Microbiology

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Herpesviruses

- **Introduction**
  - Herpes viruses are leading cause of human viral diseases, second only to influenza and cold viruses.
  - Key Property**:** Ability to establish lifelong persistent infections in hosts and undergo periodic reactivation.
  - Reactivation is more likely during periods of immunosuppression and in the elderly.
  - All herpesviruses share identical morphology under electron microscopy.

- **Herpesviruses Classification:**
  1. Alpha Herpesviruses
     - ✓ Fast-growing, cytolytic, establish latent infections in neurons.
     - ✓ Members: HSV-1, HSV-2, VZV.
  2. Beta Herpesviruses
     - ✓ Slow growing, cytomegalic, latent in secretory glands and kidneys.
     - ✓ Members: CMV, HHV-6, HHV-7.
  3. Gamma Herpesviruses
     - ✓ Variable, lymphoproliferative, latent in lymphoid cells.
     - ✓ Members: EBV, HHV-8.

- **General Properties of Herpesviruses:**
  - Virion**:** Spherical, 150-200 nm in diameter (icosahedral).
  - Genome**:** Double-stranded DNA, linear, 125-240 kbp, with reiterated sequences.
  - Proteins**:** More than 35 proteins in virion.
  - Envelope**:** Contains viral glycoproteins and Fc receptors.
  - Replication**:** Occurs in the nucleus, buds from the nuclear membrane.
  - Outstanding Characteristics**:**
    - ✓ Encode many enzymes.
    - ✓ Establish latent infections.
    - ✓ Persist indefinitely in infected hosts.
    - ✓ Frequently reactivated in immunosuppressed hosts.
    - ✓ Some cause cancer.

- **Replication Process:**
  1. α-Proteins: Products of immediate-early genes, stimulate transcription of early genes.
  2. β-Proteins: Products of early genes, function in DNA replication, yielding concatemeric DNA.
  3. γ-Proteins: Products of late genes, primarily viral structural proteins, participate in virion assembly.

- **Important Clinical Viruses:**
  - HSV-1, HSV-2, EBV, CMV, VZV, HHV-6, HHV-8.

  1. **Herpes Simplex Viruses (HSV)**
     - ✓ Properties**:**
       - Belong to the alpha herpesvirus subfamily.
       - HSV-1 and HSV-2 infect epithelial cells and establish latent infections in neurons.
       - HSV-1: Associated with oropharyngeal lesions (above the belt).
       - HSV-2: Associated with genital infections (below the belt), though anatomical specificity is diminishing.

- ✓ Transmission:
  - HSV-1: Spread by contact with infected saliva.
  - HSV-2: Transmitted sexually.

- ✓ Genome Homology: HSV-1 and HSV-2 share 50-70% homology and several cross-reactive epitopes.

- ✓ Epidemiology:
  - Spread: Via contact, as the virus is shed in saliva, tears, genital and other secretions.
  - Infection Peaks: First peak at 0-5 years, second peak during late teens with sexual activity.
  - Genital HSV: 10% of the population acquires HSV via the genital route, with the risk concentrated in young adulthood.
  - Recurrence: 45% of orally infected individuals and 60% of genital herpes patients experience recurrences.

- ✓ Pathogenesis and Pathology:
  - Cytolytic Infections: Necrosis of infected cells and inflammation.
  - Primary Infection: Virus spreads locally, with short-lived viremia.
  - Latency: The virus resides in ganglia (trigeminal or sacral) in a nonreplicating state and persists for life.
  - Reactivation: Triggered by stress, infection, fever, or UV sunlight.

- ✓ Clinical Manifestations:
  - Acute Gingivostomatitis: Common in primary herpetic infection; painful bleeding gums, ulcers, fever.
  - Herpes Labialis (Cold Sore): Reactivation of oral HSV after primary infection; prodrome of tingling and itching.
  - Ocular Herpes: Severe keratoconjunctivitis, recurrent lesions may cause permanent blindness.
  - Genital Herpes (HSV-2): Painful vesiculoulcerative lesions, fever, malaise, dysuria, inguinal lymphadenopathy.
  - Herpes Simplex Encephalitis:
    - Neonatal form: Global brain involvement, nearly 100% mortality.
    - Focal disease: Temporal lobe involvement, high mortality without treatment.

