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ORIGINAL ARTICLE

Herpes simplex virus-2 transmission following solid organ transplantation: Donor-derived infection and transplantation from prior organ recipients

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Abstract

Background: Owing to limited availability of donor organs, previous solid organ transplant (SOT) recipients are increasingly considered as potential organ donors. We report donor-derived transmission of herpes simplex virus type-2 (HSV-2) to two clusters of SOT recipients with transmission from the original donor and an HSV-2–infected recipient who subsequently became a donor.

Methods: We reviewed medical records of the donors and recipients in both clusters. Pre-transplant serology and virological features of HSV-2 were characterized. Genotyping of HSV-2 isolates to determine potential for donor transmission of HSV-2 through transplantation of organs from prior organ recipients was performed.

Results: A kidney-pancreas recipient died day 9 post transplant. Following confirmation of brain death, the lungs and recently transplanted kidney were donated to two further recipients. The liver was not retrieved, but biopsy confirmed HSV-2 infection. Testing on the original donor showed negative HSV-2 polymerase chain reaction and HSV immunoglobulin (Ig)M, but positive HSV-2 IgG. The liver recipient from the original donor developed HSV-2 hepatitis and cutaneous infection that responded to treatment with intravenous acyclovir. In the second cluster, lung and kidney recipients both developed HSV-2 viremia that was successfully treated with antiviral therapy. Genotyping of all HSV-2–positive samples showed 100% sequence homology for three recipients.

Conclusions: Donor-derived HSV infection affected two clusters of recipients because of transplantation of organs from a prior organ recipient. HSV should be considered as a possible cause of illness in febrile SOT recipients in the immediate post-transplant period and may cause disseminated disease and re-infection in HSV-2–seropositive recipients. Testing of HSV serology and prophylaxis may be considered in SOT recipients not receiving cytomegalovirus prophylaxis.

KEYWORDS:

allograft re-use, donor-derived infection, hepatitis herpes simplex virus, transplantation

1 INTRODUCTION

Solid organ transplantation is life-saving for many patients with end-stage organ disease but a significant disparity exists in the supply of organs for transplant and the number of patients registered on waiting lists.[1] This imbalance has led to increasing efforts to use organs from non-traditional sources, including considering previous organ recipients as donors.[2-4] From 2000 to 2012 in the United States, 762 organs were recovered from 718

donors who had been previous organ recipients.[5] Reports on the outcomes of this practice are limited, although rare donor-derived disease transmissions have been reported to organ procurement agencies (M.G. Ison, personal communication).

In 2014, the lungs, kidneys, pancreas, and the liver were retrieved from an Australian deceased donor. The kidney-pancreas recipient from this original donor died in the immediate post-transplant period. This recipient subsequently became an organ donor and his lungs and recently transplanted kidney were transplanted into two recipients, but the liver was not retrieved because of concern regarding possible ischemic injury. Histological examination of the liver subsequently showed features of herpes simplex virus (HSV) infection and this was confirmed with polymerase chain reaction (PCR). The recipient of the liver transplant from the original donor also developed suspected HSV-2 hepatitis, cutaneous infection, and viremia. HSV-2 viremia was noted in both recipients from the second donor. An investigation was conducted to determine whether these clusters of HSV-2 infection were coincidental or transmitted through transplantation.

2 CASE REPORTS

Two clusters of organ transplantation are described. The first involved transplantation of the heart and lungs, kidney-pancreas, single kidney, and liver from the deceased donor (Donor 1) and the second involved transplantation of lungs and re-transplantation of the kidney from the deceased kidney-pancreas recipient (Recipient 1 / Donor 2) (Figure 1). A previous publication from our group describes two of the cases.[6]

2.1 Donor 1

The original organ donor died from hypoxic brain injury. At time of death, no evidence of clinical HSV-2 infection was seen, and the patient had no past history of recurrent HSV-2 infection. Laboratory features are shown in Table 1. Of note, HSV-2 viremia was not detected when performed retrospectively on serum from the time of organ

donation; although the patient's serology was positive for HSV-2 immunoglobulin (Ig)G (Table 1), as occurs in 12% of Australian adults.[7]

