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КАФЕДРА ДЕТСКИХ ИНФЕКЦИОННЫХ БОЛЕЗНЕЙ
С КУРСОМ ПОВЫШЕНИЯ КВАЛИФИКАЦИИ И ПЕРЕПОДГОТОВКИ

**О. В. Симаченко, Е. В. Дивакова**

# ИНФЕКЦИИ, ВЫЗВАННЫЕ ГЕРПЕС-ВИРУСАМИ У ДЕТЕЙ

# HERPESVIRUS INFECTIONS IN CHILDREN

Учебно-методическое пособие

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На английском языке

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## ABBREVIATIONS

1° — primary
2° — secondary
CNS — central nervous system
CSF — cerebrospinal fluid
EBV — Epstein–Barr virus
EIA — enzyme immunoassays
FBC — full blood count
HHV — human herpesvirus
HIV — human immunodeficiency virus
HSE — herpes simplex encephalitis
HSV — herpes simplex virus
HSVI — herpes simplex virus infection
HV — herpesviruses
HVI — herpesvirus infection
IgG — immunoglobulin G
IgM — immunoglobulin M
IM — infectious mononucleosis
IV — intravenous
IVIG — intravenous immunoglobulin
KICS — Kaposi sarcoma inflammatory cytokine syndrome
KS — Kaposi sarcoma
MCD — multicentric Castleman disease
PCR — polymerase chain reaction
SEM — skin-eye-mouth disease
SNHL — sensorineural hearing loss
VZIG — varicella-zoster immunoglobulin
VZV — varicella-zoster virus

## MOTIVATIONAL CHARACTERISTICS OF THE THEME

**Total in-class hours:** 6.

Herpesviruses (HV) are widespread in the human population. Currently, HV is strictly classified and combined into a large family Herpesviridae, including more than 100 representatives. Pathogenic for human are eight HV. Polymorphism

of the clinical manifestations of herpesvirus infection (HVI) is due to several factors, among them — the type and pathogenicity of the virus, age, premorbid background of the patient, the state of immunological reactivity and others. Some biological properties of HV (a long persistence in the ganglion cells of the central or peripheral nervous system, the ability to repeatedly re-infected with new strains, while active or latent coexistence of several types and strains of the virus, the likelihood of reactivation of infection in case of violation of dynamic equilibrium with the immune homeostasis, etc.) make serious problem in the fight against this disease. Most HV refers to opportunistic infections: they are clinically manifested in conditions of immunodeficiency. The manifestation of HVI, in turn, has an immunosuppressive effect, which creates prerequisites for the subsequent reactivation of latent infection and its possible expansion. All this makes it necessary to study the clinical, diagnostic and therapeutic tactics at HVI, especially in children.

**The objective of the lesson.** To study the pathogenesis, clinical features of symptomatology of infections caused by HV in children based on epidemiological and laboratory data, to master the methods of quality diagnosis and treatment of patients with HVI, as well as the organization of preventive and anti-epidemic measures in the focus of infection.

**Class tasks.** *The student should know:*

– aetiology, classification, pathogenesis of HVI in children;

– the main clinical form of HVI caused by the herpes simplex virus (HSV) in childhood (HSVI);

– clinical manifestations of HVI in children for each nosology;

– peculiarities of HVI in young children;

– clinical and epidemiological indications for hospitalization of children with HVI;

– specific laboratory diagnosis and differential diagnosis of HVI;

– main complications and outcomes of HVI in children;

– principles of treatment of patients with different clinical forms of HVI: etiological treatment, pathogenetic therapy, symptomatic therapy HSVI, varicella, herpes zoster, infectious mononucleosis (IM), cytomegalovirus (CMV), sudden exanthema in children;

– principles and methods of prevention of various forms of HVI in children.

*The student should be able to:*

– collect complaints, medical history and life in various forms of HVI;

– make epidemiological analysis of the HVI;

– carry out systematic clinical examination of a child with various forms of HVI;

– establish a preliminary (working) diagnosis;

– make a plan for examination of a child with various forms of HVI;

– determine the necessity or compulsory for hospitalization of a child with HVI;

– perform the differential diagnosis of chickenpox, herpes zoster with other diseases associated with vesicular rash;

– perform the differential diagnosis of diseases that occur with clinic of mononucleosis syndrome;

– evaluate the results of the laboratory (clinical, serological, biochemical, immunological, etc.) and instrumental examinations (ultrasound examination, X-ray, etc.);

– draw the medical documentation at HVI in children on the stages of identification, treatment and dispensary observation;

– organize the preventive measures in the focus of infection.

*The student should master the skills:*

– to estimate the epidemic situation and to develop preventive measures for HSVI, IM, sudden exanthema in children;

– to make anti-epidemic measures of varicella, herpes zoster in children with the development plan, including the definition of the indications for isolation, hospitalization, establishing quarantine, monitoring of contact persons;

– to master the complex argumentation of the final diagnosis of each form of HVI;

– to make a plan of treatment with consideration the clinical form, disease severity, time of disease, characteristics of the course and age;

– to organize vaccinations in children with varicella and HSVI.

**Requirements to initial level of knowledge.** Revise:

– Human anatomy: anatomical and morphological structure of the skin, mucous membranes, tonsils, salivary glands, lymphatic system, central nervous system in children;

– Microbiology, virology and immunology: properties of HV, bases of formation of immunity;

– Clinical pathological physiology: mechanisms of occurrence, development and outcome of pathological processes, the most common diseases, a pathogenetic substantiation of principles of their diagnosis, treatment, prevention, principles of formulating of a diagnosis;

– Neurology and neurosurgery: methods of examination in neurology and neurosurgery.

**Questions for self-control from related disciplines:**

1. Give a description and name the basic properties of viruses of the Herpesviridae family.

2. What are the primary and secondary elements of the rash you know? Give them a description.

3. What are the pathological changes in the skin and mucous membranes in various infectious rashes?

4. Which organs and tissues have ectodermal origin?

5. What material is sent to a laboratory for virological and serological studies?

**Control questions of the lesson:**

1. Give a description of HV — I, II, III, IV, V, VI, VII, VIII types. What diseases do they cause?

2. Describe the epidemiological aspects of infections caused by HSV: the source of infection, the mechanism and routes of transmission, the index of contagiousness.

3. Describe the clinical picture in different forms HSVI.

4. Who of children can have eczema herpeticum?

5. Describe the clinical manifestations of herpes encephalitis in children?

6. What are the principles of treatment HSVI depending on the clinical form and localization of the pathological process?

7. Describe the epidemiological aspects of varicella: the source of infection, the mechanism and routes of transmission, the index of contagiousness.

8. Describe the main clinical symptoms of varicella.

9. What are the main methods of diagnosis of different clinical forms of HSVI and varicella?

10. What is herpes zoster?

11. What complications of varicella and HSVI do you know? What is the time of their occurrence?

12. What are the features of post-varicella encephalitis?

13. What are the indications for hospitalization and principles of treatment HSVI and varicella?

14. What methods of prevention of varicella and HSVI do you know?

15. Describe the etiological factors and links of the epidemiological process of IM.

16. Describe the etiological factors and links of the epidemiological process of CMV infection.

17. Describe the etiological factors and links of the epidemiological process of roseola.

18. Describe the main clinical symptoms of IM.

19. Describe the main clinical symptoms of congenital and acquired CMV infection.

20. What are the supporting symptoms of diseases caused by HV — VI, VII, VIII types?

21. What are the characteristic changes in the peripheral blood of IM?

22. What serological tests are used to diagnose HVI?

23. What are the principles of treatment of children with IM?

24. What is the management of patients with congenital and acquired CMV infection?

25. What are the principles of treatment of children with roseola?

26. What are the anti-epidemic and preventive measures of IM, CMV infection, roseola?

## OVERVIEW

The Herpesviridae is a large family of double-stranded DNA viruses that cause disease in humans and their livestock. They are large in size, varying from 120 to 260 nm and have a relatively complex structure. There are more than 130 viruses classified as *Herpesviridae,* with species that infect mammals, birds, fish, reptiles, amphibians, or even molluscs.

*Herpesviridae* are classified into three subfamilies:

– Alphaherpesvirinae, include HSV-1 and HSV-2 (also known as human herpesvirus (HHV)-1 and HHV-2 following the criteria of the International Committee on Taxonomy of Viruses), and varicella-zoster virus (VZV, or HHV-3);

– Betaherpesvirinae, represented by human cytomegalovirus (CMV or HHV-5), human herpesviruses 6A and 6B (HHV-6A and HHV-6B), and human herpesvirus 7 (HHV-7);

– Gammaherpesvirinae, the members are Epstein–Barr virus (EBV or HHV-4), and Kaposi's sarcoma-associated herpesvirus (also known as HHV-8).

HV can persist in the host in a latent state for life, and reactivate to produce a lytic infection under certain circumstances. HSV-1 and HSV-2 cause orolabial and genital infections, VZV is the etiological agent of chickenpox and shingles, CMV is responsible for mononucleosis-like syndrome and several systemic and organ-specific diseases (e.g., retinitis, myocarditis, and encephalitis, among others), and EBV is associated with mononucleosis and several cancers. Their viral DNA polymerases play a key role in the lytic phase of the infection and therefore are attractive targets for therapeutic intervention.

All of the HV cause lifelong infection because the virus remains within its host cell in an inactive (dormant or latent) state. Sometimes the virus reactivates and produces further episodes of disease. Symptoms from reactivation can be different than the symptoms of the initial infection. Reactivation may occur rapidly or many years after the initial infection.

Transcription, genome replication, and capsid assembly occur in the host cell nucleus. Genes are replicated in a specific order:

1) immediate-early genes, which encode regulatory proteins;

2) early genes, which encode enzymes for replicating viral DNA;

3) late genes, which encode structural proteins.

The tegument and envelope are acquired as the virion buds out through the nuclear membrane or endoplasmic reticulum. Virions are transported to the cell

membrane via the Golgi complex, and the host cell dies as mature virions are released. Alternatively, in selected cell types, the virus may be maintained in a latent state. The latent viral genome may reactivate at any time; the mechanism of reactivation is not known.

## HERPES SIMPLEX VIRUS INFECTIONS

Infections with HSV-1 traditionally involve the face and skin above the waist. However, an increasing number of genital herpes cases are attributable to HSV-1. Infections with HSV-2 usually involve the genitalia and skin below the waist in sexually active adolescents and adults. Although both HSV-1 and HSV-2 infections are frequently asymptomatic, they can produce a variety of signs and symptoms. These include recurrent oral or perioral lesions ("cold sores"), skin and mucous membrane lesions, including genital lesions, ocular infections (e.g., herpetic keratitis), and serious systemic illnesses such as encephalitis and neonatal disease involving multiple organs.

**Transmission.** HSV infections can be transmitted from people who are symptomatic or asymptomatic with primary or recurrent infections. The most likely portal of entry for HSV primary (1°) infection appears to be via the mucous membranes, following which it ascends the peripheral nervous system.

**Pathogenesis.** 1° infection usually occurs in childhood and adolescence, but relapses can occur at any time. Following 1° infection, HSV has the ability to develop latent viral infection, usually in the trigeminal or dorsal root ganglion. During this latent period, restricted viral replication takes place, and certain areas of the HSV genome have been described that may account for this ability to replicate without apoptosis and maintain a latent infection in the dorsal root ganglion. During the cycle of HSV recurrences, the virus undergoes reactivation from latent to lytic replication in trigeminal or sacral ganglia neurons with anterograde axonal transport to epithelial cells. The virus replicates in epithelial cells and may be shed asymptomatically or may be associated with clinically apparent ulcerations.

