18 | HUMAN HERPESVIRUS-8

18.1 | Disease agent

- Human herpesvirus 8 (HHV-8 or Kaposi's Sarcoma Herpesvirus, KSHV)

18.2 | Disease agent characteristics

- Family: *Herpesviridae*; Subfamily: *Gammaherpesvirinae*; Genus: *Rhadinovirus*.
- Virion morphology and size: Enveloped, icosadeltahedral nucleocapsid symmetry, spherical to pleomorphic virions, 120–200 nm in diameter.
- Nucleic acid: Circular in latent phase and linear in lytic phase, double-stranded DNA genome, ~170–210 kb in length.
- Physicochemical properties: Fragile particle that is sensitive to brief treatments with organic solvents, degradation by detergents, proteases, heating to 60°C, prolonged storage at temperatures of −10°C or above, and extremes of pH (<6.2 or >7.8).

18.3 | Disease name

- Kaposi's sarcoma (KS)
- Primary effusion lymphoma (PEL)
- Multicentric Castleman's disease (MCD)

18.4 | Priority level

- Scientific/Epidemiologic evidence regarding blood safety: Very low.
  - No cases of transfusion transmitted HHV-8 disease have been reported in the United States using paired donor-recipient samples, although transfusion transmission is plausible.
  - In countries with a high prevalence of HHV-8 (primarily sub-Saharan Africa) increased HHV-8 seroconversion has been associated with the transfusion of fresh, non-leukoreduced blood from HHV-8 seropositive donations.
- Public perception and/or regulatory concern regarding blood safety: Low.
- Public concern regarding disease agent: Very low.

18.5 | Background

- HHV-8 is an ancient human infection having entered human population in excess of 35,000 years ago.
- Identified/associated with human disease in 1994 in patients with AIDS-associated KS after epidemiological evidence suggested it was caused by a sexually transmitted viral pathogen.
- Diagnosis of HHV-8 mediated disease increased during the HIV epidemic, in association with cellular immune compromise.

18.6 | Common human exposure routes

- HHV-8 DNA has been detected in semen and female genital tract samples but is present in much higher concentrations in saliva. Sexual transmission is believed to be the result of oral or oral-genital transmission.
  - Sexual transmission has been associated with men having sex with men (MSM). Increased seropositivity is associated with sexual behaviors in males. However, heterosexual transmission is not considered to be an important route of transmission based on serological studies performed in the United States.
- HHV-8 seroprevalence in pediatric populations in endemic areas suggests that transmission occurs via salivary exchange. Transmission likely occurs within families, and infection is highest among children whose mother, first-degree relative, or next-older sibling is also seropositive.
- Parenteral transmission is suspected as seropositivity is increased among injection drug users; however, the relative importance of this route is unclear.
- Organ transplantation is associated with HHV-8 infection via reactivation of latent recipient infection, primary recipient infection from commonly recognized routes, or primary infection from an infected donor allograft.
  - In the US from January 2021–September 2025, 46 cases of suspected donor-derived KSHV-related complications were reported among transplant recipients, compared with nine during 2016–2020 (>400% increase). Most donors and recipients were HIV-negative, while 2/3 of the donors had a history of nonmedical inhalation or injection drug use. CDC concluded that "[I]n general, the benefits of transplantation outweigh the risk for infection, with donor-derived transmission occurring among fewer than 0.5% of all transplant recipients. The number of persons awaiting transplantation far exceeds the number of available organs. Organs from donors with risk factors for infectious diseases, including KSHV, may still be used safely (maintaining a high level of suspicion for KSHV infection by clinicians caring for organ transplant recipients could facilitate prompt diagnosis and reporting)", and screening the donor population could be useful to mitigate risks in

recipients.

18.7 | Likelihood of secondary transmission

- Person-to-person transmission (likely from saliva) is the major route of transmission in endemic populations.

18.8 | At-risk populations

- In countries with low HHV-8 seroprevalence, risk fac-tors associated with HHV-8 seropositivity are similar those associated with HBV and HCV, and HIV.
- Low socioeconomic status has been associated with higher rates of seropositivity. This risk may reflect crowded or less hygienic living conditions that has been shown to play a role in transmission of other oncogenic viruses. Pediatric populations (HHV-8 endemic areas)
- Organ transplant recipients.

18.9 | Vector and reservoir involved

- Human reservoir

18.10 | Blood phase

- HHV-8 may be found in peripheral blood mononuclear cells (PBMCs) of 35%–75% of patients with KS and less frequently in asymptomatic populations.
- The virus is highly cell-associated and has not been readily identified as free virus in plasma except in immunosuppressed HIV-infected patients.

18.11 | Survival/persistence in blood products

- Survival of the virus in blood components has not been formally assessed.
- Among African children who received transfusion, transfusion transmission was significantly associated with use of blood <4 days old compared with older units.

18.12 | Transmission by blood transfusion

- Linked donor-recipient samples from the US Transfusion Safety Study (TSS) repository and the Jamaica Transfusion Study Repository found no evidence of transfusion transmission in 32 recipients of components from HHV-8 seropositive donations.
- Evaluation of samples from the US Frequency of Agents Communicable by Transfusion Study (FACTS) repository demonstrated 2 of 284 cardiac surgery patients who received blood transfusions developed HHV-8 seroconversion within 6 months following surgery.
- Evaluation of linked donor-recipient blood samples from the US Transfusion Transmitted Virus Study (TTVS) failed to demonstrate a difference in seroconversion rates between transfused and non-transfused surgical control patients.
- HHV-8 DNA was not detected using a sensitive PCR assay in B-cell samples from 684 US blood donations, including 40 HHV-8 seropositive donations.
- A study of pediatric transfusion recipients in Uganda demonstrated increased rates of HHV-8 seroconversion following transfusion of fresh (<4 days old), non-leukoreduced blood from seropositive donors com-pared with seronegative donors.
- Other studies performed in highly endemic popula-tions suggest transmission (HHV-8 seroconversion) in association with transfusion of non-leukoreduced products.