2.2 Cluster 1 – Initial transplantation

2.2.1 Recipient 1 / Donor 2

Recipient 1 / Donor 2 was a man in his 30s with a past history of type 1 diabetes mellitus and diabetic nephropathy requiring peritoneal dialysis. Kidney-pancreas transplantation was performed using organs retrieved from Donor 1. Clinical features, including immunosuppression, are summarized in Table 2. Two days post transplant, the patient had an acute myocardial infarction and cardiac arrest requiring 20 minutes of cardiopulmonary resuscitation. He had a concomitant decrease in hemoglobin from 100 to 67 g/L, prompting exploratory laparotomy, where the transplanted kidney and pancreas appeared well perfused. Empiric antimicrobial therapy with piperacillin-tazobactam was commenced for aspiration pneumonia, then vancomycin, ciprofloxacin, and fluconazole were added because of intermittent fevers over the next 4 days. Bacterial and fungal cultures of blood, bronchoalveolar lavage fluid, and urine remained negative. On day 7 post transplant, the patient had further deterioration with increased insulin and inotrope requirements and worsening renal function. A further exploratory laparotomy was undertaken, because of concern for pancreatic thrombosis, but was unremarkable with no evidence of bleeding and a healthy-appearing transplanted kidney and pancreas. The patient showed minimal neurological response despite weaning of sedation. On day 9, brain death was confirmed; his lungs and previously transplanted kidney were retrieved and transplanted into Recipients 5 and 6, respectively.

At time of organ retrieval from Recipient 1 / Donor 2, macroscopic fatty changes were noted in the liver, and biopsy was performed. Subsequent histopathological examination showed features suggestive of HSV infection including coagulative parenchymal necrosis with nuclear inclusions and moderate parenchymal cholestasis. A PCR performed on the liver biopsy specimen confirmed HSV-2 infection (see Table 1).

Biopsy of the transplant kidney was performed before re-transplantation and histopathology was also consistent with HSV infection with histiocytes with enlarged nuclei containing possible viral inclusions noted in capsular fibrous tissue. HSV-specific immunohistochemical staining showed strong staining of the histiocyte nuclei, consistent with renal involvement and the diagnosis of disseminated HSV infection. This diagnosis was further suggested by the high-level HSV-2 viremia noted at the time of Recipient 1's death (Table 1), in comparison with an undetectable viral load at time of the initial transplant. The investigations suggestive of HSV-2 infection only became available following organ implantation into the subsequent recipients. HSV-1 and HSV-2 serology performed retrospectively on pre-transplant samples was negative, showing Recipient 1 / Donor 2 had no pre-existing HSV immunity, which is a risk factor for HSV-2 viremia.

2.2.2 Recipient 2

Recipient 2 was a female in her 20s who underwent liver transplantation from Donor 1 following fulminant hepatic failure secondary to an idiosyncratic drug reaction (see Table 2 for clinical features). The patient was initially asymptomatic, but had investigation for possible subclinical HSV-2 infection after detection of HSV-2 in organ retrieval samples from Recipient 1 / Donor 2. The recipient was HSV IgM negative, HSV-1 IgG positive, and HSV-2 IgG positive pre-transplant (see Table 1). On day 13 post transplant, evidence of hepatitis was noted (alanine aminotransferase 236 units/L, aspartate aminotransferase 72 units/L, gamma-glutamyl transferase 130 units/L, Supplementary Figure S1, Panel A) and HSV-2 viremia, prompting a change from valganciclovir 900 mg 12-hourly, which had been used per unit protocol as anti-cytomegalovirus (CMV) prophylaxis, to valacyclovir 1 g 8-hourly. On day 19, a disseminated rash suspicious for cutaneous HSV (Supplementary Figure S1, Panel B) was detected. The patient was admitted and commenced on intravenous acyclovir 600 mg 8-hourly, and prednisolone was stopped. The hepatitis and rash resolved and the patient was discharged on oral valacyclovir 500 mg 8-hourly (adjusted for renal function).

Valacyclovir was changed to valganciclovir (450 mg 12-hourly) on day 32 post transplant and the patient remained symptom free at 12 months of follow-up.

2.2.3 Recipient 3

Recipient 3 was a woman in her 40s who underwent combined heart and bilateral lung transplantation for severe heart failure from congenital heart disease (see Table 2 for clinical features). She had no immediate post-transplant complications. The recipient had negative HSV IgM, HSV-1 IgG, and HSV-2 IgG serology (see Table 1). Because of a CMV mismatch, the recipient received CMV prophylaxis with intravenous ganciclovir and CMV hyper-immune globulin and was ultimately transitioned to oral valganciclovir (see Table 2). No evidence of HSV viremia or disease was noted during the recipient's course and the recipient remained well at 12 months of follow-up.