HSV neurovirulence and latency are thought to influence disease in children. Neurovirulence is the affinity of HSV for neuronal tissue, through which the virus is propagated.

### Neonatal infection

**Epidemiology.** Incidence differs between countries. The estimated incidence of neonatal HSV infection ranges from 3 to 30 per 100,000 live births. The wide variation is likely due to differences in the prevalence of genital herpes in different areas around the world and differences in reporting practices. Globally, there are an estimated 14,000 cases of neonatal HSV infection per year.

**Transmission.** Neonatal infection is usually transmitted from mother to child through viral shedding from the birth canal during delivery (85 %). Transplacental infection is rare (5 %), and postnatal infection via an orolabial lesion from contact with a family member is uncommon (10 %). Maternal 1° infection with HSV at the time of delivery has the highest risk of transmission (25–57 %), compared with recurrent maternal genital HSV (2 %). The majority of infants with HSV are born to mothers who are asymptomatic.

The **risk factors** known to influence HSV transmission include:

– lack of maternal antibody;

– increasing duration of rupture of membranes;

– breeching of mucocutaneous barriers (e.g. use of scalp electrodes);

– mode of delivery (vaginal versus Caesarean in women with active shedding of HSV at delivery).

The **incubation period** for neonatal HSV is 1–6 days.

**Clinical features and sequelae.** The clinical presentation in neonates can be broadly classified into three distinct forms with different outcomes, but overlap syndromes occur:

– skin-eye-mouth (SEM) disease;

– disseminated disease with or without central nervous system (CNS) involvement;

– CNS disease.

There is some overlap in these categories. For example, disseminated HSV disease may have SEM and/or CNS involvement in addition to other organs, and SEM disease may progress to CNS or disseminated disease if not treated early. Both HSV-1 and HSV-2 may cause SEM, CNS, or disseminated disease; however, HSV-1 is more likely to be associated with SEM disease, while HSV-2 is associated more often with CNS disease and with a poorer outcome.

**Skin-eye-mouth disease.** SEM disease accounts for approximately 35 to 45 % of neonatal HSV. Neonatal HSV SEM disease may appear benign at onset of illness but is associated with a high risk of progression to CNS or disseminated disease if not treated. SEM disease usually presents in the first two weeks of life but may occur at any time during the first six weeks of life.

Localized skin disease is associated with coalescing or clustering vesicular lesions with an erythematous base (fig. 1).

Vesicles may begin or cluster at the presenting part of the body, or at sites of localized trauma, such as scalp monitor sites (fig. 2). Skin vesicles also may appear late in the course of disseminated disease.

HSV infection of the eye may initially appear asymptomatic. In the neonate, early signs include excessive watering of the eye, crying from apparent eye pain, and conjunctival erythema (fig. 3). Periorbital skin vesicles may or may not be present at the time of presentation. HSV keratoconjunctivitis may progress to corneal scarring, cataracts, and chorioretinitis and result in permanent vision impairment.

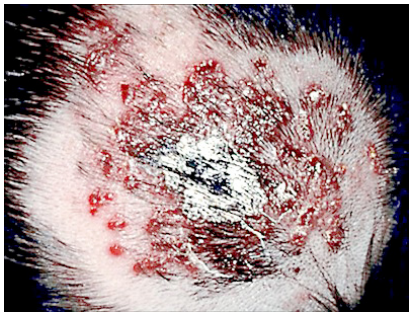

*Fig. 1.* Neonatal herpes simplex virus scalp vesicles

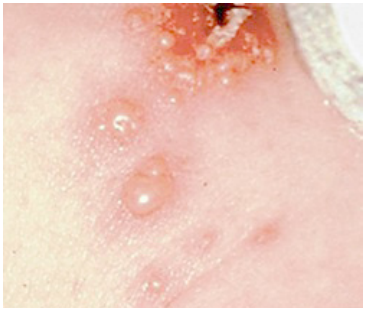

*Fig. 2.* Neck vesicles in neonate with herpes simplex virus infection

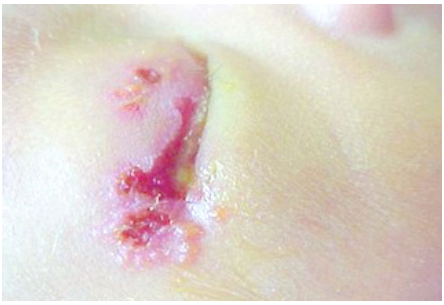

*Fig. 3.* Eye vesicles in neonate with herpes simplex virus infection

HSV infection of the oropharynx may initially be asymptomatic but also may be characterized by localized ulcerative lesions of the mouth, palate, and tongue. It should be differentiated from other causes of oral lesions in the newborn such as local trauma or other viral infections (e.g., enterovirus).

Neonates and infants up to six weeks of age with evidence of SEM disease should undergo a thorough evaluation for CNS and disseminated disease. Infants with SEM disease may have associated HSV viremia. However, if there is no evidence systemic disease (e.g., no liver, lung, kidney, cardiovascular, or CNS involvement), most experts would not consider such infants as having disseminated HSV disease. If SEM disease is treated early, before CNS or disseminated disease occurs, the outcome is favorable.

**Central nervous system disease.** Approximately one-third of neonatal HSV disease involves the CNS. It may occur as a result of localized retrograde spread from the nasopharynx and olfactory nerves to the brain or through hematogenous spread in neonates with disseminated disease. Neonatal HSV CNS disease (also called neonatal HSV encephalitis, HSE) usually presents in the second or third week

of life, but may occur at any time during the first six weeks of life. CNS disease may occur with or without SEM involvement and with or without disseminated disease. Between 60 and 70 percent of neonates with HSE have skin vesicles at some point during the disease course.

Clinical manifestations of neonatal HSE include seizures (focal or generalized), lethargy, irritability, tremors, poor feeding, temperature instability, and full anterior fontanel. Early in the course of HSE, none of these signs or symptoms may be apparent.

Cerebrospinal fluid (CSF) analysis in neonates with HSV CNS disease classically shows a modest mononuclear cell pleocytosis, normal or moderately low glucose concentration, and mildly elevated protein; however, CSF studies may be normal early in the course of the illness. Abnormalities of the CSF may be more pronounced as CNS disease progresses. Red blood cells are not significantly associated with neonatal HSE and are more likely to be caused by an apparent "bloody tap".

The electroencephalogram often is abnormal very early in the course of CNS disease and may show lateralized periodic discharges.

Computed tomography and magnetic resonance imaging of the brain may be normal early in the course of CNS disease. Several days to a week into illness, neuroimaging studies may show parenchymal brain edema or attenuation, hemorrhage, or destructive lesions involving the temporal, frontal, parietal, or brainstem regions of the brain (fig. 4).

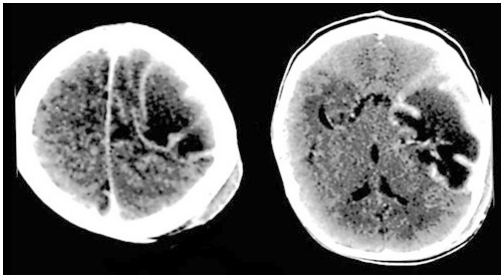

*Fig. 4.* Computed tomography scan of the brain of an infant with CNS HSVI

In the absence of vesicles, the initial presentation of HSV CNS disease may be indistinguishable from other causes of neonatal sepsis or meningitis. Many experts recommend evaluation for HSV CNS disease with HSV DNA polymerase chain reaction (PCR) and other CSF studies (i.e., cell counts, protein, and glucose), and empiric treatment with acyclovir in all neonates with aseptic meningitis or other signs and symptoms of meningoencephalitis without an obvious bacterial cause.

Neonates with certain underlying primary immune disorders (e.g., functional natural killer cell deficiencies, toll-like receptor deficiencies) are at risk for

developing severe HSV encephalitis and postinfectious complications such as HSV-mediated autoimmune encephalitis.

**Disseminated disease.** Approximately 25 to 30 % of neonatal HSV disease is the disseminated form, which is sepsis-like presentation, involving multiple organs:

– liver, including hepatitis with elevated liver transaminases, ascites, and direct hyperbilirubinemia that can progress to liver failure requiring liver transplantation;

– lungs, including progressive interstitial pneumonitis (fig. 5) and hemorrhagic pneumonitis, with or without effusion, that can progress to respiratory failure, requiring mechanical ventilation or extracorporeal life support;

– CNS, which is involved in 60 to 75 % of cases, usually through a hematogenously acquired meningoencephalitis;

– heart, including myocarditis and myocardial dysfunction in severe disseminated neonatal HSV;

– adrenal glands;

– bone marrow and coagulation system, including disseminated intravascular coagulation, thrombocytopenia, and neutropenia;

– kidneys;

– gastrointestinal tract, including necrotizing enterocolitis;

– skin and mucous membranes lesions, which may appear late in the course of disseminated HSV disease; however, 20 to 40 % of neonates with disseminated HSV disease do not have vesicles.

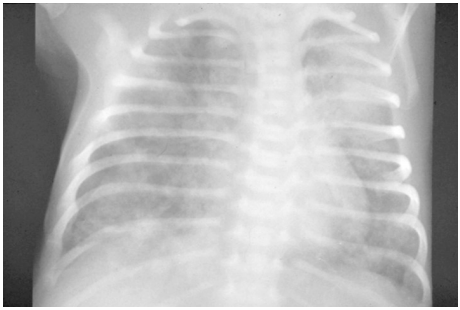

*Fig. 5.* Chest radiograph of neonatal HSV pneumonitis

Neonates with disseminated HSV often present in the first week of life with nonspecific signs and symptoms of neonatal sepsis, including temperature dysregulation (fever or hypothermia), apnea, irritability, lethargy, respiratory distress, abdominal distension, hepatomegaly, and ascites. Rarely, neonates with HSV infection may present with fever alone. In advanced disseminated neonatal HSV disease, fever is often absent, and hypothermia is more prominent.

The diagnosis of disseminated neonatal HSV disease often is delayed until the second week of life, awaiting the results of evaluation for bacterial sepsis. In treated infants, the risk of mortality associated with disseminated HSV infection is approximately 40 to 50 %; in untreated infants, mortality exceeds 80 %.

**Diagnosis.** Neonatal HSV infection is clinically challenging. Early manifestations may be subtle and nonspecific. Unfortunately, the diagnosis is sometimes made or confirmed at autopsy, after extensive organ damage has occurred. Efforts are focused on identifying high-risk neonates with a sepsis-like picture, meningoencephalitis, progressive pneumonitis, or hepatitis, who should undergo testing for HSV and empiric antiviral therapy.

Clinical suspicion. Neonatal HSV infection should be suspected in neonates and infants up to six weeks of age with:

– mucocutaneous vesicles or ulcers;

– sepsis-like illness (fever or hypothermia, irritability, lethargy, respiratory distress, apnea, abdominal distension, hepatomegaly, ascites, coagulopathy);

– CSF pleocytosis, especially with a mononuclear predominance;

– seizures;

– focal neurologic signs;

– abnormal neuroimaging;

– respiratory distress, apnea, or progressive pneumonitis;

– thrombocytopenia;

– elevated liver transaminases, viral hepatitis, or acute liver failure;

– conjunctivitis, with watery discharge, excessive tearing, or painful eye symptoms, especially if unilateral.

