16 | HERPES VIRUSES (OTHER THAN CMV, EBV, AND HHV-8)

16.1 | Disease agent

- Herpes simplex viruses 1 and 2 (HSV-1, 2)
- Varicella-zoster virus (VZV)
- Human herpesviruses-6A/B, and 7 (HHV-6A/B,7)

16.2 | Disease agent characteristics

- Family: *Herpesviridae*; Subfamilies: *Alphaherpesvirinae* (HSV-1, 2; VZV), *Betaherpesvirinae* (HHV-6A/B, 7); Genus: *Simplexvirus* (HSV-1, 2); *Varicellovirus* (VZV); *Roseolovirus* (HHV-6A/B, 7).
- Virion morphology and size: Enveloped; icosadeltahedral nucleocapsid symmetry, spherical to pleomorphic particles, 160-200 nm in diameter. Between the capsid and the envelope is an amorphous layer of proteins termed the tegument.
  - HHV-6 was reclassified into distinct species, HHV-6A and HHV-6B. Currently available serologic assays do not distinguish between the two viruses. The term HHV-6 collectively refers to both species.
- Nucleic acid: Linear, double-stranded DNA about 125–170 kb in length.
- Physicochemical properties: Nonionic detergents solubilize the envelope; virus stable when frozen, especially at −80°C or below; virus inactivated by UV light, gamma-irradiation, standard disinfectants, and heating. Herpes viruses do not, in general, survive for long periods outside the host.

16.3 | Disease name

- Multiple, including oropharyngeal and genital herpes (HSV-1,2); chickenpox, herpes zoster, or shingles (all caused by VZV); and exanthem subitum, roseola infantum, or sixth disease (HHV-6A/B,7)

16.4 | Priority level

- Scientific/Epidemiologic evidence regarding blood safety: Theoretical
- Public perception and/or regulatory concern regarding blood safety: Absent
- Public concern regarding disease agent: Absent

16.5 | Background

- Primary herpesvirus infections are followed by subsequent lifelong latency; thus, the potential for reactivation syndromes in both healthy and immunocompromised hosts exists.
  - HSV-1,2 and VZV are latent in nerve cells after primary infection.
  - HHV-6A/B and HHV-7 are latent in lymphocytes after primary infection. There has been a marked decrease in the incidence of primary VZV (chickenpox) following the implementation of immunization programs. Single dose vaccination for children 12–18 months was recommended in the United States in 1996 with the goal of universal vaccination and was modified to two doses in 2006.
- Data from the National Health and Nutrition Examination Survey demonstrate that the seroprevalence of HSV-1, and to a lesser degree HSV-2, have declined modestly in the United States over the past 2 decades, with the decline most pronounced in pediatric populations. Racial and ethnic disparities are persistent.
- The seroprevalence of HHV-6A/B and 7 are reported to be high in developing countries.
- Seroconversion occurs early in life between 6 months and 2 years of age (HHV-6A/B).

16.6 | Common human exposure routes

- Contact with infected human secretions (saliva, semen) most common; aerosols also possible.

16.7 | Likelihood of secondary transmission

- Moderate

16.8 | At-risk populations

- All populations are at risk for infection for most of these agents. Seroprevalence rates are fairly high in developed countries (VZV, HSV-1, HHV-6A/B and HHV-7), with seroconversion often occurring in childhood.
- Typically, greater risk of disease in immunocompromised hosts is seen in patients following bone marrow or solid organ transplantation.

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16.9 | Vector and reservoir involved

- Infected humans

16.10 | Blood phase

- HSV and VZV viremia in symptomatic neonates and immunocompromised hosts is well described.
- Viremia in immunocompetent hosts occurs with both primary, and to a lesser extent, reactivated HSV and VZV infection, although for short intervals and at relatively low levels.
- HHV-6A/B, 7 circulates as latent virus in lymphocytes over the long-term (lifelong) with the potential for reactivation later in life in association with immunosuppression.

16.11 | Survival/persistence in blood products

- Unknown

16.12 | Transmission by blood transfusion

- While the lymphocyte association of HHV-6A/B,7 suggests the possibility of transfusion transmission, well documented case reports or series are not available.
  - Case reports of HHV-6 transmission by peripheral blood stem cells have used molecular methods to detect integrated donor HHV-6 DNA in the chromosomes of engrafted donor cells. This appears to be transmission of virus associated with latent infection rather than of active infection.
  - Furthermore, transplant recipients may reactivate preexisting HHV-6 infection, thereby confounding the evaluation of potential transfusion transmission.
- Although viremia occurs during both primary and reactivation infections with HSV and VZV, transmission by blood has never been reported for HSV-1, HSV-2, or VZV. A case report described the detection of VZV DNA in an aliquot of plasma from an interdicted blood donation, following a donor with self-reported VZV infection.

