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CMV Infection After Transplant: Who's at Risk and How to Manage?

### Announcer Intro:

You're listening to ReachMD. This medical industry feature, titled "CMV Infection After Transplant: Who's at Risk and How to Manage?", is sponsored by Takeda.

Here's your host, Dr. Jennifer Caudle.

### Dr. Caudle:

Welcome to ReachMD. I'm your host, Dr. Jennifer Caudle, and joining me to discuss cytomegalovirus infection after hematopoietic-cell and solid-organ transplant, also known as HCT and SOT, respectively, is Dr. Cedric Spak. He's a Physician Partner at Texas Centers for Infectious Disease Associates. Dr. Spak, it's great having you here today.

### Dr. Spak:

Thanks so much for having me!

### Dr. Caudle:

So let's begin with a brief overview of cytomegalovirus infection. Dr. Spak, what can you tell us here?

### Dr. Spak:

Well, cytomegalovirus, or CMV for short, is a member of the Herpesviridae family of DNA viruses,<sup>1</sup> and it can be transmitted any number of ways: through bodily fluids like blood, saliva, semen, or urine; from mother to fetus; or from a tissue graft or a transplanted organ,<sup>1,2</sup> which is what we'll be focusing on today. After an initial infection, the virus begins to lie dormant, and a person can also be infected with additional strains.<sup>1,3</sup> In immunocompetent people, CMV has very little consequence; they either remain asymptomatic or show mild symptoms as their bodies force the virus into latency and prevent further harm.<sup>1</sup> But the virus continues to lie dormant and can then reactivate and cause infections in response to biologically stressful events, like inflammation, other infections that are also present, and in cases where patients are on immunosuppressants and have weakened immune systems, like after SOT and HCT.<sup>1</sup> And so it's important to recognize that CMV infection is very common—both across the globe and in the United States. In fact, the seroprevalence in the general U.S. population is estimated to be between 40 and 80 percent.<sup>4</sup>

Now, nearly 43,000 SOTs were performed in the United States in 2022, which was a 3.7 percent increase from the year before and a new annual record.<sup>5</sup> And in 2020, over 22,000 HCTs were performed.<sup>6</sup> Unfortunately, CMV infection occurs in many of these patients. And while the incidence varies considerably, it occurs in as high as 75 percent of SOT recipients and up to 30 percent of HCT recipients.<sup>3</sup>

### Dr. Caudle:

Given that prevalence, Dr. Spak, what kind of impact does CMV infection have on patients after they receive a transplant?

### Dr. Spak:

In patients who've received an HCT, a high CMV viral load of over 1,000 IUs per milliliter is associated with over double the rate of overall mortality and non-relapse mortality.<sup>7</sup> Even seropositivity alone confers a lower overall survival rate.<sup>8</sup> And CMV seropositivity and replication after SOT are also associated with graft rejection and loss, particularly in patients who've received a lung, liver, or kidney transplant.<sup>9</sup>

So with all this being said, CMV can be a major cause of morbidity, mortality, graft failure, and other organ and tissue infections.<sup>7-11</sup> Now, a wide range of factors contribute to the risk of CMV infection and disease, but immunosuppression is central when it comes to risks of infection in transplant recipients.<sup>1,10</sup> So what are some of the drivers of immunosuppression and risk of infection in the transplant recipient?

For one, CMV itself has direct effects on the immune system and increases the risk of co-infections.<sup>10,11</sup> Post-transplant complications, like rejection and graft-versus-host disease, or GvHD for short, are managed through immunosuppression, and this renders transplant recipients vulnerable to CMV.<sup>3</sup> Additional risk factors include: the recipient's age, with the risk increasing in older patients; the early post-transplant period, where risk is particularly pronounced through day 100; and the CMV serostatus of donor and recipient.<sup>1,12,13</sup>

**Dr. Caudle:**

Now you just mentioned serostatus between donor and recipient, and I'm curious as to how that affects patients after transplantation?

**Dr. Spak:**

Well, in patients receiving HCT, those who are seropositive have some of the highest risk for CMV reactivation.<sup>1,13,14</sup> Donor-recipient pairs where the donor is CMV negative and the recipient is positive carry the highest risk of CMV reactivation at 36 percent.<sup>14</sup> That's because immunological anti-CMV reconstitution takes longer in the absence of CMV-specific memory T cells.<sup>14</sup> The next-highest risk comes in pairs where both the donor and recipient are CMV-seropositive, where the risk of infection is 32 percent.<sup>14</sup> And I'd like to point out that these percentages were compiled from multiple studies conducted before 2018.<sup>14</sup> Beyond that, other risk factors include previous CMV reactivation, the use of T cell-depleted transplant conditioning protocols, and systemic immunosuppression.<sup>13,14</sup>

But when it comes to SOT on the other hand, donor-recipient pairs where the donor is positive and the recipient is negative are associated with the highest risk of late-disease CMV, with an average risk of between 17 and 37 percent, and that's because seronegative recipients lack cellular or humoral immunity to CMV. Again, these percentages are from studies completed prior to 2018.<sup>15,16</sup> Other risk factors for CMV infection are immunosuppression potency and what type of organ or tissue is being transplanted, with lung, intestinal, and composite tissue transplant leading the pack.<sup>16</sup>

**Dr. Caudle:**

So, Dr. Spak, now that we've touched on the most important risk factors for developing post-transplant CMV, are there any other risk factors that clinicians should be aware of?