Early in the clinical course, some neonates with HSV infection may present with persistent fever and negative bacterial cultures.

Neonatal HSV infection remains a possibility in infants born to mothers who received suppressive **acyclovir** (= aciclovir) therapy during pregnancy. Although suppressive therapy markedly reduces the risk of asymptomatic shedding, it does not completely eliminate it. Neonates with perinatal exposure to HSV (particularly maternal active genital lesions, but also postnatal direct exposure to individuals with active HSV oral lesions) should be monitored for evidence of HSV infection.

**Investigations should include:**

1. Scrapping of the base of the vesicles, if present.

2. Surface skin lesion swabs, nasopharynx, mouth, conjunctiva, blood, and CSF for HSV DNA PCR.

3. FBC, liver function tests, and clotting screen.

4. CSF for cell analysis and HSV PCR. CSF testing is an essential component of the diagnostic work-up; CSF should be tested as soon as it is safe to perform a lumbar puncture in any child with suspected encephalitis. It is important to take enough CSF for local laboratory requirements; it is common that insufficient

CSF volumes reach the laboratories for all the necessary tests. Children produce ~0.35 mL/kg of CSF per hour, and it is safe to take up to 0.2 mL/kg of CSF.

5. Computed tomography or magnetic resonance imaging (better) of the brain should be considered in patients with CNS disease (plus electroencephalogram if CNS disease is suspected — temporal lobe spike and wave). The only urgent brain imaging available may be a computed tomography scan, preferably with contrast, and will help exclude hemorrhage as a cause of the symptom complex but should not be performed solely to determine the safety of proceeding to a lumbar puncture.

6. Ophthalmological review to exclude HSV retinitis.

**Viral culture.** Isolation of HSV by viral cell culture and serotyping HSV-1 or HSV-2 was traditionally the standard for definitive diagnosis of neonatal HSV infection. However, in the current era, many diagnostic virology laboratories and clinical reference laboratories offer PCR assays, which are an accurate and rapid method for detection and diagnosis of HSV infection

**Direct immunofluorescence assays and enzyme immunoassays.** Direct immunofluorescence assays and enzyme immunoassays (EIA) methods permit rapid detection of HSV antigens in skin and mucous membrane lesions.

Direct immunofluorescence assays has high specificity for HSV infection, and typing of the HSV antigens may be done directly on material on the slide. However, direct immunofluorescence assays is not as sensitive as PCR since the accuracy of direct immunofluorescence assays depends on the adequacy of the specimen (i. e., it must contain sufficient cells) and the skill of the technician.

EIA is primarily used to screen asymptomatic or pregnant people for HSV genital infection. Use of rapid EIA for diagnosis of neonatal HSV infection is **not** recommended since its performance in this setting is not well established.

**Serology.** Serologic tests generally are **not** helpful in the diagnosis of neonatal HSV infection but may be used in the following circumstances:

– to identify HSV-2 infection in pregnant people so that steps can be taken to prevent neonatal infection;

– to confirm the diagnosis of neonatal HSV infection when there is diagnostic uncertainty during the newborn period. Persistence of HSV type-specific immunoglobulin G (IgG) antibody beyond the time period of transplacental IgG antibody duration (i.e., beyond six months) can help confirm the diagnosis if direct detection of the virus at the time of illness was not successful or possible.

**Management and treatment.** Neonates with HSV infection should be treated with high-dose IV aciclovir. Recommended duration of therapy is a minimum of 14 days for SEM disease, and a minimum of 21 days for disseminated and CNS disease (table 1).

A repeat CSF HSV PCR is recommended at the end of the course of therapy in patients with CNS involvement to confirm clearance of the virus.

*Table 1*

**Treatment of HSE (assuming normal renal function and hydration)**

| **Treatment for acute HSE** | | |
|---|---|---|
| **Birth to 3 months** | **All children >3 months** | |
| *Aciclovir IV:*<br>20 mg/kg tds for 21 days | *Aciclovir IV:*<br>3 months to 12 years: 500 mg/m² tds for 21 days<br>Over 12 years: 10 mg/kg tds for 21 days | |
| **Prophylaxis against HSE recurrence** | | |
| **Birth to 3 months** | **Immunocompetent children > 3 months** | **Immunocompromised children > 3 months** |
| *Aciclovir PO:*<br>300 mg/m² tds for at least 12 months<br>*Valaciclovir PO:*<br>Not recommended — no neonatal data | *Aciclovir PO:*<br>300 mg/m² tds for 6–12 months<br>OR<br>1340 mg/m² bd for 6–12 months<br>*Valaciclovir PO:*<br>1 month to 12 years<br>25–40 mg/kg tds for at least 3 months | *Aciclovir PO:*<br>300 mg/m² tds for at least 12 months<br>OR<br>1340 mg/m² for at least 12 months<br>*Valaciclovir PO:*<br>1 month to 12 years<br>25–40 mg/kg tds for at least 12 months |

**Prevention.** ***During pregnancy.*** Suppressive treatment from 36 weeks of gestation onwards is recommended by some experts to reduce the emergence of lesions around the time of delivery and the need for a Caesarean section. However, this approach reduces, but does not completely eliminate, asymptomatic shedding, and its efficacy and safety in pregnant women have not been clearly established.

***At delivery.*** Caesarean section should be considered in women with prodromal symptoms or active lesions of genital HSV at the time of delivery. It should be performed within 4–6 hours from the rupture of membranes. Non-randomized studies have shown that neonatal transmission decreases (but is not completely eliminated) using this approach. Caesarean section should be supplemented with aciclovir therapy to the mother.

Asymptomatic neonates born to mothers with a 1° genital lesion, either vaginally or by Caesarean section, with risk factors (rupture of membranes > 6 hours prior to delivery; fetal scalp electrodes; chorioamnionitis; cervicitis) should receive a full diagnostic evaluation for HSV if there is no serological evidence of past maternal infection. Treatment with IV acyclovir should be initiated, until the evidence of active infection has been ruled out.

Asymptomatic neonates born vaginally to a mother with a recurrent genital infection can have HSV surface swabs (nasopharynx, mouth) taken at 24–48 hours to rule out active replication of the virus and may be monitored clinically at regular

intervals in the first few weeks of life. Some clinicians will also treat these infants prophylactically with acyclovir.

***After skin-eye-mouth disease.*** Recurrence of symptoms after neonatal HSE are recognized, and, although most occur within 3 months of completing an initial course of IV acyclovir, late relapse is well recognized. Prophylaxis with acyclovir has been shown to prevent this significantly. While 6–12 months of antiviral prophylaxis is adequate for some children following neonatal HSE, late central or dermal flares may indicate that longer-term, or even lifelong, prophylaxis may be required. Findings from a small patient series proposed doses of 1340 mg/m² of aciclovir given twice daily (total daily dose 2680 mg/m²), based on CSF penetration data, but a more recent, larger placebo-controlled RCT validated oral aciclovir given at 300 mg/m² three times daily (900 mg/m²) as adequate at improving neurodevelopmental outcome.

## Childhood infection

**Epidemiology.** Most childhood infections are caused by HSV-1, whereas HSV-2 infection occurs in adolescents after the onset of sexual activity. Prevalence of HSV-1 seropositivity in children varies, according to the geographical location and social class status. The vast majority of 1° infections in children are asymptomatic. The virus remains latent for life (HSV-1 trigeminal ganglia; HSV-2 sacral sensory neural ganglia) with possible episodes of reactivation and neural axonal spread ("cold sores" or genital herpes) and periods of asymptomatic shedding.

**Transmission and incubation period.** Transmission of HSV-1 occurs through mucocutaneous contact, often with asymptomatic children who are shedding the virus. Patients with 1° gingivostomatitis shed the virus for ≥ 1 week. Patients with recurrent symptoms shed the virus for a shorter duration of 3–4 days.

The **incubation period** is 2 days to 2 weeks.

**Clinical features and sequelae.** The clinical manifestations of HSVI depend upon the anatomic site involved and whether the clinical episode is due to 1° infection or reactivation disease. While infection is lifelong, it is rarely fatal in the immunocompetent host.

**Mucous membranes manifestations.** ***Gingivostomatitis*** is a classical paediatric presentation of HSV-1. Prodromal symptoms include fever, nausea, malaise, and anorexia. This is followed by the appearance of numerous vesicles, which break down rapidly to enlarging erythematous lesions with central ulcerations covered by yellow-grey membranes. Lesions are painful and may coalesce. Main clinical problem is dehydration; rarely needs hospital admission. Areas involved may include the buccal mucosa, tongue, posterior pharynx, and gingiva. Commonly, satellite lesions are seen on the skin around the mouth. Healing occurs in 10–21 days (fig. 6).

***Herpes labialis ("cold sores").*** Following 1° infection, one-third of patients have episodes of viral reactivation, consisting of orolabial lesions at the outer edge of the vermillion border (fig. 7). Fever or non-specific stressors can trigger episodes, which are usually preceded by a tingling or pain sensation at the site. Episodes last for 4–5 days, though HSV shedding is detected by PCR in between acute episodes.

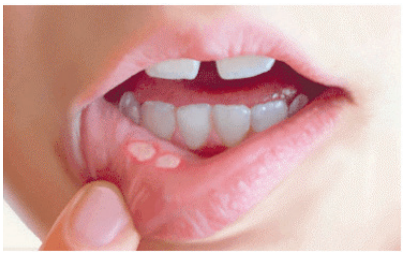

*Fig. 6.* Herpetic gingivostomatitis

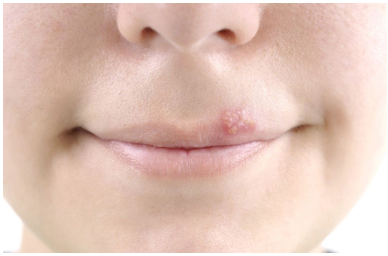

*Fig. 7.* Cold sores

**Genital HSVs infections.** Patients with primary genital HSVI typically present with bilateral genital ulcerations and tender lymphadenopathy. Systemic symptoms such as fevers, headache, and myalgias can also occur. Autonomic dysfunction with hyperesthesia or anesthesia of the perineal region with concomitant urinary retention or constipation may develop in some patients, and in this setting, physical examination may be notable for increased bladder size on percussion, decreased sacral sensation, and poor rectal tone.

Genital HSV-1 lesions may recur, particularly in the first year after infection; however, multiple recurrences are rare. HSV-2 recurs much more often in the genital area

Genital HSVI viral shedding may occur without symptoms, which can lead to transmission of the virus.

**Ocular manifestations.** ***Keratoconjunctivitis.*** Follows auto-inoculation in a child with gingivostomatitis or herpes labialis. The episode presents with acute onset of pain, photophobia, and excessive lacrimation. This is followed by chemosis and periorbitaloedema. The infection leads to corneal ulceration, with pathognomonic branching dendritic lesions of the cornea and blurred vision. Resolution of the episode takes up to 4 weeks. Recurrent infections may lead to corneal opacification and corneal blindness.

***Acute retinal necrosis*** is a rare, potentially blinding, retinal disease resulting from ocular infection with HSV or VZV. Acute retinal necrosis is characterized by decreased vision and has been reported in immunocompetent hosts, pregnant people, and persons with HIV infection. Bilateral acute retinal necrosis has been reported in children.

