Position Statement

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Human Herpesvirus-8 (HHV-8)

Summary

Human Herpesvirus-8 (HHV-8) is the underlying infectious cause of Kaposi's sarcoma (KS) and other proliferative diseases, namely Multicentric Castleman's disease (MCD) and Primary Effusion Lymphoma (PEL). It causes lifelong infection but unlike other herpesviruses, it is not ubiquitous. Transmission via blood transfusion has been described. The limited evidence available suggests that the current risk of HHV-8 transmission via blood transfusion in non-endemic countries is very low. Leucodepletion is likely to further reduce the risk of transmission through blood. Given the well documented and continued reports of transmission of HHV-8 through solid organ transplantation, with high impact on recipients, SaBTO have recommended screening of deceased organ donors in the UK. This is a very specific risk-benefit scenario that considers all the limitations of currently available virological tests and testing algorithms.

Background

HHV-8 is a large double-stranded DNA virus which is related to Epstein-Barr virus (EBV), both members of the gamma herpesvirus group. HHV-8 is classified as a group 1 biological carcinogenic agent, defined as having sufficient evidence to definitively establish a link to carcinogenicity in humans. HHV-8 is now recognised as the cause of several human tumours arising from distinct cell types, including KS and PEL, in individuals with human immunodeficiency virus (HIV) and almost all cases of MCD. It has also been implicated in the KSHV/HHV-8 inflammatory cytokine syndrome (KICS). Likelihood of developing disease is greatly increased among immunosuppressed individuals. There are significant geographical and subpopulation variations in the prevalence of HHV-8 infection and main mode of transmission varies according to local epidemiology. Seroprevalence in the UK is <5%. Immunisation is not currently available. Large, enveloped DNA viruses are reasonably susceptible to pathogen reduction methods and HHV-8 susceptibility to such methods should be no different to other herpes viruses.

Serological assays are commercially available, but their sensitivity and specificity vary greatly. They may be useful for epidemiological purposes, but careful validation of assays and testing algorithms are required before using them as diagnostic or screening tools.

HHV-8 is transmissible by sexual or intrafamilial contact, so there is potential for secondary transmission to close contacts of an infected recipient. There are reports of a higher prevalence of HHV-8 infections in injecting drug users compared to controls, consistent with an (inefficient) parenteral route of transmission. Vaginal contact is believed to be an inefficient transmission route.

Infection and viraemia

In the early stage of an acute infection, there is a high load of virus in both plasma and peripheral blood mononuclear cells (PBMCs). This is rapidly cleared and only reappears when immunosuppression and/or KS or other HHV-8 related diseases occur. The reappearance of detectable viraemia may precede the development of KS and other tumours by months or years. Early antibody is produced against viral structural proteins associated with lytic infection; thereafter, the antibody profile changes to a predominant response against latency associated nuclear antigens (LANA) and in the absence of viral reactivation, anti-LANA antibody titres may decline to levels that renders detection difficult.

HHV-8 shows a broad cellular tropism, but specific tropism for predominantly B cells among PBMCs. However, HHV-8 DNA is only reliably detectable in KS tissues and is usually only present in the peripheral blood of patients with extensive KS and other tumours. It is often undetectable by highly sensitive PCR in blood from asymptomatic individuals who are seropositive for anti-HHV-8.

Risk of HHV-8 transmission through substances of human origin (SoHO)

Results from historical cohorts suggest that the risk of HHV-8 transmission via blood transfusion in non-endemic countries, such as the UK, is likely to be low and HHV-8 DNA is not usually detected in blood of seropositive, asymptomatic, immunocompetent individuals. As the prevalence of HHV-8 infection in the UK is low (<5%), recipient susceptibility is high although studies (based on relatively small number of study subjects) have found no evidence for infection of recipients of red cells or platelets from seropositive donors. It is thought that storage of red blood cell components for up to 42 days at 4°C could reduce the likelihood of HHV-8 transmission. Such storage conditions are known to decrease the infectivity of other transfusion-transmissible herpesviruses, such as cytomegalovirus. Leucodepletion of blood products appears to be effective at removing low viral loads of cell-associated HHV-8. However, the theoretical risk of cell free viraemia in a recently infected donor who is asymptomatic at the time of donation remains, particularly via non-leucodepleted components, given the high cell-associated nature of HHV-8.

