Short notes for clinicians

HHV-screening in deceased organ donation

These are short notes to assist communication with patients; the suggested follow up protocol for recipients is shown on the last page. Please feel free to contact us for further discussion, as required.

The virus

Human herpes virus type 8 (HHV-8) belongs to the Herpesviridae family of viruses; other members of this family include Herpes simplex, Varicella zoster and Cytomegalovirus. Once infection occurs, HHV-8 remains latent, and most people will never experience any symptoms. Under immunosuppression, HHV-8 can reactivate and lead to the development of symptoms, most commonly Kaposi's Sarcoma, a type of cancer that affects the skin and visceral organs. HHV-8 has also been linked to other conditions, such as primary effusion lymphoma, multicentric Castleman disease and Kaposi Sarcoma Inflammatory Cytokine Syndrome.

Epidemiology

Unlike the other related viruses mentioned above, which are very common in the general population, HHV-8 Infection is not very common in the UK. High endemicity areas such as sub-Saharan Africa may have seroprevalence rates greater than 50%. Some parts of the Mediterranean and Middle East are areas of intermediate prevalence, with 20-35% rates reported from Sicily, in Italy; other examples include Greece, Israel and Saudi Arabia. Non-endemic areas such as the USA and Western Europe report rates of 0 to 6%. In these regions, HHV-8 infection can be more commonly seen amongst men who have sex with men (MSM) and migrants from endemic regions. Where known, infection rates as high as 25-35% have been described among some MSM communities. Intravenous drug use is another route of transmission known to have gained significance in some non-endemic countries such as the USA. Seroprevalence data is lacking for many regions in the world.

Screening for evidence of infection

Antibody tests are required to detect asymptomatic infection, but they are not readily available, are not amenable to high throughput testing hence they have mostly been used for research and epidemiological purposes. There are very few commercially available tests and with variable performance, which must be used only in specific situations. Antibody tests have no role in the diagnosis of HHV-8 related illness, where tissue diagnosis and viral load measurements in blood must be used, depending on disease type.

Deceased organ donation and transplantation

Because the infection is uncommon in non-endemic countries such as the UK, diseases caused by HHV-8 are rarely seen in patients. In solid organ transplantation, a recipient can be affected by this virus if they already had the infection before receiving the transplant and the virus reactivates post-transplant, usually causing Kaposi Sarcoma of the skin or the mucosa. An organ recipient may also get infected after the transplant and remain without symptoms or develop KS. Where the infection comes from the donor organ i.e., primary infection derived

from the transplant, there is a possibility of more significant disease, as compared to reactivation of previously existing infection in a patient on standard immunosuppression, as we see with other herpesviruses. This is an observation, based on case series seen in the UK and abroad, where there is risk of bias because before the introduction of screening, we only came to know about transmission to recipients if they became ill and had a diagnosis of HHV-8 disease.

The exact determinants and rate of HHV-8 transmission to recipients of organs from infected donors are not known; limited data suggests that seroconversion rate in recipients of organs from seropositive donors may be in the order of 20 to 50% but many variables will influence the numbers quoted so caution is required when interpreting them. If the virus transmits, it may stay dormant or it may go on to cause symptoms in the recipient, in the form of Kaposi sarcoma or other forms of disease that can

affect the lymph nodes, the transplanted organ or other organs too. Non-neoplastic forms of HHV-8 disease such as Kaposi sarcoma inflammatory cytokine syndrome, KICS, may be diagnosed late hence it is hoped that knowledge of exposure to the virus is helpful.

Post-donation testing and recipient monitoring

At the present time, it is not advisable nor possible to test deceased donors before organ donation and transplantation have been completed. If an organ donor is screened for HHV-8 and is subsequently found to be antibody positive after transplantation, the recipient can be followed up virologically for evidence of acquisition of (donor-derived) infection, in the first place. Should transmission occur, virological and clinical monitoring may provide the means of improving patient outcomes by having low thresholds for investigating rapid increases in viral load or compatible disease presentation. On a case-by case, as it is similarly done for other opportunistic infections, changes to the immunosuppressive regimen can be considered and this is usually done in symptomatic disease; based on the experience with AIDS patients and limited experience in transplantation, therapeutic options are available, but the HHV-8 related disease type must be determined to allow selection of most appropriate approaches. It is also possible that the blood tests show signs of infection (e.g., low and stable viral load measurements in blood) with absence of symptoms. This process is akin to the monitoring of other viral infections such as CMV and EBV for example. An illustrative chart is available on the next page, as a guide to the virological testing proposed to detect a new infection.