***Conjunctivitis and blepharitis.*** HSV-1 can present as a unilateral conjunctivitis and/or blepharitis with the development of vesicles on the lid margin (fig. 8). Associated symptoms include chemosis, edema of the eyelids, and tearing.

***Chorioretinitis,*** also known as posterior uveitis, is a manifestation of disseminated HSVI that can be seen in neonates.

**Cutaneous manifestations.** ***Herpetic whitlow (herpetic paronychia).*** Result of auto-inoculation in children with orofacial HSVI. Characterized by the swelling of a finger (usually the thumb from sucking) and the appearance of one or several painful, clear, fluid-filled vesicles, later becoming opaque. Typically side of finger on the distal phalanx (fig. 9). Larger than vesicles seen in hand, foot, and mouth disease. Symptoms last for 1–2 weeks.

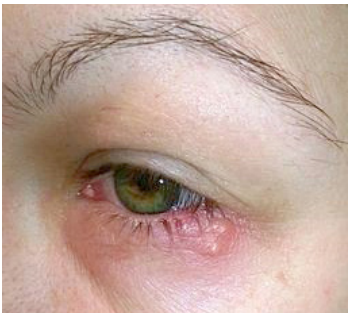

*Fig. 8.* Herpes simplex virus blepharitis

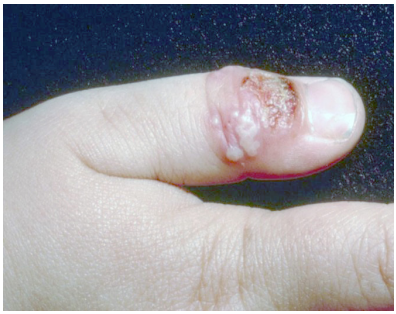

*Fig. 9.* Herpetic whitlow

***Eczema herpeticum.*** HSV skin superinfection in patients with underlying eczema. In one-third of children, there is a recent history of herpes labialis in one of the parents. Vesicles appear in areas of recently healed atopic dermatitis but rapidly become "punched-out" ulcers and can spread quickly destroying skin. Fever develops 2–3 days after the appearance of vesicles and usually lasts for 4–5 days. Toxic symptoms may be severe, and viraemia with visceral involvement has been reported.

***Herpes gladiatorum — scrum pox.*** Lesions present on the face, neck, or arm of children involved in contact sports such as wrestling or rugby. Viral inoculation results from close contact between injured skin and oral secretions.

***Herpes simplex virus-associated erythema multiforme.*** Disease characterized by an autoimmune response to HSV DNA fragments present in the patient's skin, with the development of distinctive cutaneous target lesions. Episodes usually follow an episode of herpes labialis and lasts for 10 days. Recurrences are common, and direct testing for HSV by culture or PCR is negative.

**Central nervous system infection.** HSV is the commonest identified cause of severe encephalitis. In older infants and children, the classic features of HSE

are: fever, encephalopathy, a deteriorating level of consciousness, focal seizures, or focal neurological abnormalities; however, the infective source is usually elusive.

**Other infections.** A number of other manifestations of HSV have been described in the immunocompetent host, including pneumonitis, exudative tracheobronchitis, oesophagitis, hepatitis, recurrent aseptic meningitis, myelitis, and facial nerve (Bell's) palsy.

**Diagnosis.** Diagnosis and typing of HSV can be readily performed by PCR assay of lesions and various body fluids, or via immunofluorescence or direct antibody (EIA or ELISA) testing, or viral culture.

CSF PCR for HSV, as for neonatal HSV, is vital if CNS disease is suspected. HSV PCR is a highly sensitive and specific test (94 and 96 %, respectively), *except* during the first 24 hours of the disease when as many as 10 % of HSE CSF samples can be falsely negative. Serological testing is available but has limited diagnostic utility.

**Management and treatment.** A variety of formulations are available for the treatment of HSV, including oral, topical, and IV aciclovir, oral valaciclovir and famciclovir, and IV foscarnet. In addition to aciclovir, the following are important management considerations:

*Gingivostomatitis:* to adequately manage any pain, to ensure adequate hydration, and to promote healing. Especially for infants and small children, careful assessment for decreased feeding, short-term weight loss, and poor urine output are important. Dehydration can result insidiously, especially where reduced fluid intake is coupled with increased insensible losses from mouth breathing and drooling, particularly if the need for effective symptomatic relief is not appreciated. Topical local anaesthetics (washes, gels, sprays, lozenges, etc.) are widely used to provide some short-term symptomatic relief, which also help improve oral intake.

*Skin infections:* there are few efficacy data available to recommend treatment in skin infection, except eczema herpeticum, which should be treated with IV aciclovir. Treatment of infections in immunocompromised hosts and burn patients should be considered because of the potential severity of symptoms

*CNS infections:* early initiation of treatment with high-dose IV aciclovir has shown to significantly reduce morbidity and mortality in patients with encephalitis.

**Recurrence.** Recurrence of neonatal HSE can be as devastating as the original disease, and neonates remain prone to late recurrences of infection for months to years after their initial illness. It is thought that early-life infection impairs the development of an effective adaptive immune response, but prolonged antiviral prophylaxis can prevent recurrence. It is common for neonates who have had an initial HSE to develop recurrence of dermal flares. Some rare cases of recurrent childhood HSE may be due to an underlying immunodeficiency in the innate immune system.

# VARICELLA-ZOSTER VIRUS INFECTIONS

VZV is known by many names, including chickenpox virus, varicella virus, zoster virus, and HHV-3, and distributed worldwide. VZV causes two clinically distinct forms of disease: varicella (chickenpox) during 1° VZV infection, and herpes zoster (shingles), as a result of endogenous reactivation of latent VZV. VZV develops latency in the dorsal root ganglion. Following 1° infection, reactivation can occur throughout life.

## Chickenpox

1° varicella infection in children is generally a mild disease compared to more severe presentations in adults or immunocompromised patients of any age. Each child in a family who develops varicella tends to develop sequentially worse disease, with the final child being the most unwell. Young infants, adolescents, adults, and pregnant women tend to have more severe disease with a higher rate of complications.

**Epidemiology.** Chickenpox is a highly contagious viral illness that occurs mainly during childhood. It is possible to contract 1° chickenpox from a person with shingles. Varicella can develop between 1 and 16 days of life in infants born to mothers with active varicella around the time of delivery.

**Transmission and incubation period.** Chickenpox is one of the most contagious childhood infections, and the household attack rate for non-immune individuals who come into close contact is around 90 %. School contact tends to be lower at 12–33 %. The virus is spread by direct contact or airborne droplets, followed by mucosal invasion of the upper respiratory tract and conjunctiva or direct contact with infected vesicles. Asymptomatic infection is unusual, but some cases are so mild that they go unrecognized.

There is a 1° viraemic phase, followed by a 2° viraemia to the skin and mucosal surfaces. Children are contagious from 1 to 2 days before the onset of the rash, due to respiratory excretion, and then via the skin until all the lesions have crusted over.

The incubation period is 10–21 days, but most children usually become ill around 14–16 days after contact. The incubation period can be much shorter in immunosuppressed patients or longer if the child has received varicella zoster immunoglobulin (VZIG).

**Clinical features.** The classical sign of chickenpox infection is the generalized, cropping vesicular rash and intense pruritus. The rash is seen mostly on the head and trunk but can occur in any area of the skin and conjunctiva. The rash appears in crops, lesions in varying stages of development (papules, vesicles) and resolution (crusting), low-grade fever, and other systemic symptoms. New lesions

are occurring for 3–6 days following the 1° lesion. The majority of lesions will heal without scarring, and the disease resolves within about 7–10 days following symptom onset (fig. 10).

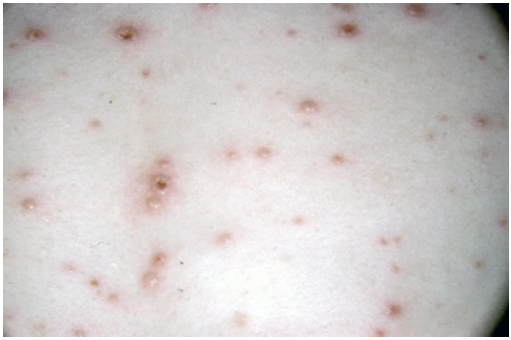

*Fig. 10.* Primary varicella lesions (Chickenpox)

A detailed medical history is crucial in cases where the diagnosis is uncertain, and establishing recent exposure to varicella can be helpful. Diagnosis is important, so that parents are counselled about contact avoidance and symptom relief. Hospital admission should be avoided, wherever possible, to avoid unnecessary nosocomial outbreaks. Adolescents may complain of a prodrome of nausea, myalgia, headache, and loss of appetite, but symptoms in younger children are usually non-specific, although fever is practically universal.

In immunocompromised children, including those with HIV or on long-term steroids, progressive, severe varicella can develop. This is characterized by high fever of long duration, continuing eruption of cropping lesions, and the appearance of complications. In some cases, despite adequate treatment, the disease can be fatal. Haemorrhagic varicella, with bleeding into and around lesions, is also seen, but is rare.

Patients **most at risk** of developing recurrent varicella or shingles infection:

– HIV infection;

– high-dose corticosteroids (over 2 mg/kg daily for longer than a week);

– congenital T-lymphocyte deficiencies or combined immunodeficiency;

– children with chronic cutaneous or pulmonary disorders.

**Differential diagnosis.** Chickenpox is usually distinctive, but other causes of vesicular rash include: HSVI (not usually disseminated), herpes zoster (usually dermatomal), hand, foot, and mouth disease (Coxsackie virus), enterovirus, impetigo, syphilis, and smallpox.

**Complications.** Any child with fever beyond 5 days of rash onset should have a medical review to rule out bacterial infection.

***Pneumonitis.*** Varicella pneumonia primarily occurs in older children and adults. Respiratory symptoms usually appear 3–4 days after the rash. The pneumonia may be unresponsive to antiviral therapy and may lead to death.

***2° skin infection.*** Skin lesion infections are common and occur in 5–10 % of children. These lesions provide a portal of entry for virulent organisms; rapidly spreading cellulitis, septicaemia, and other serious infections may occur (fig. 11).

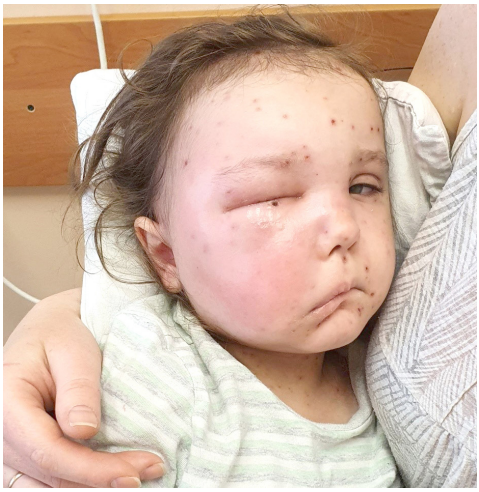

*Fig. 11.* Secondary bacterial infection (Chickenpox complication)

The commonest infectious organisms are Group A Streptococcus (GAS) and S. aureus. Varicella places the patient at high risk for acquiring invasive GAS disease. In addition to toxic shock syndrome, GAS may cause necrotizing fasciitis, bacteraemia, osteomyelitis, pyomyositis, gangrene, subgaleal abscess, arthritis, and meningitis. Staphylococci may cause cellulitis, impetiginous pox infections, staphylococcal scalded skin syndrome, toxic shock syndrome, pericarditis, and osteomyelitis.