16.13 | Cases/frequency in population

- HSV seroprevalence is 50%–90% globally, increasing with age; US population: 40%–60% HSV-1; 7%–22% HSV-2
- VZV: 98% seropositive (US Population)
- HHV-6A/B: >90% seropositive in developed countries
  - Current serologic assays do not discriminate between HHV-6A and HHV-6B.
- HHV-7: 70%–90% seropositive

16.14 | Incubation period (primary infection)

- HSV-1,2: 2–12 days
- VZV: 10–21 days
- HHV-6A/B,7: 5–15 days

16.15 | Likelihood of clinical disease

- HSV: Mucocutaneous disease (orolabial and genital herpes) common. Severe disease is rare in immunocompetent hosts, but, if it occurs, it can be deadly (e.g., severe encephalitis).
- VZV: chickenpox was previously very common (approximately 4 million cases/year in the United States before recommendations for universal childhood vaccination), but rates have fallen by as much as 90% in some communities and will continue to decline.
- Herpes zoster due to reactivation of latent virus increases after age 60 years in unvaccinated individuals with lifetime risk ∼50% among persons who survive to 85 years (1.7 cases/1000 population in the United States).
  - Immunization to protect against zoster/shingles is recommended by CDC for adults over 50 or with immunocompromising conditions.
- HHV-6A/B,7: High in children; prevalent in febrile children if sought.

16.16 | Primary disease symptoms

- HSV-1 and -2
  - Gingivostomatitis and orolabial ulcers (cold sores) historically associated primarily with HSV-1.
  - Genital herpes historically associated primarily with HSV-2.
  - Aseptic meningitis (sometimes recurrent).
  - Encephalitis and disseminated infections seen in neonates and immunocompromised hosts.
- VZV
  - Disseminated rash (chickenpox) and dermatomal rash.
  - Widespread visceral dissemination in immunocompromised hosts.

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- HHV-6A/B,7
  - Exanthem subitum (or roseola infantum) is a very common self-limited, benign childhood rash. Nonspecific febrile illness is also frequently observed.
  - HHV-6 and 7 have been associated with more serious acute and chronic conditions in both immunocompetent and immunocompromised adults; however, causality has never been established. This may be especially difficult to ascertain given relative viral ubiquity, and chronicity. Active, symptomatic infection in immunocompetent hosts is generally associated with primary infection, while reactivations or exogenous reinfections are asymptomatic.
  - Reactivation of latent HHV-6A/B,7 in immunocompromised hosts can result in disseminated infection of multiple organs and is associated with poor clinical outcomes, especially in recipients of hematopoietic transplantation.

16.17 | Severity of clinical disease

- Primary infections in immunocompetent hosts are generally self-limited with full recovery.
  - Reactivation of latent infections with HSV-1 and 2 causes self-limited illness.
  - Reactivation of VZV as shingles generally heals with few sequelae but can cause relatively severe disability because of postherpetic neuralgia.
  - HHV-6A/B,7 infections in children are usually benign.
- Primary infection or reactivation of any of these viruses in an immunocompromised host can cause severe disease.

16.18 | Mortality

- Rare, except in immunocompromised patients

16.19 | Chronic carriage

- Yes; lifetime latency is typical of herpesviruses.

16.20 | Treatment available/efficacious

- There are a variety of nucleoside analog drugs used to treat herpes virus infections, including acyclovir, famciclovir, valacyclovir, ganciclovir and valganciclovir, cidofovir, and foscarnet. All of these drugs suffer from the selection of resistant mutants. As with HSV, acyclovir (or other nucleoside analogs) can be useful, particularly in preventing VZV disease. Varicella immunoglobulin also can be used. Unlike HSV-1 and 2, and VZV, there are no drugs proven effective for HHV-6A/B or 7, although there is uncontrolled evidence and *in vitro* data suggesting that several of the above drugs have activity for HHV-6 infections.

16.21 | Agent-specific screening question(s)

- No specific question is in use.
- Not indicated because transfusion transmission has not been definitively demonstrated
- No sensitive or specific question is feasible. Most infections are acquired during childhood, and the prevalence of latent infections is so high as to make questions impractical.

16.22 | Laboratory test(s) available

- No FDA-licensed blood donor screening test exists.
- Serology, NAT, and cultivation of viruses

16.23 | Currently recommended donor deferral period

- No FDA Guidance or AABB Standard exists.
- Persons with symptomatic primary genital or orolabial HSV may not feel well on the day of donation and would often be deferred.
- Deferral practices for recurrent HSV infection, if reported by the donor, vary by collection facility.
- Prudent practice would be to defer prospective donors with primary (chickenpox) or recurrent (shingles/zoster) VSV infection until signs and symptoms are gone.

16.24 | Impact on blood availability

- Agent-specific screening question(s): Not applicable
- Laboratory test(s) available: Not applicable

16.25 | Impact on blood safety

- Agent-specific screening question(s): Not applicable
- Laboratory test(s) available: Not applicable

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16.26 | Leukoreduction efficacy

- Viruses that have a blood phase (esp. HHV-6A/B,7) are typically present within WBCs; therefore, leukoreduction is likely to be effective by analogy to human cytomegalovirus. However, cell-free virus also has been detected in cases of primary infection in children.

16.27 | Pathogen reduction efficacy for plasma derivatives

- No specific data are available for these viruses, but because these viruses are lipid-enveloped and relatively labile, fractionation and associated inactivation techniques should be robust.

16.28 | Other prevention measures

- None

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