2.2.4 Recipient 4

Recipient 4 was a man in his 40s who had previously received a renal transplant for cystinosis 9 years prior that had failed. He received a second renal transplant from Donor 1 (see Table 2 for clinical features). He was on valganciclovir 450 mg 12-hourly as anti-CMV prophylaxis following the transplant per unit protocol and did not develop any symptoms of HSV-2 infection. Pre-transplant serology showed that the recipient had negative HSV IgM, positive HSV-1 IgG and negative HSV-2 IgG. Valganciclovir was ceased 3 months post transplant and the recipient had an uncomplicated course at 12 months follow-up.

2.3 Cluster 2

2.3.1 Recipient 5

Recipient 5 was a man in his 60s who received a renal transplant from Recipient 1 / Donor 2. The patient had a history of end-stage kidney disease secondary to reflux nephropathy and had been on hemodialysis. The patient had positive HSV-1 IgG and HSV-2 IgG but negative HSV IgM at time of transplantation (see Table 1). His virological

course is shown in Table 1. On day 1 post transplant, he was commenced on valacyclovir 1 g daily (adjusted for renal function) because of concern regarding possible disseminated HSV-2 in the second donor. On day 5, HSV-2 viremia was noted (Table 1) and the patient was switched to intravenous acyclovir 400 mg daily (adjusted for renal function). Subsequent clinical course is depicted in Table 2. The patient had resolution of HSV-2 viremia with no evidence of clinical disease and the patient has had an uncomplicated course at 12 months of follow-up.

2.3.2 Recipient 6

Recipient 6 was a female in her 60s who received a bilateral lung transplant from Recipient 1 / Donor 2 for underlying chronic obstructive pulmonary disease with associated pulmonary hypertension (see Table 2 for clinical features). The patient's pre-transplant serology showed that she was HSV IgM negative and HSV-1 IgG and HSV-2 IgG positive (see Table 1). Intravenous ganciclovir 5 mg/kg was commenced on day 1 post transplant per unit protocol and HSV-2 viremia was detected on day 2 post transplant, prompting commencement of valacyclovir 1 g 8-hourly. The viremia resolved and no further complications developed (see Table 2). The patient had no further HSV-2 viremia or disease at 12 months of follow-up.

3 MATERIALS AND METHODS

We obtained pre- and post-transplantation blood samples for retrospective testing from the deceased donor, Recipient 1 / Donor 2 (kidney-pancreas) and Recipient 2 (liver) from Cluster 1. Samples were also obtained from Recipients 5 (kidney) and Recipient 6 (lungs) from Cluster 2. Liver and kidney biopsy samples were obtained from Recipient 1 / Donor 2. For Recipient 1 / Donor 2 and Recipients 2, 5, and 6, type-specific HSV-1 and -2 IgG (Focus Diagnostics, Cypress, CA, USA) and HSV IgM (Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany) serology were performed. On the same blood samples, HSV-1 and -2 real-time TaqMan PCR was performed targeting glycoprotein-B (modified from Druce et al.[8]) and, where possible, viral load calculated by

Droplet Digital PCR (Bio-Rad, Pleasanton, CA, USA) (see Table 1). For Donor 1 and Recipients 3 and 4, HSV was detected using a commercial quantitative PCR from Argene (BioMerieux Diagnostics, Sydney, Australia), with type-specific IgG antibody for HSV-1 and HSV-2 detected using a Focus Diagnostics enzyme immunoassay (EIA) kit (Focus Diagnostics, Cypress, CA, USA) and HSV IgM detected using the Diesse Chorus EIA (Diesse Diagnostica, Milan, Italy). In order to demonstrate molecular relatedness of the identified HSV-2 strains, sequencing and phylogenetic analysis of fragments of the UL53 and US1 genes was performed, as described by Kaneko et al.[9] Sequences were compared with other HSV-2 sequences available on the GenBank public database.[10]

Ethical approval for all sites was obtained from Austin Health Human Research and Ethics Committee, Melbourne, Australia (Reference number LNR/15/Austin/39) and from St. Vincent's Hospital Sydney Human Research and Ethics Committee, Sydney, New South Wales, Australia (Reference number LNR/15/SVH/197).