**Neurological complications.** *Acute post-infectious cerebellar ataxia* is the commonest neurological complication, with an incidence of one case per 4000 patients with varicella. Ataxia has a sudden onset that usually occurs 2–3 weeks after the onset of varicella. Manifestations may range from mild unsteadiness to complete inability to stand and walk, with accompanying incoordination and dysarthria. Manifestations are maximal at onset; a waxing and waning course suggests another diagnosis. The sensorium is clear, even when the ataxia is profound. The condition may persist for 2 months. The prognosis for patients with ataxia is good, but a few children may have residual ataxia, incoordination,

or dysarthria. Brain imaging should be considered to rule out a concurrent space-occupying lesion.

*Diffuse encephalitis* occurs in 1.7 patients per 100 000 cases of varicella among otherwise healthy children aged 1–14 years. The disease manifests during acute varicella a few days after rash onset. Lethargy, drowsiness, and confusion are the usual presenting symptoms. Some children may have seizures, and encephalitis can rapidly progress to deep coma. This serious complication of varicella has a 5–20 % mortality rate.

*Reye's syndrome* was associated with varicella when aspirin use was common. Identification of this association now has made paracetamol/acetaminophen the preferred drug, and Reye's syndrome has become very rare.

Other neurological complications include aseptic meningitis, myelitis (including Guillain–Barré syndrome), polyradiculitis, stroke, and meningo-encephalitis.

## Herpes zoster — shingles

Herpes zoster recurrence is a delayed complication of varicella-zoster infection, occurring months to years after the 1° infection in about 15 % of patients. The complication is caused by virus that persists in the sensory ganglions. Herpes zoster consists of a unilateral vesicular rash, limited to 1–3 dermatomes (fig. 12).

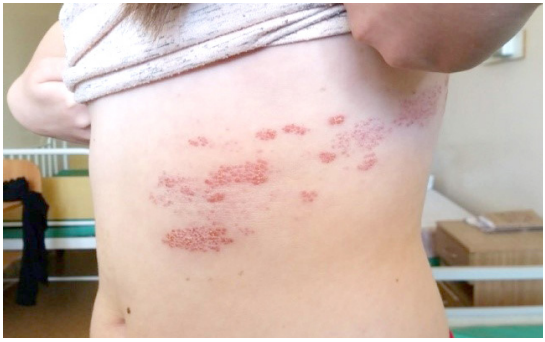

*Fig. 12.* Shingles

The rash is often painful in older children and adults. Among the health benefits of routine varicella immunization in childhood may be a lifelong decreased risk for reactivation of the virus as shingles.

There are few systemic symptoms and no systemic dissemination in immunocompetent individuals, but post-herpetic neuralgia can persist for weeks to months after resolution of the rash.

**Complications:**

1. Otitis media in 5 % of children.

2. Hepatitis is a self-limited accompaniment of varicella. Severe hepatitis with clinical manifestations is infrequent in otherwise healthy children with varicella. Liver involvement is independent of the severity of skin and systemic manifestations. Identify right upper quadrant pain with or without associated jaundice.

3. Retinitis and optic neuritis have been reported as rare complications of varicella in children who are immunocompetent.

4. Other reported complications include glomerulonephritis, haemorrhagic varicella, thrombocytopenia, myocarditis, appendicitis, pancreatitis, Henoch–Schönlein purpura, orchitis, iritis, and keratitis. Extracutaneous complications increase proportionately to the age of the patient.

## Varicella in pregnancy

Non-immune pregnant women coming into contact with varicella are at risk of developing in utero infection leading to congenital varicella syndrome or contracting severe disease themselves.

Infection of the fetus during the first 20 weeks of gestation can cause fetal death or the very rare congenital varicella syndrome, mainly characterized by limb atrophy and scarring of the skin of the extremities. In some cases, CNS and eye diseases can occur.

Infection of the fetus during the second 20 weeks of pregnancy can cause unapparent fetal varicella, with subsequent herpes zoster in early life, without having had extrauterine varicella.

In newborn infants, varicella can be fatal if the mother develops the disease from 5 days before to 2 days after delivery. If varicella develops in the mother $> 5$ days before delivery and the gestational age is $\geq 28$ weeks, the neonate is likely to be protected by maternal specific IgG antibodies.

**Diagnosis.** No investigations are usually necessary in an otherwise well child. In children where the diagnosis is unclear or where the diagnosis has implications for other family members or in pregnant women, detection of viral DNA from vesicular fluid by PCR has the highest sensitivity. VZV can be detected by PCR or isolated by culture from scrapings of a vesicle base during the first 3–4 days of eruption. Isolation from other sites is less sensitive.

Determination of specific IgG antibody in serum can be useful to retrospectively confirm the diagnosis. These antibody tests may be false-negative and are not as reliable in the immunocompromised.

Determination of specific IgM is not reliable for routine confirmation of acute infection, but positive results indicate current or recent VZV infection.

**Management and treatment.** The mainstay of treatment is **supportive care.** This includes adequate oral fluid, antipyretics, and observation of possible complications. There is some evidence that overwrapping can lead to worse disease eruptions, so parents should be counselled to keep the child cool. An increased risk of Reye's syndrome has been suggested where children with varicella are treated with aspirin.

Calamine lotion can alleviate itching. Chlorphenamine (INN) can also alleviate itching caused by chickenpox in children aged over 1 year. Advice should be given to keep the child's nails short in order to prevent further skin trauma and 2° bacterial infections.

Several drugs are available with activity against varicella, but these are only routinely used in the immunocompromised population.

***Aciclovir*** is currently the only drug licensed for the use of varicella in children. Studies have shown that, in otherwise healthy children, aciclovir treatment shortens the disease course by only ~1 day of feverand rash. Some experts recommend oral aciclovir for non-immune household contacts, as they are likely to have more severe disease. If considering aciclovir treatment, bear in mind that the drug is only effective if given within the first 48 hours of the rash eruption, as viral replication ceases 72 hours after the first crop of vesicles appear.

***Valaciclovir*** has been licensed for use in adults, and recent data suggest that this has good oral bioavailability in children, but there is no current plan to license for chickenpox. Aciclovir should only be given to adolescents and adults and should not be routinely prescribed in otherwise healthy children over 1 month of age in whom the disease is likely to be mild. However, children of any age with severe disease should be treated with IV aciclovir.

***Immunoglobulin therapy:*** immunoglobulin therapy is not effective once the disease is established but should be considered in neonates and the immunocompromised. This takes the form of intramascular VZIG or IVIG. Immunoglobulin should ideally be given within 96 hours of significant exposure and not delayed past 7 days.

***Varicella vaccine:*** in susceptible individuals, additional prevention is available in the form of the vaccine, given 3–5 days after exposure, where indicated. The varicella vaccine is currently not part of the routine vaccination schedule in many countries. In those countries where vaccine routinely administered, varicella epidemiology was significantly modified, both reducing clinical disease and shifting the incidence to higher age groups, especially where vaccination is not universally taken up. In surveillance areas with high vaccine coverage, the rate of varicella disease decreased by ~85 %.

**Prevention.** In addition to standard cleanliness, airborne and contact precautions are recommended in medical facilities for children with varicella or herpes zoster until crusting of the skin lesions. This period can last up to 1 week

(until all lesions have crusted over) for otherwise healthy subjects with mild disease or several weeks for immunocompromised children with severe disease. For exposed susceptible patients, airborne and contact precautions from 10 days until 21 days after exposure to the index patient are indicated. These precautions should be maintained until 28 days after exposure for those who received VZIG or the usual IVIG. Respiratory precautions are recommended for neonates born to mothers with varicella and should be continued until 21 or 28 days of age if they received VZIG or IVIG. Infants with varicella embryopathy do not require isolation. For children managed in the community, the following advice should be given:

– stay away from school or nursery, and do not go on air travel until 6 days after the last spot has appeared;

– avoid contact with people who are immunocompromised, pregnant women, and infants aged ≤ 4 weeks.

For immunocompetent patients with localized zoster, contact precautions are indicated until all lesions are crusted.

Immunocompromised patients who have zoster (localized or disseminated) and immunocompetent patients with disseminated zoster require airborne and contact precautions for the duration of illness.

In case of exposure to VZV, chemoprophylaxis is not routinely indicated. Potential interventions for susceptible people exposed to a person with varicella include varicella vaccine, administered 3–5 days after exposure, and, when indicated, VZIG (one dose up to 96 hours after exposure) or, if VZIG is not available, IVIG (one dose up to 96 hours after exposure). Definition of significant exposure

The Department of Health in the UK considers the presence of the following factors as indicative of significant exposure to VZV:

– type of VZV infection in index case: contact with chickenpox, disseminated zoster, immunocompetent individuals with exposed lesions, and immunosuppressed patients with localized zoster (because of greater viral shedding);

– timing of exposure: exposure to index case from 48 hours before onset of rash until crusting of lesions; or day of onset of rash until crusting (for localized zoster);

– closeness and duration of contact: residing in the same household, maternal/neonatal contact, contact in the same room for a significant period of time (15 minutes or more), face-to-face contact, hospitalized in the same paediatric ward or hospital room as a patient with varicella; close contact (i.e. touching or hugging) with a person with active herpes zoster lesions;

– establishing a history of chickenpox or demonstrating IgG antibodies to VZV determines susceptibility in healthy people;

– in immunocompromised persons testing for VZV, IgG antibodies is recommended, regardless of their history of chickenpox.

**Varicella-zoster vaccine.** Varicella vaccine is the best option for the prevention of VZV infection in immunocompetent people. It is a live-attenuated preparation of the serially propagated and attenuated wild Oka strain. Subcutaneous administration is recommended, although IM administration has been demonstrated to result in similar rates of seroconversion. The following patients should not receive varicella vaccine:

– people who are receiving high doses of systemic corticosteroids (2 mg/kg per day or more of prednisone or its equivalent) for at least 14 days. The recommended interval between discontinuation of corticosteroid therapy and immunization with varicella vaccine is at least 1 month;

– children with impaired humoral immunity may be immunized, but VZV vaccine should not be administered to children with cellular immunodeficiency. Exceptions include children with acute lymphocytic leukaemia in continuous remission for at least 1 year, with a lymphocyte count > 700/microlitre and a platelet count > 100 × $10^3$/microlitre, and children with HIV infection in CDC class 1 or 2 with a stable CD4+ T-lymphocyte percentage of ≥ 25 %;

– pregnant women, because the possible effects on fetal development are unknown. On the contrary, varicella vaccine should be administered to nursing mothers who lack evidence of immunity.

There is no evidence of excretion of the vaccine strain in human milk or of transmission to infants who are breastfeeding.

Varicella vaccine should not be administered to people who have had anaphylactic-type reaction to any component of the vaccine, including gelatin and neomycin.

Otherwise healthy children with moderate or severe acute disease, with or without fever.

An immunocompromised person or a pregnant mother in the same household is not a contraindication for immunization of a child.

Varicella vaccine is safe and well tolerated. Adverse events, usually mild, occur in 5–35 % of the cases in the first 42 days after vaccination (mainly between days 5 and 26). High fever is rare, and it occurs with the same frequency as in children receiving placebo; 3–5 % of vaccinated children develop a generalized varicella-like rash, which includes only 2–5 skin lesions, usually maculopapular, rather than vesicular. Severe adverse events, such as anaphylaxis, encephalitis, ataxia, erythema multiforme, Stevens–Johnson syndrome, pneumonia, thrombocytopenia, seizures, Guillain–Barré syndrome, and death, have been reported, but, in most of the cases, a causal association cannot be determined and/or the patient was immunocompromised.