If infection is demonstrated, patients should be made aware of relevant symptoms and how to examine their skin, which is part of the routine pre and post transplantation care. Regular monitoring and early detection of HHV-8-related symptoms can help prevent the development of serious complications. Symptomatic primary infection in SOT recipients can have features that overlap with other conditions; hence a high level of suspicion must be maintained. These can include fever, night sweats, lymphadenopathy, effusions, hepatosplenomegaly, cytopenia and a picture of acute systemic inflammatory illness that can be mistaken for severe sepsis.

Living donors and recipients

Decisions around introduction of new screening programs are complex and require a balanced approach between what is practically achievable (including test availability and resources), the

expected benefits and potential risks. In considering the current guidance on HHV-8 screening, the following must be taken into consideration:

Description of severe primary donor-derived infection come from our UK series and some clusters published from other non-endemic countries. These observations have so far been linked to deceased donation. Screening of potential living organ donors and candidate recipients for HHV-8 serological status prior to organ donation and transplantation needs to be considered by transplant programs. A risk-based assessment option for living donors and recipients can be considered in the appropriate context, based on transplant centre experience of HHV-8 disease and their donor and recipient epidemiology. For most centres, HHV-8-driven disease is extremely rare and when seen, it is mainly due to reactivation of pre-existing disease in the recipient, with largely non-fatal outcomes. Enhanced awareness of HHV-8 brought about by the introduction of testing in response to the severe outcomes seen in deceased organ donation should also inform future guidance for living donors and recipients.

SaBTO position statement on HHV-8 can be found here:
https://www.gov.uk/government/publications/sabto-virology-subcommittee-recommendations-on-kshv-infection

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May 2023, reviewed September 2023

SURVEILLANCE OF RECIPIENTS WHERE THE ORGAN DONOR TESTS POSITIVE FOR HHV-8 ANTIBODIES

Important disclaimer: in the absence of national or international consensus guidelines, this algorithm is based on current available knowledge extracted from the scientific literature, clinical experience in leading previous investigations and national and international expert opinion.

DONOR HHV-8 POSITIVE (ANTIBODY POSITIVE +/- DNA POSITIVE)

Recipient testing: This is an indicative plan; it may be adapted to coincide with other time points when patients are reviewed clinically and samples are routinely collected, or due to changes in immunosuppression or clinical status. Primary aim is to make an early diagnosis and minimize risk of severe disease which is more often seen in donor-derived infection.
Exclusion of HHV-8 in the presence of compatible signs and symptoms remains important, regardless of donor results.

RECIPIENT's BASELINE STATUS

Antibody POSITIVE = infection acquired before the transplant [#1]

Possibility of reactivation/reinfection
Clinical monitoring, low threshold for investigations
Assess case by case or devise local protocol

HHV-8 DNA measurements in relation to transplant date, for detection of reactivation /reinfection [#2] (modify according to intensity of immunosuppression and clinical status):

- Consider monitoring by PCR monthly for first six months post-transplant; clinical monitoring is most important, regardless of viral load.
- Consider continuation of PCR monitoring on a case by case, particularly during periods of significant increase in immunosuppression
- If viral DNA becomes detectable, trends in viral load and clinical correlation may be informative. Involve specialists.
- There is no evidence to support change in immunosuppression based on isolated, low level viral load in an otherwise well person.

Antibody NEGATIVE = susceptible to HHV-8 infection[#1]

Surveillance required, risk of primary infection

Frequency and duration to be determined depending on individual requirements. Illustrative plan with minimum time points shown below. Discuss.