4 RESULTS

Serological and virological findings are summarized in Table 1 and show Recipient 1 / Donor 2 and Recipient 3 were the only patients without any evidence of pre-existing HSV-1 or -2 antibodies. Recipient 1 / Donor 2 subsequently went on to become HSV-2 viremic, with a viral load >15 million copies/mL, and had HSV-2 detected in liver and kidney biopsies at the time of organ retrieval. The HSV-2 strains recovered from Recipients 1 and 2 allowed analysis of a 1010-nucleotide sequence from the HSV-2 UL53 gene and an 805-nucleotide sequence from the HSV-2 US1 gene. Shorter fragments of these genes were also available for analysis from Recipient 5. Insufficient HSV-2 amplified product was available for analysis from Recipient 6. All fragments sequenced from Recipients 1, 2, and 5 showed 100% homology. Comparison with 15 HSV-2 sequences available on GenBank indicated 98%-99% homology. The HSV-2 sequences on GenBank were derived from (predominantly genital) HSV-2 isolates from Japan, South Africa, Uganda, United Kingdom, and United States. These findings demonstrate the close genetic relatedness of the HSV-2 strains sequenced from the recipients.

5 DISCUSSION

Transplantation of organs from prior organ recipients has been reported both early and late post transplant and is a potential way to increase the donor pool.[11] This report describes inadvertent transmission of HSV-2 infection from Donor 1 to Recipient 1 / Donor 2 that was further transmitted to a second cluster of organ recipients. Proven or probable donor-derived infections through transplantation of organs from prior transplant recipients have not been described previously, to our knowledge. Although suspected donor-derived HSV infections have been reported,[12-15] this report demonstrates clear outcomes with definitive molecular epidemiology showing HSV-2 transmission to multiple recipients in two clusters.

Donor-derived HSV transmission is rare and has been suspected in multiple previous reports,[12-15] but has been difficult to prove because of the possibility of re-activation or new primary infection in transplant recipients.[14,16] We were able to use molecular methods to confirm an epidemiological link, reflecting the increasing role of these techniques in investigating suspected donor-derived infection.[17-20] In our report, the initial organ donor was not HSV-2 viremic when serum samples taken before organ retrieval were tested. However, it is possible the donor had an HSV-2 re-activation at time of organ retrieval, despite our inability to detect it, or that latent virus was in the transplanted organs that reactivated *in vivo* in susceptible hosts. Donor-derived HSV-2 infection had a variety of clinical presentations in our report, likely related to variable host HSV immunity and different CMV prophylaxis regimens, which would also control HSV-2 infection and reactivation. Recipient 1 / Donor 2, who had negative HSV-1 and -2 antibodies and did not receive antiviral therapy, rapidly developed disseminated disease, with an absence of skin lesions, similar to other solid organ transplant (SOT) recipients with disseminated HSV infection.[14,21,22] Conversely, Recipients 5 and 6 were HSV-2 immunoglobulin (Ig)G positive, implying pre-existing immunity and re-infection. These recipients also received post-transplant antiviral therapy with subsequently less severe clinical manifestations. It is notable, however, that we demonstrated viral transmission

and development of viremia despite evidence of recipient immunity and the use of antiviral prophylaxis. Re-infection with HSV-2 has been described previously in immunocompetent patients,[23] but is not frequently considered in the transplant setting. Our findings also confirm the utility of HSV PCR on serum in diagnosis of both viremia and invasive infection.[24] Furthermore, quantification of HSV viremia in our series seemed to correlate with severity of disease (Tables 1 and 2).

At present no consensus guideline is available on evaluation of HSV serology in SOT donors and recipients.[25] Many centers however do evaluate recipient HSV serology or administer universal prophylaxis for the first 1-3 months after transplantation,[16,25,26] predominantly to prevent HSV re-activation, which occurs in 35%-68% of HSV-seropositive recipients not receiving antiviral prophylaxis.[26] By contrast, donor-derived HSV transmission is rare, making it difficult to extrapolate recommendations for HSV testing and prophylaxis from our report. The high incidence of HSV re-activation in seropositive recipients and the morbidity and mortality of donor-derived HSV transmission in our report highlight that HSV infection remains an on-going concern post transplant. HSV serology and prophylaxis, therefore, may be considered in recipients who do not receive CMV prophylaxis or where CMV prophylaxis is delayed (as was the case in Recipient 1 / Donor 2).