**Dr. Spak:**

Yes, it's important to know that many factors may be associated with an increased risk of developing refractory CMV post-transplant. For example, we have other treatment-related factors to consider, including prolonged CMV antiviral exposure and subtherapeutic dosing.<sup>17-20</sup> There are also issues with variations in drug clearance or inadequate pro-drug conversion,<sup>17</sup> as well as a patient's human leukocyte antigen status, meaning the donor and recipient must be a complete HLA match.<sup>20</sup> So in my opinion, knowing the risk factors for post-transplant CMV can help in understanding which patients are more vulnerable than others to CMV infections.

**Dr. Caudle:**

Thanks, Dr. Spak. And with those risk factors in mind, what could you tell us about the treatment approaches that clinicians may consider for post-transplant CMV?

**Dr. Spak:**

So, there are two CMV prevention approaches to reduce the risk of CMV infection or reactivation—prophylaxis and pre-emptive therapy—and each has their own set of challenges.

The prophylaxis approach involves giving antiviral agents to either all transplant recipients in a practice, which is called universal prophylaxis, or to a subset of at-risk patients. This preventive method starts either immediately or at least very soon after the transplant procedure and continues for a limited period of time, normally between about three to six months. And to further reduce the risk of relapse, secondary prophylaxis may also be considered. That's where prophylactic dosing is continued even after successful treatment.<sup>2,15,21</sup> Now, as I mentioned, there are some risks involved in this approach, namely that potentially unnecessary exposure to antiviral medications increases the risk of developing resistance to antivirals. And also, adding medications increases the likelihood of adverse events.<sup>2,15,21</sup>

The other approach is pre-emptive therapy. That's where a patient's labs are monitored at regular intervals, with the objective being early detection of viral replication. Treatment only starts when viral replication reaches a certain assay threshold—ideally before

symptom development—with the goal of heading off progression to clinical disease. Specifically, labs are monitored frequently, often weekly, and there is a low threshold of tolerance for initiating therapy. Now it is important to note that the exact threshold will differ between treatment centers because there's variability between the different diagnostic assays that are available, and protocols may vary center to center.<sup>2,15,21</sup> And one of the challenges with this approach is the ability to test for viral replication reliably or consistently. It also may not prevent some of the indirect effects of CMV infection, like its impact on graft and patient survival.<sup>2,15,21</sup>

Now when CMV DNA is detected in the blood despite prophylactic therapy, the patient will move on to first-line treatment of their CMV infection, understanding that treatment is individualized based on a number of patient factors.<sup>10,15,22</sup>

Patients who have CMV levels beyond a predefined threshold in their blood after two weeks of appropriately dosed antiviral therapy are considered to have refractory CMV.<sup>23</sup> The definition of refractory can vary, but typically includes clinical and laboratory characteristics indicating suboptimal response to therapy.<sup>24</sup>

And then those who have viral genetic alterations that reduce susceptibility to one or more antiviral drugs have resistant CMV.<sup>10,22</sup> This can be complicated further when dose adjustments or discontinuation of the anti-CMV agents are needed due to intolerance, such as neutropenia, hemorrhagic cystitis, and nephrotoxicity.<sup>23</sup> Something to note, however, is that treatment duration can vary, and antiviral treatment should be continued until CMV antigenemia or DNA in the blood is no longer detectable or has declined to levels below the predefined threshold.<sup>15</sup>

**Dr. Caudle:**

Now, unfortunately, we're almost out of time, but before we close, Dr. Spak, what would you like to leave with our audience today?

**Dr. Spak:**

I think it's really important to recognize that CMV can exact a heavy toll on patients who receive HCT and SOT.<sup>7-11</sup> With high seroprevalence in the general population,<sup>4</sup> effectively managing post-transplant CMV and refractory CMV is essential to improve transplant outcomes.<sup>23</sup> And that's why it's crucial that clinicians understand the risk factors for CMV so that they may identify those who might be at higher risk for developing CMV and do everything in their power to mitigate that risk.

**Dr. Caudle:**

That's a great way to round out our discussion on such an important issue. I'd like to thank my guest, Dr. Cedric Spak, for joining me to talk about the risks and challenges surrounding CMV after transplant. Dr. Spak, it was great speaking with you today.

**Dr. Spak:**

Thanks so much for having me!

**Announcer Outro:**

This program was sponsored by Takeda. If you missed any part of this discussion, visit ReachMD.com, where you can Be Part of the Knowledge.

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