Development of KS has not been documented in patients who acquired HHV-8 through transfusion. However, symptomatic HHV-8 infection occurs in the setting of significant immunosuppression, and it may take years to manifest, hence length of follow up is important. Infection can occur without manifestation of symptoms, so seroconversion needs to be demonstrated on follow up.

Application of donor selection criteria (risk factors for HHV-8 overlap with those for sexually transmitted diseases) and routine universal leucodepletion of blood components should contribute significantly to an overall low risk of transmission via transfusion. Residual risk due to use of non-leucodepleted components (e.g. granulocytes) is currently unknown but expected to be low. Regarding the implementation of the For the Assessment of Individualised Risk (FAIR) donor selection policy from June 2021 in the UK; MSM can donate under FAIR if they have not had anal sex with new/multiple partners within 3-months and all other criteria apply. HHV-8 was considered in the FAIR review, and it was concluded that the current steps to mitigate risk of transmission were sufficient and that the risk of transmission was low.

As for blood, transmission through haematopoietic stem cell transfusion (HSCT) is also theoretically possible but given what is known about level and frequency of viraemia (except in primary infection), risk is still believed to be low. To date, there have been no reports of transmission. Given the low incidence of HHV-8 associated disease in HSCT recipients, the European Bone Marrow Transplant Society does not recommend routine serological screening and NAT monitoring of donors and recipients.

Transmission of infection via solid organ grafts has been well described. Several cases of donor-derived transmission have also been documented in the UK, including cases where the donor did not have detectable virus in blood by molecular tests. Post-transplant KS can develop in solid-organ transplant patients, following HHV-8 reactivation or a new infection. Alternatively, KS progenitor cells may seed after solid-organ transplantation, survive in the recipient host and undergo neoplastic transformation.

Given the well documented and continued reports of transmission of HHV-8 through solid organ transplantation, with high impact on recipients, SaBTO have recommended serological screening of deceased organ donors in the UK. For all other SoHO there is insufficient evidence to justify HHV-8 screening.

Considerations for tissue donation

Given the known transmission via organ transplantation, transmission via vascularised tissues that undergo processing with low-risk reduction for enveloped viruses is theoretically possible. To date, there have been no reports of transmission via any type of transplanted tissue. On this basis and as for the other SoHO (except solid organs), there is insufficient evidence to justify screening of tissue donors at this point. However, tissue donors who are also organ donors will be tested and in the event of a positive HHV-8 antibody result being generated, the following should be considered:

a) **When an organ donor tests positive for HHV-8 antibodies, tissues from this donor can be released for use in the following scenarios:**

- The tissue is avascular, making it unlikely that virus will be present in the tissue,
  and/or
- The tissue will undergo processing regarded as effective against enveloped DNA viruses such as HHV-8 (assessment by individual Tissue Establishments, according to local processing).

b) **When an organ donor tests positive for HHV-8 antibodies, tissues may be discarded as a precautionary safety measure or released for use after a risk assessment, in the following scenarios:**

- The tissue is vascularised,
  and/or
- Processing steps applied are not regarded as effective against enveloped DNA viruses such as HHV-8 (assessment by individual Tissue Establishments, according to local processing).

Assessment: The responsible officer authorising clinical release of tissues shall assess the clinical utility and need versus perceived or theoretical risk, given the valuable nature of some of these tissues. For example, when there is a need to size match a graft, where clinical requirement exceeds availability of suitable grafts (the graft will provide a high clinical benefit), and when there is no/short availability of suitable alternative allografts. The risk assessment will be specific to the individual tissue and process used by the Tissue Establishment, considering all available information including test results (serology and PCR), information on follow-up from organ recipients, and expert virology advice when needed.

c) When a transmission event has been documented, the fate of all tissues, cells and organs will be reviewed as per standard practice (investigation of Serious Adverse Events and Reactions, SAER):

- Vascularised tissues should be discarded. If already issued, recipient centre should be contacted according to standard SAER processes.

- Tissues not considered to hold a risk (non-vascularised and/or undergone effective processing) and still in stock, will not have to be discarded. If already issued, decision to inform transplant centre is at discretion of the responsible officer.

d) Release of tissue for research is permitted.

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