- ✓ Laboratory Diagnosis:
  - Direct Detection:
    - Electron microscopy, immunofluorescence, PCR for herpes simplex encephalitis.
  - Virus Isolation: HSV-1 and HSV-2 are easy to culture (1-5 days for results).
  - Serology: Not useful in the acute phase.
  - Cytopathology: Multinucleated giant cells, ballooning of cells.

- ✓ Management and Prevention:
  - Indications for Antiviral Therapy:
    - Severe primary infection, dissemination, sight threatened, encephalitis.
    - **Drug of Choice**: Acyclovir.
  - Prevention: Avoid contact with lesions (asymptomatic shedding possible), safe sexual practices, Cesarean section for infected mothers.

2. Varicella-Zoster Virus (VZV)

✓ Epidemiology:

- Primary Varicella (Chickenpox): Endemic, with highest prevalence in children aged 4-10 years.
- Transmission: Highly communicable, 90% attack rate in close contacts.

✓ Pathogenesis:

- Entry: Via the respiratory tract, spreads to the lymphoid system.
- Latency: Virus remains latent in cerebral or posterior root ganglia.
- Reactivation: 10-20% may experience recurrent infections (Shingles).

✓ Clinical Manifestations:

- Varicella (Chickenpox):
  - Incubation period: 14-21 days.
  - Fever, lymphadenopathy, widespread vesicular rash.
  - Rash progresses in stages (macules, papules, vesicles, crusts).
  - Diagnosis based on clinical features.
  - Rare complications: Pneumonia, encephalitis, hemorrhagic chickenpox.
- Herpes Zoster (Shingles):
  - Typically affects a single dermatome.
  - Characterized by pain and vesicular eruption in the dermatome.
  - Complications: Postherpetic neuralgia, eye and facial involvement, disseminated herpes zoster in immunocompromised.

✓ Laboratory Diagnosis:

- Virus Isolation: Rarely performed (2-3 days for results).
- Direct Detection: Electron microscopy, immunofluorescence, PCR.
- Serology: IgM (recent infection), IgG (past infection).
- Cytopathology: Multinucleated giant cells.

✓ Management and Prevention:

- Uncomplicated Varicella: Self-limiting, acyclovir can speed recovery.
- Immunocompromised Patients: Acyclovir recommended.
- Vaccine: Live attenuated vaccine available for prevention.
- Zoster Immunoglobulin (ZIG): Used for urgent protection, especially in immunocompromised individuals.

3. Cytomegalovirus (CMV)

✓ Epidemiology:

- Transmission: Vertically (in utero), perinatally (via genital secretions or breast milk), postnatally (saliva, sexual contact, blood, organ transplants).
- Infection: Worldwide prevalence, with high infection rates in developed (40% in adolescents) and developing countries (90%+ by adulthood).

✓ Clinical Manifestations:
- Congenital Infection: May cause cytomegalic inclusion disease, leading to mental handicap (second most common cause after Down's syndrome).
- Perinatal Infection: Usually asymptomatic.
- Postnatal Infection: Usually asymptomatic; may cause infectious mononucleosis with fever, lymphadenopathy, and splenomegaly.
- Immunocompromised Patients: Severe CMV disease such as pneumonitis, retinitis, colitis, encephalopathy.

✓ Laboratory Diagnosis:
- Direct Detection: Biopsy specimens examined for CMV inclusion antibodies/antigens.
- Virus Isolation: Conventional culture (4 weeks), rapid methods (DEAFF test) provide results in 24-48 hours.
- Serology: IgM indicates primary infection, IgG indicates past infection.
- PCR: CMV-DNA detection.

✓ Treatment:
- Congenital Infection: Diagnosed in symptomatic mothers; abortion may be offered.
- Immunocompromised Patients: Prompt antiviral therapy is crucial.
- No licensed vaccine available.

4. Epstein-Barr Virus (EBV)

✓ Epidemiology:
- Transmission: Through saliva, often via kissing.
- Infection Peaks:
  - In developed countries: Ages 1-6 and 14-20.
  - In developing countries: By age 2, 90% are seropositive.

✓ Pathogenesis and Diseases:
- Carrier State: Lifelong, low-grade replication.
- Immortalization: EBV can immortalize B-lymphocytes in vitro and in vivo.
- Diseases:
  - Infectious mononucleosis.
  - Burkitt's lymphoma.
  - Nasopharyngeal carcinoma.
  - Lymphoproliferative diseases in immunosuppressed.

✓ Clinical Manifestations:
- Infectious Mononucleosis: Fever, lymphadenopathy, splen

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