



# What Is The True Significance of Donor-Related Cytomegalovirus Transmission in the Setting of Facial Composite Tissue Allotransplantation?

C.R. Gordon, W. Abouhassan, and R.K. Avery

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## ABSTRACT

Face transplantation (FT) is fraught with complications parallel to solid organ transplantation (SOT). As such, donor-related cytomegalovirus (CMV) transmission remains one of the most commonly feared viruses associated with FT. With this in mind, a review of the literature seemed justified, knowing that two of the first four face transplant recipients acquired CMV donor-related viral infection. Although the risk of CMV transmission is acceptable in the setting of SOT, the scenario for those composite tissue allotransplantation (CTA) patients, who are often young and healthy, may be different. Experiences from France and Cleveland have both confirmed suboptimal events related to CMV transmission following transplantation. Therefore, using the information provided here, it is imperative that all FT teams remain aware of these potential risks. Furthermore, all patients pursuing facial CTA should be fully informed as to the risks of donor-related CMV transmission, understand the importance of prophylaxis, and be aware of alternative therapies required to prevent symptomatic disease.

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**F**ACE TRANSPLANTATION (FT) is complicated, with struggles similar to solid organ transplantation (SOT) including those associated with donor-related cytomegalovirus (CMV) transmission.<sup>1-3</sup> At this time, there is no guidance for teams performing complex facial composite tissue allotransplantation (CTA) related to CMV management. This, together with two published reports of donor-related transmission within the first four patients worldwide, suggests that a thorough review of the CMV literature and its current guidelines is warranted.<sup>4-9</sup> Therefore, our purpose here is to (1) review the world's experience thus far with CMV and FT; (2) summarize the most current treatment strategies related to CMV, CTA, and SOT; and (3) shed insight and provide guidance to those teams preparing institutional review board protocols with plans to perform FT.

## METHODS

A thorough search of the online medical journal literature of the National Library of Medicine (PubMed) was performed in October 2010 in an effort to identify all peer-reviewed citations relating CMV to CTA, SOT, and FT. All pertinent articles related to these subjects are summarized, namely CMV prophylaxis, antiviral guidelines, and recommended treatment modalities.

## RESULTS

There are currently no review articles, other than two case reports,<sup>7,9</sup> summarizing CMV transmission, infection, and/or related complications pertaining to FT. There are, however, a few landmark articles related to CMV involvement with respect to hand transplantation which provided valuable insight,<sup>10,11</sup>. Nevertheless, the majority of information summarized here has been extrapolated from the SOT literature.<sup>12-18</sup>

CMV is an opportunistic pathogen complicating the lives of numerous SOT patients. It is classified as an immunomodulatory beta-herpesvirus. For a majority of carriers not on immunotherapy, this virus remains asymptomatic for

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From the Division of Plastic & Reconstructive Surgery (C.R.G.), Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA, Department of Plastic Surgery, Institute of Dermatology and Plastic Surgery (C.R.G., W.A.) and Department of Infectious Disease, Medicine Institute (R.K.A.), Cleveland Clinic, Cleveland, Ohio, USA.

Address reprint requests to Chad R. Gordon, DO, Harvard Medical School, Division of Plastic and Reconstructive Surgery, Department of Surgery, Massachusetts General Hospital, 15 Parkman Street, WACC #435, Boston, MA 02114. E-mail: [cgordon5@partners.org](mailto:cgordon5@partners.org)

life. However, infections in the setting of CTA occur either via donor transmission or from reactivation of the recipient's own CMV strain (due to obligatory immunosuppression).<sup>19</sup> Those at highest risk for severe CMV disease are the seronegative patient group receiving seropositive alloflaps (D+/R-), mainly because they acquire primary CMV infection during immunotherapy induction.<sup>20,21</sup> More importantly, long-term outcomes in similar circumstances often depend upon CMV-related disease, and therefore a donor-recipient mismatch scenario should be avoided if possible.<sup>19,21</sup>

CMV viremia, and the sequelae surrounding it, is now considered a modifiable risk factor since it may lead to posttransplant allograft dysfunction in some patients.<sup>22</sup> Seroprevalence in the general population ranges from 60% to 80% specific to geographic location or age population. This means that a majority of potential maxillofacial donors/recipients will have had previous exposure.<sup>23,24</sup> Therefore, all face transplant surgeons should (1) review and implement a preferred strategy for preventing transplant-related CMV infection<sup>14–18,23–29</sup> and (2) outline all ethical and psychological drawbacks associated with donor-related CMV transmission in seronegative candidates.<sup>20,30</sup>

