficient nor necessary for PTLD diagnosis. I mean, even if you have very high counts of the EBV virus, that doesn't necessarily mean they have PTLD. Along the same lines, not every PTLD patient you can detect EBV that are in the blood, not in the tissue specimens. So let's see if I can do-- for example, I'll show you these two cases.

These are both from the clinic. So this patient A, he's currently maybe three years out of transplantation. Both of these are EBV high risk, D+, R-. And we've monitored them. This patient was transplanted maybe 2014.

So I just picked up a few EBV copies. He always had what we would consider as not very small amounts of copies, 30,000, and persistent. Never had any signs of a mononucleosis-like syndrome, or lymph nodes, or I think he also had PET scans. No lymphoma.

This is a patient I saw in clinic just two weeks ago. The patient was transplanted almost 15 years ago. And he's also had EBV copies at low levels, again, never demonstrated any evidence of lymphoma. But we were sort of tracking it, but presented a couple of weeks ago with a sore throat of one month and inability to swallow, and basically had a large oropharyngeal mass, which we biopsied. And just I just referred him to the hematologist. The concern is that he's got PTLD.

So basically goes to say that the copies, per se, won't give you the full picture. But I think it's still useful. Because early PTLDs rarely happen without any EBV viremias. One of the consequences of just monitoring too much and reacting is, just like I told for BK, you don't want to reduce anti-rejection medicines too frequently and too aggressively, because ultimately, we want the patients to benefit from transplantation. So we wait for other evidence of malignancy.

So we do monitor them, but then it gives us a chance to sort of have low suspicion to recognize nonspecific symptoms, like diarrhea or like weight loss. Subtle symptoms, they could be manifestations of lymphomas. And the reason is, although it is treatable with, like Dr. Harry said, with rituximab, plus or minus chemotherapy, there are patients who don't do well. We have had deaths from PTLD. So we would like to at least monitor it, so that we can act on it earlier if it turns out to be PTLD.

There are other organ transplant protocols, like Dr. Harry mentioned. PTLD is a much bigger problem for intestinal transplants or lung transplants. And in some other kidney transplant programs, they do it differently. They monitor viremias. And they preemptively sometimes, based on the viral copy level, treat them with rituximab, because they just think-- Although there are no control studies, they believe that at least it reduces the risk of those high viremia patients progressing to PTLD.

So bottom line, monitoring is useful, I think probably more useful for early PTLDs. But care should still be taken to avoid like aggressive immunosuppression deduction for patients that don't have other features of PTLD. So this is my last slide. So overall summary, so these CMV, BK, and EBV are viruses that establish latency in humans, particularly problematic for transplant recipients. And properly monitoring and judicious immunosuppression reduction is a key for sort of all three different viruses.