The potential risks associated with an organ recipient subsequently becoming an organ donor also require consideration and may differ if subsequent donation occurs soon after or remote from the donor having received an organ transplant. Our report illustrates that particular care must be taken to ensure that an infectious complication did not contribute to the potential donor's death. Donation of organs from recipients late after initial transplantation carries risks of transmission of multidrug-resistant organisms or organisms that typically occur later post transplant (eg, *Cryptococcus*, *Nocardia*), as demonstrated in a report of a suspected transmission from an organ recipient of ganciclovir-resistant CMV through kidney transplantation.[4]

Our report has several limitations. First, we were unable to identify HSV-2 in the initial organ donor's clinical samples. However, the fact that multiple recipients in both

clusters developed HSV-2 viremia and disease with highly genetically-related virus would nonetheless support that donor-derived transmission has occurred. Second, we encountered difficulty in determining the relatedness between HSV-2 strains because of the highly conserved nature of the HSV-2 genome. The sequences obtained were identical between recipients. However, relatively high levels of sequence similarity with the publicly available HSV-2 sequences were also noted, limiting our ability to prove donor-derived transmission. To overcome this limitation, longer segments of the HSV-2 genome would need to be sequenced, which becomes challenging when utilizing PCR amplification methodology. Future efforts will be assisted by the use of emerging technology such as whole genome sequencing. Finally, post-transplant testing was not complete in all recipients (particularly Recipient 4).

In conclusion, our report demonstrates donor-derived HSV infection in multiple SOT recipients that caused significant morbidity. Of note, HSV infection affected two clusters of recipients. One of these was caused by transplantation of organs from a prior organ recipient, highlighting that this practice may carry specific risks. HSV should be considered as a possible cause of illness in febrile SOT recipients in the immediate post-transplant period, as diagnosis can be difficult even in patients with disseminated disease and re-infection may occur in HSV-seropositive recipients. Testing of HSV serology and prophylaxis may be considered in SOT recipients not receiving CMV prophylaxis. Among the herpes viruses, CMV may justly occupy the attentions of transplant and infectious diseases physicians, but our experience suggests that HSV can be "forgotten, but not gone."[24]

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Author contributions:

N.M.: Study design, collection of clinical data, writing and editing of article; I.J.A.: Study design, collection of clinical data, performance of microbiological assays, genetic sequencing and analysis, writing and editing of article; M.K. and J.D.: Genetic sequencing and analysis, writing and editing of article; A.G.R. and P.J.G.: Collection of clinical data, writing and editing of article; P.D.H., H.O. and P.D.R.J.: Study design, collection of clinical data, writing and editing of article; T.M.K., W.R.M., P.J.O., M.C.P., and S.S.: Collection of clinical data, writing and editing of article; W.D.R.: Performance of microbiological assays, genetic sequencing and analysis, writing and editing of article.

Disclosures:

The authors declare no conflicts of interest

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Figure Legends

FIGURE 1 Initial transplantation and organ re-transplantation clusters in donor-derived herpes simplex-2 infection

Supplementary material is available online with this article:

Supplementary Figure S1 – Clinical characteristics of herpes simplex virus-2 (HSV-2) infection in liver transplant recipient. Panel A – Liver function tests indicating initial improvement following liver transplantation and subsequent HSV-2 hepatitis on day 13. ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase.
Panel B – Photograph of disseminated rash with pustular lesions suggestive of cutaneous HSV-2 infection (upper chest)

TABLE 1 Serologic and virologic characteristics of donor-derived herpes simplex virus (HSV)-2 infection through organ re-transplantation