There are two types of prevention strategies used for CMV. One is centered around prophylaxis, while the second encompasses preemptive therapy. "Prophylaxis" describes using antiviral therapy for a defined time of usually 3 to 6 months posttransplant. Benefits of this strategy were recently shown in a large SOT meta-analysis.<sup>28</sup> "Preemptive therapy" involves administering antiviral medications to those patients who develop CMV viremia posttransplant found during frequent monitoring (ie, CMV polymerase chain reaction, pp65 antigenemia). This not only allows early CMV detection, it allows effective treatment of "late CMV" (defined as infection following cessation of prophylaxis), which, if undiagnosed, can have devastating complications.<sup>23,24</sup>

The most common antiviral used today for CMV prophylaxis is valganciclovir. Its duration is usually 3 months.<sup>31</sup> However, there is increasing evidence that longer durations may confer additional benefits.<sup>32,33</sup> Of note, ganciclovir- and valganciclovir-associated neutropenia is a major side effect that may limit its application in the setting of maintenance immunotherapy.<sup>34</sup> Also concerning, as illustrated in the third FT performed in France, is that (1) this recipient acquired a donor-related CMV-strain resistant to ganciclovir and (2) that his CMV infection was found to coincide with severe acute graft rejection, which ultimately required eight weeks of foscarnet therapy.<sup>7</sup>

As mentioned, concern over CMV and donor-related transmission with respect to hand transplantation (ie, Gordon type III) was published by Schneeberger et al in 2005 and Bonnati et al in 2009.<sup>10,11</sup> Interestingly, the correlation between graft rejection and CMV infection has also been well described in other SOT settings, but may be particularly strong in CTA. This is because we know from prior experimentation by Kobayashi et al that skin allografts

serve as potential vectors of transmission. Their study showed that CMV seronegative patients with severe burn injuries requiring cadaveric skin allografts were susceptible to CMV transmission and infection.<sup>35</sup> Obviously, this raises much concern for reconstructive surgeons transplanting CTAs with large skin components, such as face and upper extremities, for example.<sup>36</sup>

Also concerning is the fact that the fourth FT patient (D+/R-) developed recurrent CMV viremia. This was complicated by ganciclovir/valganciclovir neutropenia, despite the use of filgrastim.<sup>37</sup> Because neutropenia confers a high risk for opportunistic infection and foscarnet and cidofovir therapies are rarely benign, this patient received an investigational drug named "CMX001" (Chimerix, Inc, Durham, NC) as an Emergency Investigational New Drug application through the United States' Food and Drug Administration.<sup>38</sup> A recent article by this team notes that she remained free of CMV recurrences for 5 months during subsequent DNA testing and has had borderline CMV immunoglobulin 6 levels (around 4–5 AU/mL), suggesting incomplete seroconversion at 20 months posttransplant.<sup>37</sup>

Following the lessons learned by the two FT patients described here, it seems straightforward that all FT teams should preferentially avoid high-risk CMV D+/R- FT when possible. Unfortunately, many areas throughout the United States may have high levels of asymptomatic CMV donors in their organ pool.<sup>39–41</sup> Therefore, this strategy may delay donor identification in those seronegative patients wait-listed for face transplantation.<sup>10,41</sup> Delgado and colleagues recently showed using a prospective, epidemiological SOT study that there are indeed certain risk factors associated with CMV infection. They confirmed the popular notion that knowing an organ donor was CMV-seropositive pretransplant was in fact found to be *an independent risk factor* for recipients developing CMV viremia posttransplant. This again provides strong evidence that D+/R- scenarios are suboptimal in "non-lifesaving" reconstructive transplant surgery and should be avoided.<sup>42</sup>

## DISCUSSION

FT and SOT recipients are vulnerable to a wide variety of viral pathogens. However, since facial alloflaps contain significant amounts of skin (in addition to paranasal sinus flora and respiratory mucosa in the setting of a LeFort-based maxillofacial allotransplantation), these various tissue types are exposed to the external environment unlike their solid organ counterparts. Therefore, one could in fact argue that vigilance over viral, bacterial, and fungal infections are *equally*, if not slightly more, important to SOT [Tables 1 and 2](#).<sup>37</sup>

For CMV, viremia following prophylaxis occurs at a rate of approximately 5% in the lowest risk patients (D-/R-) and up toward 50% in the highest risk patients (D+/R-). More importantly, the development of asymptomatic CMV infection/disease during the first 100 days posttransplant has been identified as an independent risk factor for

**Table 1. Antimicrobial Prophylaxis Used for the First Four Face Transplant Recipients**

Report	Bacterial	Fungal	Viral	Other
Devauchelle et al <sup>47</sup> ; Dubernard et al <sup>47</sup>	Amoxicillin-clavulanate	Not stated	Ganciclovir IV × 5 days, then valganciclovir × 5 mos	TMP-SMX × 4 mos
Guo et al <sup>48</sup>	Ceftizoxime, metronidazole	Not stated	Acyclovir	Probiotics; allicin; IVIG; surveillance bacterial cultures and preemptive therapy
Lantieri et al <sup>38</sup>	Not stated	Not stated	Valganciclovir × 6 mos	TMP-SMX × 6 mo; phenoxymethyl-penicillin for donor syphilis
Siemionow et al <sup>39</sup>	Vancomycin and piperacillin-tazobactam, then amoxicillin- clavulanate	Voriconazole	Ganciclovir IV then valganciclovir × 5 mo	TMP-SMX prophylaxis