18.13 | Cases/frequency in population

- Geographic seroprevalence estimates may be impre-cise, due to variations in the performance characteris-tics of the available HHV-8 serologic assays, and the lack of a gold standard. Globally, regions are categorized into 3 groups based on seroprevalence: low HHV-8 seroprevalence (<5%; North America, much of Europe, and Asia) intermediate seroprevalence (5%–20%; the Mediterranean, Eastern Europe, Caribbean, and Middle East), and high seroprева-lence (>50% including much of Africa and regions of the Brazilian Amazon).
- The most comprehensive study of US blood donors reported seropositivity of 3%–3.5%, based on concor-dance of at least two antibody assays.
- The Third National Health and Nutrition Examina-tion Survey 1988–1994 estimated seroprevalence in the United States general population of 1.5%–7.4%. Seroprevalence was similar in men and women and was higher in groups whose demographic profiles were suggestive of poorer socioeconomic

conditions.

- Antibody prevalence of 10%–25% in MSM without HIV and 30%–60% in MSM with HIV have been reported.
- In endemic areas, seropositivity rates begin increasing at age 2 and rise until puberty.

18.14 | Incubation period

- Unknown

18.15 | Likelihood of clinical disease

- Most infections, in otherwise healthy hosts, are asymptomatic.
  - Rarely primary infection has been reported to include rash, arthralgia and lymphadenopathy in immunocompetent hosts, or splenomegaly and marrow failure in immunocompromised individuals.
- Reactivation disease occurs in the setting of HIV infection or immunosuppression (as in transplant recipients and the aged) and occurs years after infection.

18.16 | Primary disease symptoms

- Usually none, but an acute viral syndrome can occur in immunocompetent hosts
- HHV-8 identified as causative agent of all forms of KS:
  - HIV-related;
  - classical (old men in the Mediterranean);
  - endemic (Africa); and
  - iatrogenic (post-transplant).
- Lymphoproliferative disorders of B cells in people with AIDS including primary effusion lymphoma (PEL) and Multicentric Castleman's disease (MCD) represent therapeutic challenges; several immune mediators appear to contribute to the growth, survival and spread of both.

18.17 | Severity of clinical disease

- KS, PEL, and MCD are all severe.

18.18 | Mortality

- High in PEL and MCD
- KS in AIDS patients will respond both to highly active antiretroviral therapy and specific treatment for the tumor(s).
- An observational cohort study composed primarily of pediatric transfusion recipients in Uganda reported that recipients of short-stored (≤4 days) HHV-8 seropositive blood had a higher rate of mortality within 1 week to 6 months of transfusion when compared to recipients of seropositive blood that had been stored longer (≥4 days), or seronegative blood, although cause of death data were not available.

18.19 | Chronic carriage

- Chronic (latent) infection is characteristic, but viremia is rarely detectable by NAT in healthy individuals, including blood donors.

18.20 | Treatment available/efficacious

- No direct treatment of HHV-8 infection is available, but mitigation of the underlying immunosuppression in patients with HIV-related KS (using antiretrovirals) or post-transplant KS (by stopping immunosuppressive drugs) may lead to KS regression.
- A variety of chemotherapy regimens and radiation are used for local control and palliation of advanced KS.

18.21 | Agent-specific screening question(s)

- There is no specific question to assess HHV-8 risk.
- Questions regarding MSM activity and injection drug use identify subpopulations associated with increased seropositivity when compared to the general population.
  - FDA guidance (May 2023) replaced the MSM question by an individual behavioral assessment.

18.22 | Laboratory test(s) available

- No FDA-licensed blood donor screening test exists.
- Multiple research EIA and IFA antibody assays to multiple antigens have been developed. However, poor agreement has been documented among and between laboratories, particularly when used on low-risk populations.
- PCR tests applied to PBMC or to serum/plasma have been used in research settings. However, most antibody-positive blood donors are negative for HHV-8 DNA in PBMC.

18.23 | Currently recommended donor deferral period

- No FDA Guidance or AABB Standard exists although injection drug use and some sexual practices are causes for deferral

18.24 | Impact on blood availability

- Agent-specific screening question(s): Not applicable.

18.25 | Laboratory test(s) available

- Low prevalence areas:
  - Antibody testing could defer more than 3.5% of current US blood donors.
  - The impact of NAT on donor deferral would be expected to be negligible.
- High prevalence areas:
  - The impact of serologic testing for HHV-8 on blood availability could be substantial, with deferrals for greater than 40% of potential donors depending on the region of the world and the serologic assay used.
  - Nucleic acid testing could also be substantial as DNA has been detected in 5%–20% of donors from some regions in Africa.

18.26 | Impact on blood safety

- Agent-specific screening question(s): Not applicable
- Laboratory test(s) available: Uncertain as clinically significant HHV-8 disease arising from transfusion has not been documented.

18.27 | Leukoreduction efficacy

- HHV-8 is highly cell-associated in PBMC, and leukoreduction would be expected to be effective (as is the case with cytomegalovirus); however, specific studies of HHV-8 and the efficacy of leukoreduction have not been reported.

18.28 | Pathogen reduction efficacy for plasma derivatives

- No specific data are available for this virus, but fractionation and inactivation techniques in use for plasma derivatives should be robust. Additionally, the risk in these products should be relatively low for highly cell-associated viruses.

18.29 | Other prevention measures

- None

SUGGESTED READING

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