VZV vaccine has been associated with the development of herpes zoster, mainly in immunocompromised, but also in immunocompetent children. However, herpes zoster in immunized people may also result from natural varicella infection that occurred before or after immunization.

Vaccine-associated virus transmission to contacts is rare, and only in the case of a rash developing in the immunized person. The administration of varicella vaccine during the presymptomatic or prodromal stage of illness does not increase the risk of vaccine-associated adverse events or more severe natural disease

Varicella vaccine can be administered simultaneously with other recommended vaccines. If not administered at the same visit, the interval between administration of varicella vaccine and other live-attenuated vaccines (including Measles, Mumps, Rubella) should be at least 28 days.

When the vaccine was approved, a single dose for individuals < 13 years, and two doses for older people, were recommended.

There are now data that indicate that a single dose may be ineffective in preventing outbreaks, so a routine two-dose vaccination programme is recommended in some countries (first dose at age 12–15 months and the second at least 3 months later).

Children aged ≥ 13 years and adults should receive two doses 4–8 weeks apart.

The current two-dose vaccine schedule provides 98 % immunity for children and 75 % immunity for adolescents and adults. Breakthrough infection in both groups is milder, with < 30 vesicles, low fever, and rapid recovery than unvaccinated individuals. Shingles is rare after vaccination.

Whether Reye's syndrome results from administration of salicylates after immunization for varicella in children is unknown. However, salicylates should be avoided for 6 weeks after administration of varicella vaccine.

Duration of immunity is not established. Available data suggest that protection can last for at least 20 years. However, these data have been collected in a period with a significant circulation of wild-type VZV, and consequently with a high probability of natural boosting in immunized people.

Varicella vaccination is recommended for susceptible health-care workers.

**Varicella-zoster immunoglobulin.** VZIG should be given to susceptible people at high risk of developing severe disease with significant exposure to VZV:

– immunocompromised children;

– susceptible pregnant women;

– newborn infants whose mother had onset of varicella within 5 days before delivery or within 48 hours after delivery;

– hospitalized premature infants (> 28 weeks' gestation) whose mothers lack a reliable history of varicella or serological evidence of protection, hospitalized premature infants (< 28 weeks' gestation or ≤ 1000 g birthweight), regardless of maternal history of varicella or VZV serostatus.

VZIG prophylaxis may be ineffective in preventing varicella in immunocompromised patients; careful monitoring and drug treatment at first sign of illness are recommended. Any patient to whom VZIG is administered

to prevent varicella should subsequently receive varicella vaccine, according to recommendations appropriate for their age; the first dose of vaccine should be given 3 months after VZIG administration. If VZIG has been given within 3 weeks of administering a live vaccine, the vaccine should be repeated 3 months later.

## EPSTEIN–BARR VIRUS INFECTION

Epstein–Barr virus (EBV) is a widely disseminated gammaherpesvirus (HHV-4).

**Epidemiology.** EBV is mainly spread through saliva. Exposure to bodily fluids, breast milk, and EBV-positive organ transplantation contributes to the spread of the virus. Approximately 95 % of adults are EBV antibody seropositive. Like other members of the herpesvirus family, EBV has a latency phase. The host cells for the organism in humans are B-lymphocytes, T-lymphocytes, epithelial cells and myocytes.

**Pathogenesis.** EBV infection is divided into three main phases: 1° infection and lytic replication, latency and lytic reactivation.

1° EBV infection in infants and children are common and frequently asymptomatic. The virus initially infects B cells and epithelial cells in the oropharynx. When symptoms do occur, a variety of manifestations have been observed, including otitis media, diarrhoea, abdominal complaints, upper respiratory infection, and infectious mononucleosis (IM). After primary infection, the virus remains dormant, with memory B cells serving as the main reservoir of their persistence. Most people are in the latent phase of EBV infection and show no health-threatening clinical manifestations. However, when human immunity is weakened, many EBVs can be activated and enter the lytic reactivation phase, causing specific diseases. EBV infection mainly causes four types of diseases: IM, chronic active EBV infection, EBV-associated autoimmune disease and EBV-associated tumorigenesis.

The **incubation period** averages four to eight weeks.

**Primary EBV infection-associated diseases. IM** is one of the most common manifestations of EBV infection, occurs in approximately 35–50 % of people who are first infected with EBV in adolescence. IM often begins with malaise, headache, and low-grade fever before development of the more specific signs of tonsillitis and/or pharyngitis, cervical lymph node enlargement and tenderness, and moderate to high fever. The lymphadenopathy characteristically is symmetric and involves the posterior cervical chain more than the anterior chain. Tonsillar exudate is a frequent component of the pharyngitis; the exudate can have a white, grey-green, or necrotic appearance. Severe fatigue may be prominent, while other less common findings include palatal petechiae, periorbital or palpebral edema, and rash.

In patients with IM, a generalized maculopapular or morbilliform, urticarial, or petechial **rash** (fig. 13) is occasionally seen, which may follow the administration of ampicillin and, to a lesser extent, penicillin or other antibiotics, or with no antibiotic exposure at all. The mechanism responsible for this rash is not well understood, but it may represent a transient virus-mediated immune alteration, resulting in the development of a reversible, delayed-type hypersensitivity reaction to the antibiotic. Thus, a rash arising in the setting of penicillin derivative use during IM may not predict a true drug allergy, and many patients subsequently tolerate amoxicillin or ampicillin without an adverse reaction.

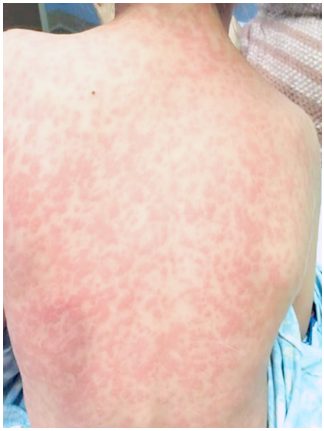

*Fig. 13.* Characteristic amoxicillin associated rash of EBV infection

Nausea, vomiting, and anorexia are frequent in patients with IM, probably reflecting the mild hepatitis encountered in about 90 % of infected individuals, but jaundice is uncommon. Hepatosplenomegaly are seen in 50–60 % of patients, and usually begins to recede by the third week of the illness.

Most patients with IM caused by EBV have prominent pharyngeal symptoms. There are, however, several other forms of the illness. Some individuals with IM present with the so-called “glandular” form of the disease in which lymph node enlargement is out of proportion to the pharyngeal symptoms; others develop a systemic form of the infection in which fever and fatigue predominate, while lymphadenopathy and pharyngitis are mild or absent. Some patients have hepatitis in the absence of other typical features of IM.

The most common **laboratory finding** in association with IM is peripheral blood lymphocytosis, with atypical lymphocytes, defined as more than 10 % of total lymphocytes. The majority of reactive lymphocytes in patients with IM are CD8+ cytotoxic T cells. Some patients have mild relative and absolute neutropenia

and thrombocytopenia. These are generally benign findings that are self-limited. Elevated aminotransferases are seen in the vast majority of patients but are self-limited.

**Complications.** ***Obstruction of the upper airway*** due to massive lymphoid hyperplasia and mucosal edema is an uncommon but potentially fatal complication of IM. Severe obstruction can be successfully treated by tracheotomy or endotracheal intubation.

***Splenic rupture*** is a rare but potentially life-threatening complication of IM. It is estimated to occur in one to two cases per thousand; approximately 70 % occur in males. The typical manifestations are abdominal pain and/or a falling hematocrit. When splenic rupture occurs, it does so spontaneously in over one-half of patients. It typically occurs approximately 14 days after symptom onset; however, it can range from four days to as far as eight weeks. In some cases, it can be the presenting symptom.

***Neurologic syndromes*** include Guillain–Barré syndrome, facial and other cranial nerve palsies, meningoencephalitis, aseptic meningitis, transverse myelitis, peripheral neuritis, optic neuritis, and encephalomyelitis. These manifestations tend to occur 2 to 4 weeks or more after the initial symptom onset. Associations between a clinical presentation of IM and the subsequent development of multiple sclerosis have been described, but mechanisms of interaction are unknown.

***Other*** — EBV can affect virtually any organ system and has been associated with such diverse disease manifestations as hepatitis or cholestasis, pneumonia, pleural effusions, myocarditis, pancreatitis and acalculous cholecystitis, mesenteric adenitis, myositis, acute kidney injury, glomerulonephritis, gastric pseudolymphoma, and genital ulceration. Two rare complications include EBV-triggered hemophagocytic lymphohistiocytosis and chronic active EBV infection.

Most individuals with primary EBV infection recover uneventfully and develop a high degree of durable immunity. Acute symptoms resolve in 1 to 2 weeks, but fatigue often persists for weeks to months.

**Persistent EBV infection-associated diseases.** Chronic active EBV infection is a rare, life-threatening progressive disease with duration of $\geq 3$ months and markedly elevated EBV DNA levels in the absence of immunodeficiency. After infection, the main clinical manifestations are persistent or recurrent IM-like symptoms and progressive chronic damage to multiple organs, such as liver function damage, multiple lymphadenopathies, hepatosplenomegaly, hemophagocytic lymphohistiocytosis, retinitis, interstitial pneumonia, vaccinia-like vesicular disease, and mosquito bite allergies. These outcomes are mainly caused by organ infiltration by EBV-infected lymphocytes.

**EBV-associated autoimmune diseases.** EBV is also associated with the occurrence and development of various autoimmune-associated diseases, such as rheumatoid arthritis, Sjögren's syndrome and systemic lupus erythematosus.

EBV infection can activate and modulate the immune system, thereby increasing the risk of autoimmune diseases. Defective EBV-specific T cells, increased viral load and expression of lytic phase proteins, and high levels of EBV antibodies all support an etiological role for EBV infection in the development of autoimmune diseases.

**EBV-associated malignant tumors.** EBV is a transforming virus and has been causally linked to a variety of malignancies, including lymphomas in transplant recipients. Malignancies include Burkitt lymphoma, tumors in patients with HIV, Hodgkin lymphoma, nasopharyngeal and other head and neck carcinomas, gastric carcinoma, and T cell lymphoma.

*Burkitt lymphoma* is the earliest lymphoma confirmed to be associated with EBV infection. Burkitt lymphoma mostly occurs in children, is aggressive and highly malignant, and progresses rapidly. Endemic Burkitt lymphoma occurs mainly in children in equatorial Africa and has been shown to be associated with EBV infection. Malaria and EBV infection are considered cofactors in the genesis of Burkitt lymphoma. The clinical manifestations of Burkitt lymphoma vary depending on the location of the disease in the body and can manifest as lymph node enlargement, maxillofacial mass, and acute abdomen pain caused by an abdominal mass. Bone marrow metastases can proceed rapidly, and these patients may present with leukemia-like symptoms.

EBV genomic DNA was first reported in tissue specimens from patients with *Hodgkin lymphoma* in 1987. In 90 % of the clinical cases of Hodgkin lymphoma, lymph node enlargement is the first symptom, which gradually spreads from a single lymph node group to systemic lymph nodes. Late-stage Hodgkin lymphoma is associated with liver, spleen, bone marrow and other organ involvement. A total of 20–30 % of patients may experience unexplained fever, night sweats, weight loss, fatigue, itching and other symptoms.