From Gordon CR, et al. CMV and other infectious issues related to face transplantation: Specific considerations, lessons learned, and future recommendations. *Plast Reconstr Surg* 2010 (In Press).<sup>37</sup>

mortality in patients both at low or high risk in many studies thus far.<sup>14,15,32</sup> Therefore, all efforts to avoid donor-related transmission, prevent disease progression following FT, and remove the D+/R- scenario could significantly improve long-term outcomes related to FT as in the case of SOT.<sup>28,43</sup> It is therefore critical that all FT teams comprehend the current strategies and guidelines for universal CMV prophylaxis and preemptive therapy in SOT.<sup>12,44–46</sup>

As the specialty of face transplantation moves forward, we may also need to extend the duration of prophylaxis with or without the additional use of immunoglobulin therapy.<sup>10</sup> Unfortunately, due to the limited applications of FT thus far, findings summarized here with respect to diagnosis, treatment, and prophylaxis have been adopted from SOT.<sup>12,15,28,44,46,47</sup> However, questions regarding the true impact of donor-related CMV transmission in the setting of facial CTA and CTAs containing large skin components remains to be answered. We do know, however, that evidence-based medicine supports all FT surgeons under-

standing the risks related to CMV transmission, and therefore all teams should conduct careful, meticulous candidate selection and facial organ matching for all R- patients.<sup>41</sup> Furthermore, with CMV's high reported complication rate and its graft rejection correlation in the setting of complex FT and hand transplantation,<sup>48</sup> which are both classified as Gordon type III CTAs (Table 3), one should greatly consider using aggressive prophylaxis in addition to preemptive therapy.<sup>10,11,49</sup>

In conclusion, it is extremely important that all FT teams remain aware of the potential risks associated with donor-related CMV transmission as we move forward.<sup>50</sup> Furthermore, all patients pursuing FT, as part of their informed consent, should be thoroughly educated as to the serious risks, various prophylactic strategies, and all available therapeutic options associated with CMV. Most importantly, evidence-based medicine in both the SOT and hand transplant literature suggests that overall morbidity and mortality among FT patients can be minimized with the proper implementation of a vigorous CMV prevention regimen,

**Table 2. Infectious Complications Seen With the First Four Face Transplant Recipients**

Report	Bacterial	Fungal	Viral	Comments
Devauchelle et al <sup>46</sup> ; Dubernard et al <sup>47</sup>	None reported	<i>Candida</i> stomatitis	HSV on lips; molluscum contagiosum	Concern over oral mucosa fungal infection vs graft rejection
Guo et al <sup>48</sup>	<i>Enterococcus</i> , <i>Staphylococcus</i> <i>epidermidis</i> , <i>Enterobacter</i> on surveillance cultures, treated pre-emptively	None reported	None reported	Stated no opportunistic infections at 2-y follow- up
Lantieri et al <sup>38</sup>	None reported	None reported	CMV (ganciclovir- resistant)	Required foscarnet × 8 wks, associated with rejection
Siemionow et al <sup>39</sup>	<i>Pseudomonas</i> and <i>Staphylococcus</i> <i>epidermidis</i> catheter- related BSI; <i>C diff</i> and <i>Aeromonas</i> diarrhea	None	CMV (relapsing)	Neutropenia from ganciclovir and valganciclovir

From Gordon CR, et al: CMV and other infectious issues related to face transplantation: Specific considerations, lessons learned, and future recommendations. *Plast Reconstr Surg* 2010 (In Press).<sup>34</sup>

**Table 3. The Gordon CTA Classification System in Relation to Overall CMV Donor-Related Transmission Risk**

Type	Complexity	Allograft Subtypes	Donor-Related CMV Transmission Risk
I	Low	Flexor tendon, tongue, uterus, vascularized nerve	(1) Absent skin component; (2) <i>reduced</i> CMV transmission risk
II	Moderate	Abdominal wall, facial subunit, ear, genitalia, penis, larynx, scalp, trachea, vascularized joint, knee	(1) Contain skin, (2) <i>increased</i> CMV transmission risk
III	High	Upper extremity, hand, face	(1) Contain skin, (2) <i>increased</i> CMV transmission risk
IV	Maximum	Concomitant CTA, face/upper extremity(s)	(1) Contain skin, (2) <i>increased</i> CMV transmission risk

Of note, those classified as *type II* or *higher* contain skin and therefore the risk of CMV donor-related transmission is more significant CTA, composite tissue allotransplantation; CMV, cytomegalovirus.

which may require a combination of CMV prophylaxis *and* preemptive therapy.

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