Specimen type	Collection time (post-transplant)	HSV-1 IgG	HSV-2 IgG	HSV IgM	HSV DNA	Viral load (copies/mL)
Donor 1						
Pre-transplant serum	Day 0	Negative	Positive	Negative	Not detected	
Cluster 1						
Recipient 1 / Donor 2 - Kidney / Pancreas						
Pre-transplant serum	Day 0	Negative	Negative	Negative	Not detected	-
Post-transplant serum	Day 9	Negative	Negative	Negative	HSV-2 detected	15 461 000
Kidney (PET)	Day 10	-	-	-	HSV-2 detected	
Liver (PET)	Day 10	-	-	-	HSV-2 detected	
Recipient 2 – Liver						
Pre-transplant serum	Day 0	Positive	Positive	Negative	Not detected	-
Post-transplant serum	Day 19	-	-	-	HSV-2 detected	3875
Follow-up plasma	Day 53	-	-	-	Not detected	-
Recipient 3 - Heart / Lungs						
Pre-transplant serum	Day 0	Negative	Negative	Negative	Not detected	
Follow-up plasma	Day 24				Not detected	
Follow-up plasma	Day 61				Not detected	
Recipient 4 - Kidney						
Pre-transplant serum	Day 0	Positive	Negative	Negative	Not detected	
Cluster 2						
Recipient 5 – Kidney						

Pre-transplant serum	Day 0	Positive	Positive	Negative	Not detected	-
Post-transplant whole blood	Day 2	-	-	-	HSV-2 detected	7688
Follow-up plasma	Day 14	-	-	-	Not detected	-
Follow-up plasma	Day 21	-	-	-	Not detected	-
Recipient 6 – Lungs						
Pre-transplant serum	Day 0	Positive	Positive	Negative	Not detected	-
Post-transplant plasma	Day 3	-	-	-	HSV-2 detected	<400

IgG, immunoglobulin G; IgM, immunoglobulin M; PET, paraffin-embedded tissue.

TABLE 2 Clinical characteristics of donor-derived herpes simplex virus (HSV)-2 infection through organ re-use

	Recipient 1 / Donor 2	**Recipient 2**	**Recipient 3**	**Recipient 4**	**Recipient 5**	**Recipient 6**
Donor	Original donor (Donor 1)	Original donor (Donor 1)	Original donor (Donor 1)	Original donor (Donor 1)	Recipient 1 / Donor 2	Recipient 1 / Donor 2
Gender, Age (decade)	Male, 30s	Female, 20s	Female, 40s	Male, 40s	Male, 60s	Female, 60s
Organ transplanted	Kidney / Pancreas	Liver	Heart / Lungs	Kidney	Kidney	Lungs
Underlying disease	Type 1 diabetes mellitus	Idiosyncratic drug reaction	Congenital heart disease	Cystinosis	Reflux nephropathy	Chronic obstructive pulmonary disease
Immunosuppression						
Induction	Basiliximab	Methylprednisolone		Basiliximab	Basiliximab	Basiliximab

On-going	Prednisolone Tacrolimus Mycophenolate	Prednisolone Tacrolimus Azathioprine	Prednisolone Tacrolimus Azathioprine	Prednisolone Tacrolimus Mycophenolate	Prednisolone Tacrolimus Mycophenolate	Prednisolone Tacrolimus Azathioprine
Clinical course	Initial AMI and cardiac arrest. Intermittent fever and critically ill. Declared brain dead and became donor for recipients 5 and 6.	Hepatitis noted day 12 post-transplant, followed by rash suggestive of cutaneous HSV on day 19. Subsequent resolution with antiviral therapy.	Asymptomatic	Asymptomatic	Asymptomatic	Asymptomatic
HSV viremia	Yes	Yes	No	No	Yes	Yes
HSV disease						
Cutaneous	No	Yes	No	No	No	No
Hepatitis	Yes	Yes	No	No	No	No
Disseminated	Yes	Yes	No	No	No	No
HSV or CMV prophylaxis	None administered. Normal protocol is to commence CMV prophylaxis day 7 post-transplant.	Valganciclovir	IV ganciclovir CMV hyperimmune globulin Valganciclovir	Valganciclovir	Valaciclovir	Ganciclovir
HSV treatment	None	Valacyclovir Acyclovir Valacyclovir	None	None	Aciclovir Ganciclovir Valganciclovir	Valaciclovir Ganciclovir

		Valganciclovir				
Duration of treatment	NA	28 days then CMV prophylaxis	CMV prophylaxis	CMV prophylaxis	26 days then CMV prophylaxis	14 days then CMV prophylaxis
Outcome	Died	Survived, no sequelae	Survived, no sequelae	Survived, no sequelae	Survived, no sequelae	Survived, no sequelae

AMI, acute myocardial infarction; CMV,cytomegalovirus; NA, not available.

Figure 1 – Initial transplantation and organ re-transplantation clusters in donor-derived herpes simplex-2 infection