EBV is one of the main causes of *nasopharyngeal carcinoma (NPC).* NPC is relatively rare in most populations; however, it is one of the most common cancers in southern China and Southeast Asia. Early detection of nasopharyngeal carcinoma is very difficult because onset is usually not apparent, and the malignancy rate is high, with 70 % of patients in an advanced stage when they first seek medical attention. Cervical lymph node metastasis is the most common clinical manifestation of NPC and may be accompanied by bloody saliva or nasal secretions, nasal congestion, ear discomfort, and headache.

It is estimated that nearly 10 % of *gastric carcinomas* worldwide carry the EBV genome. EBV-induced gastric carcinoma may be one of the most common EBV malignancies. EBV-induced gastric carcinomas usually involve the upper third of the stomach.

**Diagnosis of EBV infection.** The diagnosis is based on EBV-specific serology, as its clinical symptoms are unspecific. The mononucleosis syndrome is present in other primary infections such as CMV, human immunodeficiency virus (HIV),

and toxoplasmosis. Patients with fever, lymphadenopathy, and pharyngitis should also have a diagnostic evaluation for streptococcal infection by culture or antigen testing. The presence of lymphocytosis and increased circulating atypical lymphocytes supports the diagnosis of EBV infection. However, the diagnosis should be confirmed with EBV-specific testing. When an automated differential from a hematology analyzer flags a specimen as possibly containing atypical lymphocytes, the smear should be reviewed manually since blasts and other abnormalities cannot be reliably distinguished from atypical lymphocytes in these systems.

**EBV-specific antibodies** are the diagnostic gold standard, as they have high sensitivity and specificity for IM, and mainly include the exploration of three or four markers using automated immunoassays: anti-viral capsid antigen immunoglobulin M (anti-VCA IgM), anti-viral capsid antigen immunoglobulin G (anti-VCA IgG), anti-early antigen immunoglobulin G (anti-EA IgG), and anti-Epstein–Barr nuclear antigen IgG (anti-EBNA IgG). The combination of these markers can differentiate a primary infection from a past infection. EBV primary infection is characterized by the presence of anti-VCA IgM with or without anti-VCA IgG but always without anti-EBNA IgG. Indeed, anti-EBNA IgG appears 2–3 months after symptom onset. Anti-VCA IgG may be absent at the very start of symptoms. Anti-VCA IgM persists for 2–3 months after symptom onset, although it may be detected for a longer period. Anti-VCA IgG persists for life. Anti-EA IgG is present at the onset of clinical illness. Past infection is defined by the presence of anti-VCA IgG and anti-EBNAIgG without anti-VCA IgM (table 2).

*Table 2*

**Main Epstein–Barr virus serological profiles**

| Anti-VCA IgG | Anti-VCA IgM | Anti-EBNA IgG | Interpretation |
|---|---|---|---|
| − | − | − | Seronegativeindividual |
| −/+ | + | − | Primaryinfection |
| + | − | + | Pastinfection |
| + | − | − | Past infection (adults) or primary-infection (children) |
| + | + | + | Past infection or end of primary infection |
| − | − | + | Indeterminate |

EBV DNA in serum or plasma is detected in the first 7 days after the onset of IM but never after the 15th day. If positive, it can reinforce the diagnosis of a recent primary infection. EBV PCR in saliva can also be helpful, as it always exceeds 1 million copies/mL during the first few months after IM. However, high viral loads in saliva can also be detected in EBV reactivations in immunocompromised patients. EBV serology or PCR in cerebrospinal fluid can be of interest in cases of neurological complications due to IM. In transplant recipients, especially EBV

seronegative patients receiving EBV seropositive grafts, the detection of antibodies can be delayed after primary infection, and in some cases, the detection of EBV DNA in whole blood can confirm the diagnosis instead of serology. Current PCR assays cannot distinguish linear lytic from latent episomal EBV genomes (fig. 14).

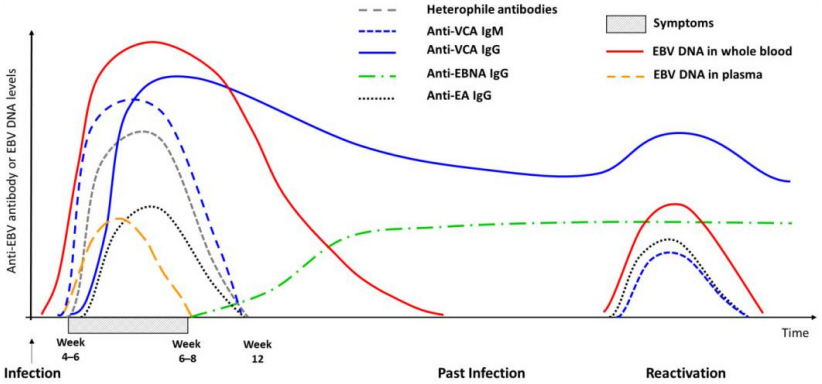


*Fig. 14.* Evolution of antibody and blood EBV DNA markers during EBV infection

**Treatment of EBV infection.** Acyclovir can only inhibit the EBV lytic replication phase not the latent infection phase, so it cannot reduce the severity, shorten the course, or decrease the incidence of complications. Therefore, symptomatic treatment is generally adopted for patients with IM, and most patients recover spontaneously. Acetaminophen or nonsteroidal anti-inflammatory drugs are recommended for the treatment of fever, throat discomfort, and malaise. Provision of adequate fluids and nutrition is also important. It is prudent to get adequate rest, although complete bed rest is unnecessary. There are scant data on the use of ganciclovir or valganciclovir for the treatment of severe EBV infection.

The use of corticosteroids in the treatment of EBV-induced IM has been controversial. Corticosteroid therapy is not recommended for routine cases of IM since it is generally a self-limited illness, and there are theoretical concerns about immunosuppression during clinical illness with a virus that has been causally linked to a variety of malignancies.

However, corticosteroids are warranted in individuals with impending airway obstruction (manifested clinically by difficulty breathing or dyspnea in the recumbent position). Corticosteroid therapy may also be considered in those with severe, overwhelming, life-threatening infection (e.g., fulminant liver failure) or other complications such as severe hemolytic or aplastic anemia.

**Prevention.** At present, there is no commercially available vaccine to prevent EBV infection.

**Return to school or work** — since EBV may be shed intermittently for months to years in people who have acquired infection, and the source of infection

is rarely known in the patient who develops IM, there are no restrictions regarding recently ill IM patients for returning to school or the workplace. The decision to return to full activities should be guided by the level of fatigue and other constitutional symptoms.

## CYTOMEGALOVIRUS INFECTION

CMV, or HHV-5 is a member of Betaherpesvirinae subfamily. 1° infection is followed by latency established primarily in cells of the myeloid lineage. In cell culture, infected cells swell up (cyto — cells, megalo — increase size, virus).

**Epidemiology.** CMV is ubiquitous. Seropositivity increases with age and varies within and between populations. A higher prevalence is generally described in populations with lower socio-economic status. The majority of children in resource-poor countries are seropositive by 1 year of age, with a slower, more gradual increase in acquisition over time in developed countries (around 25 % seropositivity by 1 year of age).

The prolonged excretion of high levels of virus observed during the early years of childhood (whether congenitally or postnatally acquired) is thought to be a major contributor to the spread of CMV infection in the developed world, particularly in the day-care setting.

In Europe, congenital infection is reported in around 3–5/1000 live births and is now the commonest congenital infection.

**Transmission and incubation period.** Transmission is only from human to human and is most commonly via urine and saliva, although CMV may be detectable in many other body fluids. The median duration of excretion of CMV in urine in those infected congenitally/postnatally is around 4 years, and 95 % of congenitally infected babies are still excreting virus at 1 year of age.

Congenital infection is thought to be transmitted from maternal blood via the placenta and is 40 times commoner following 1° infection in the mother during pregnancy than in those who have serological evidence of previous CMV infection. Perinatal/postnatal acquisition may be through cervical secretions during transition through the birth canal but is more commonly due to ingestion of infected breast milk. Rates of transmission are higher in premature and low-birthweight neonates and in those fed fresh breast milk, as opposed to frozen or pasteurized milk.

Infection via blood transfusion was common prior to the routine use of leucodepleted and CMV-negative blood in high-risk subjects.

**Incubation** has been predicted to be around 4–8 weeks, based on studies in the settings of perinatal, post-transplant, and blood transfusion-acquired infection. In the case of congenital infection, it is uncertain whether there is a maternal incubation, followed by a fetal incubation period, which has implications for the diagnostic timing of the amniotic fluid.

**Clinical manifestations** (table 3).

*Table 3*

**Clinical manifestations, treatment, and outcome of cytomegalovirus infections in infants, children, and adolescents**

| | Congenital infection | Early postnatal infection | Infection in immunocompetent children and adolescents | Infection in immunocompromised children and adolescents |
|---|---|---|---|---|
| Clinical manifestations | At birth, 90 % of cases are asymptomatic.<br>Clinical and laboratory findings include:<br>– petechiae;<br>– jaundice at birth;<br>– hepatosplenomegaly;<br>– petechial rash;<br>– small size for gestational age;<br>– thrombocytopenia;<br>– microcephaly;<br>– intracranial calcifications;<br>– polymicrogyria;<br>– ventriculomegaly;<br>– sensorineural hearing loss;<br>– chorioretinitis;<br>– seizures | Term infants — most infants are asymptomatic.<br>Clinical and laboratory findings are usually transient and include:<br>– fever;<br>– hepatosplenomegaly;<br>– mild pneumonitis;<br>– abnormal blood counts;<br>– abnormal liver function tests.<br>Premature and VLBW infants — infection can be severe and life-threatening.<br>Clinical and laboratory manifestations include:<br>– sepsis-like syndrome;<br>– hepatosplenomegaly;<br>– pneumonitis;<br>– hepatitis;<br>– NEC;<br>– abnormal blood counts | Most children are asymptomatic.<br>Clinical and laboratory findings include:<br>– fever;<br>– fatigue;<br>– pharyngitis;<br>– mononucleosis-like syndrome;<br>– adenopathy;<br>– hepatitis;<br>– headache;<br>– abdominal pain;<br>– diarrhea;<br>– arthralgias;<br>– rash;<br>– lymphocytosis or lymphopenia;<br>– thrombocytopenia;<br>– abnormal liver function tests;<br>– negative monospot test | Infection can be severe and life-threatening.<br>Clinical and laboratory findings include:<br>– fever;<br>– malaise;<br>– leukopenia;<br>– hepatitis;<br>– pneumonitis;<br>– colitis;<br>– graft loss (in patients with organ transplant);<br>– myocarditis;<br>– retinitis;<br>– encephalitis/ encephalopathy (especially in patients with HIV) |

*End of the table 3*

| | Congenital infection | Early postnatal infection | Infection in immunocompetent children and adolescents | Infection in immunocompromised children and adolescents |
|---|---|---|---|---|
| Treatment | Asymptomatic infants do not require antiviral treatment. Ganciclovir or valganciclovir for symptomatic infections* | Most term infants and asymptomatic preterm infants do not require antiviral treatment. Ganciclovir or valganciclovir for severe symptomatic infections in premature infants* | Antiviral treatment is generally not indicated. Supportive care with hydration and fever control | Ganciclovir or valganciclovir |
| Outcome | Overall mortality rate is 4 to 8 %. Mortality rate with severe fulminant disease is as high as 30 %. Long-term sequelae include hearing loss, cerebral palsy, intellectual disability, vision impairment, and seizures | Term infants — no permanent sequelae. Premature and VLBW infants — Mortality rate with symptomatic infection is 5 to 10 %. There does not appear to be increased risk of hearing loss, cerebral palsy, or other neurodevelopmental disability; however, long-term outcomes are not clearly understood | No permanent sequelae | High risk of morbidity and mortality, which depends in part on the underlying condition |

**Congenital CMV.** Congenitally infected infants are broadly categorized into those who are symptomatic or asymptomatic at birth. Around 90 % of babies with congenital CMV are asymptomatic at birth, and the major concern in these babies is the 5–10 % risk of developing hearing loss during the preschool years.