HHV-8 antibodies[#3] and DNA measurements in relation to transplant date, for detection of 1ry infection (modify according to intensity of immunosuppression and clinical status). Virologists should be informed about sample referral for testing

- Monthly for the first 3 months (month 1, 2,3)
- Quarterly for the next 9 months (month 6, 9, 12)
- Seroconversion should be detected within 3months; disease usually apparent by 18 months post-transplant; onset of severe presentation usually observed within first 6months post-transplant. These are only indicative timepoints.
- Review monitoring during relevant clinical events (e.g. rejection, change in immunosuppression)
- High level of clinical suspicion for the development of all forms of HHV8–related syndromes
- If infection is demonstrated, confirm and intensify surveillance due to possibility of progression to disease within the first 6-9 months. Involve specialist (virologist/ID/oncologist/haematologist) at early stages.

[#1] In practice, where the first post-transplant sample is tested, a negative antibody result precludes the need to identify an archived pre-transplant sample
[#2] Most symptomatic reactivations reported within 3 years post-transplant, but this is variable
[#3] Antibodies can be added to samples taken at month 1,6,12 but monitoring for early and/or sustained viraemia is the most pragmatic tool.

PRECAUTIONARY SURVEILLANCE OF RECIPIENTS WHERE THE ORGAN DONOR HHV-8 ANTIBODY STATUS IS INDETERMINATE

Important disclaimer: in the absence of national or international consensus guidelines, this algorithm is based on current available knowledge extracted from the scientific literature, clinical experience in leading previous investigations and national and international expert opinion.

DONOR HHV-8 serostatus INDETERMINATE (DNA not detected)

Precautionary recipient testing: Less intense surveillance suggested, given the observed very low risk of transmission with this donor profile. This indicative plan may be adapted to coincide with time points when patients are reviewed clinically and samples are routinely collected, or due to changes in immunosuppression or clinical status. Exclusion of HHV-8 in the presence of compatible signs and symptoms remains important, regardless of donor results.

RECIPIENT's BASELINE STATUS[#2]

Antibody POSITIVE = infection acquired before the transplant

Possibility of reactivation/reinfection
Clinical monitoring, low threshold for investigations
Assess case by case or devise local protocol

HHV-8 DNA measurements in relation to transplant date, for detection of reactivation /reinfection (modify according to intensity of immunosuppression and clinical status):

- Consider monitoring by PCR monthly for first six months post-transplant; clinical monitoring is most important, regardless of viral load[#3]
- Consider continuation of PCR monitoring on a case by case, particularly during periods of significant increase in immunosuppression
- If viral DNA becomes detectable, observe trends in viral load and correlate clinically. Involve specialists
- There is no evidence to support change in immunosuppression based on isolated, low level viral load in an otherwise well person

Antibody NEGATIVE = susceptible to HHV-8 infection

Surveillance required, risk of primary infection

Frequency and duration to be determined by individual requirements. Illustrative plan with minimum time points shown below. Discuss.

HHV-8 antibody and DNA measurements in relation to transplant date, for detection of viraemia in the early stages of 1ry infection (modify according to intensity of immunosuppression and clinical status). Virologists should be informed about sample referral for testing

- Month 1,3 and 6 post transplantation
- Seroconversion should be detected within 3months; disease usually apparent by 18 months post-transplant; onset of presentation usually observed within first 6months post-transplant. These are only indicative timepoints based on observed cases.
- Review monitoring during relevant clinical events (e.g., rejection, change in immunosuppression), compatible signs and symptoms of neoplastic and non-neoplastic HHV-8 disease
- High level of clinical suspicion for the development of all forms of HH-8 disease, neoplastic and non-neoplastic. Tissue diagnosis required.
- If infection is demonstrated, confirm and intensify surveillance due to possibility of progression to disease within the first 6-9 months. Involve specialist (virologist/ID/oncologist/haematologist) at early stages, for a management plan.

[#1]Inconclusive serology can be seen in 1-2% of cases, mostly due to high background fluorescence or possible underlying auto-immune conditions, rendering interpretation difficult.
[#2] In practice, where the first post-transplant sample is tested, a negative antibody result precludes the need to identify an archived pre-transplant sample
[#3] Most symptomatic reactivations reported within 3 years post-transplant, but this is variable