Around 10 % of congenitally infected babies have symptoms of CMV disease at birth, including petechiae due to thrombocytopenia, blueberry muffin rash due to extramedullary haemopoiesis, intrauterine growth retardation, hepatosplenomegaly, and hepatitis/jaundice. CNS features are common, including microcephaly and intracranial calcification, along with ocular abnormalities, including chorioretinitis, optic atrophy, and strabismus.

Sensorineural hearing loss (SNHL) is one of the commonest manifestations of congenital CMV infection. It can be unilateral or bilateral, fluctuates, and is progressive up to around 7 years of age. Half of babies with SNHL and CMV infection identified at birth will have no other clinical findings of CMV. SNHL may, however, be delayed in onset in around 30 %, and progressive in 50 %, of cases. SNHL is therefore reported by 5 years of age in around 35 % of those with symptoms at birth, and about 10 % of those babies with no disease noted at birth. Overall CMV probably contributes to 25 % of all SNHL.

Long-term neurological disability (excluding SNHL) is reported in around 50 % of those with, and < 5 % of those without, symptoms identified at birth.

**Postnatal CMV.** Postnatal disease is now most commonly seen in very low birth weight infants neonatal units, who received CMV-infected breast milk from their mothers. It presents as pneumonitis, hepatitis, hepatosplenomegaly, lymphadenopathy, gastro-intestinal disease, thrombocytopenia, and a sepsis-like syndrome.

Long-term sequelae in these babies do not, according to current literature, seem attributable to CMV infection

**Immunocompromised children.** Immunocompromised patients (usually bone marrow or organ transplant) present with generalized systemic symptoms (often referred to as CMV syndrome) or organ-specific disease (including hepatic, pulmonary, and GI manifestations, and occasionally CMV encephalitis). In the transplant group, CMV can also have indirect effects on outcomes, such as graft rejection, and risks of other opportunistic infections.

**Immunocompetent children.** Acquired CMV infection in healthy children and adolescents is most often asymptomatic. However, approximately 10 percent of acquired CMV infections produce symptoms. CMV can cause a mononucleosis-like syndrome; the most common manifestations are fever, fatigue, pharyngitis, adenopathy (especially cervical adenopathy), and hepatitis. Headache, abdominal pain with diarrhea, arthralgias, and rash also may occur. Laboratory abnormalities can include abnormal lymphocyte count (lymphocytosis or lymphopenia), neutropenia, thrombocytopenia, and elevated transaminases. Unlike mononucleosis

caused by Ebstein–Barr virus, the heterophile antibody (Monospot) test is negative in CMV-associated mononucleosis-like illness.

**Diagnosis.** ***Direct methods.*** Direct tissue culture of body fluids has traditionally been the gold standard for identifying infection; confirmation of a positive result may take up to 3 weeks, making this method impractical for early diagnosis.

PCR amplification of viral DNA offers a rapid alternative with similar sensitivity and specificity; methods utilizing immunofluorescent or immunoperoxidase-labelled monoclonal antibodies directed against the early antigen of CMV may also be used.

Urine or saliva PCR is positive in up to 100 % of infected individuals (although intermittent detection has been reported) and remain the diagnostic samples of choice for congenital infection.

Isolation of CMV from a specimen acquired within the first 3 weeks of life is necessary to discriminate between congenitally and postnatally acquired infection.

Blood PCR is only positive for CMV in around 80 % of babies with CMV disease at birth. Recent data would suggest that blood samples should be taken within the first 10–14 days of life to completely exclude post-natal infection.

Detection and quantification of virus in blood (using PCR or methods detecting the presence of CMV antigen) are important for monitoring and detecting CMV viral load early in the transplant setting. Most children are now screened weekly post-transplantation by serial blood CMV PCR.

Identification of CMV by PCR in the amniotic fluid may establish whether antenatal transmission has occurred. Samples should ideally be acquired at least 7 weeks after maternal symptoms (if present), and after 21 weeks' gestation, to minimize false negative reports.

Dried blood spots (Guthrie card) taken shortly after birth may be used retrospectively to confirm the presence of congenital CMV using PCR.

Blood viral load is always lower than urine and saliva. The sensitivity and specificity of this method currently varies widely between laboratories, depending on the extraction methods used, the amount of starting material, and the part of the CMV genome being amplified. If dried blood spots are negative on testing for CMV PCR, congenital CMV is not excluded.

**Serology.** Serology is of limited use in those under 1 year of age but may be helpful as a first step in diagnosis in older children. IgM measurement may indicate 1° infection but is only positive in around 70 % of congenitally infected infants; false positive results are not uncommon, particularly during pregnancy.

The use of IgG avidity is helpful in identifying 1° infection in adults, particularly during pregnancy, but there are no published data on CMV IgG antibody maturation in younger children. High-avidity (stickiness/efficacy) IgG shows the presence of a more mature immune response.

This implies an established infection that was not recently acquired.

**Management and treatment.** Congenitally infected babies should be fully evaluated for signs of disseminated and CNS CMV disease. Baseline investigations should include FBC, liver function tests, clotting (in the presence of hepatomegaly or hepatitis), ophthalmologic review, and formal audiological assessment. Renal function should also be assessed prior to starting treatment with ganciclovir. Cranial ultrasound, carried out by a skilled operator, is sufficient in the 1° assessment of an asymptomatic baby with confirmed congenital CMV infection. Magnetic resonance imaging should be performed for all symptomatic babies and is increasingly being used in asymptomatic babies, particularly if mild abnormalities on cranial ultrasound.

Follow-up investigations should include paediatric neurodevelopmental follow-up, audiology, and ophthalmic assessments. In the UK, it is currently recommended that both symptomatic and asymptomatic babies have 6-monthly hearing assessments until 3 years old, then annual checks until 6 years old; in symptomatic babies, yearly ophthalmic follow-up until 5 years old, as late-onset chorioretinitis has been reported. Completely asymptomatic infants do not require ophthalmic follow-up after the baseline assessment.

Antiviral treatment with the nucleoside analogue ganciclovir, given twice daily IV for 6 weeks, has been shown to decrease progression of SNHL and improve neurodevelopmental outcome in those with CNS disease if started early in neonatal life. A randomized study comparing 6 weeks to 6 months of valganciclovir, the oral prodrug of ganciclovir, in babies with symptomatic congenital CMV disease suggests that 6 months of treatment results in improved audiological and neurodevelopmental outcomes at 2 years of age. In the UK, the only clear indication for treatment in congenital CMV infection is currently symptomatic CNS disease.

CMV viral load, FBC, and liver and renal function should be assessed regularly during treatment to assess treatment efficacy, and monitor disease progression and treatment side effects.

Therapeutic drug monitoring can also be performed to guide management and is essential in treatment failure; however, there are very limited pharmacokinetic data on ganciclovir and valganciclovir in premature infants and older children.

There is at present no clear evidence for the use of antiviral treatment in postnatally infected neonates. Treatment may, however, be considered in those with severe liver disease or pneumonitis where other conditions have been excluded and the risk of treatment is balanced by the severity of disease.

In transplant recipients and other immunocompromised children, CMV infection and disease should be screened for regularly, and pre-emptive therapy started if a positive blood CMV PCR is found, according to local protocols, in order to prevent the significant morbidity and mortality associated with CMV in these groups. Alternatively, CMV prophylaxis should be commenced and continued until the child is considered at lower risk of CMV disease.

Side effects of standard antiviral drugs are significant, and the risks and benefits of treatment need to be discussed with families. The commonest side effects relate to bone marrow suppression (mainly neutropenia), which usually reverses on termination of therapy. The theoretical risk of longer-term side effects identified in ganciclovir and valganciclovir animal models, which include carcinogenicity and impaired fertility, is not fully evaluated in the clinical setting — no evidence has been found in limited follow-up studies.

**Prevention.** Advice to CMV-seronegative pregnant women to avoid contact with potentially infected secretions in younger children has been shown to decrease transmission in the research setting. However, in most countries, women are not offered routine antenatal serological screening for CMV, as it is currently of unproven benefit for the widespread prevention of CMV disease in neonates.

Currently, neonatal screening is not routine; however, a recent study has shown that early detection of congenital CMV infection and enhanced hearing follow-up is feasible and may enable early audiological input to maximize hearing in the prelinguistic stage.

Antiviral treatment may also prevent hearing deterioration and lead to improved neurological function at 2 years of age.

Preventive strategies using antiviral agents in the post-transplant period have significantly decreased morbidity and mortality attributable to CMV in this patient group.

An effective vaccine against CMV does not currently exist, although a number of vaccine candidates are currently undergoing clinical trials.

Randomized antenatal studies are under way of both valaciclovir and immunoglobulin in pregnant women with 1° infection, aiming to reduce vertical transmission.

## HUMAN HERPESVIRUS 6A / B INFECTION

Human herpesvirus 6A (HHV-6A) and human herpesvirus 6B (HHV-6B), collectively termed HHV-6A/B, are lymphotropic viruses, members of the *Roseolovirus* genus, subfamily *Betaherpesvirinae*. In 2012, HHV-6A and HHV-6B were recognized as distinct species rather than as variants of the same species. HHV-6B causes the majority of documented 1° infections and reactivations events. Little is known about the epidemiology or clinical implications of HHV-6A. As with all HHV, they establish lifelong latency after initial acquisition and may reactivate in immunocompromised hosts, especially after allogeneic hematopoietic cell transplantation.

**Epidemiology.** HHV-6 infects most children within the first two years of life. In developed countries, the rate of seroprevalence among adults is generally > 70 %.

Transmission may occur:

– prenatally — generally occurs through germline transmission of chromosomally integrated HHV-6 from either parent. In utero transmission of reactivated virus or primary infection (i. e., initial infection or infection with a new strain) occurs rarely;

– postnatally — occurs mainly through saliva. Transmission through breast milk or blood products has not been reported. Transmission through organ or hematopoietic cell donation has been reported rarely.

**Pathogenesis.** Latency of HHV-6 usually occurs in monocytes, capable of later reactivation. HHV-6 may also establish a latent state through integration into the telomeric region of a human chromosome as a result of homologous recombination, typically in a small proportion of somatic cells. However, integration into germline cells is responsible for congenital HHV-6 infections. In approximately 1 % of people, HHV-6 DNA is integrated into chromosomes, including chromosomes in germline cells. Children born to individuals with chromosomally integrated HHV-6 can have one copy of virus per nucleated cell. When an individual with chromosomally integrated HHV-6 donates hematopoietic stem cells, the transplant recipient will have integrated virus in their nucleated hematopoietic cells.

Although there are few data regarding the **incubation period** of HHV-6 infection, it is thought to be approximately 9 days (range 5 to 15 days).

The **clinical manifestations** of HHV-6 infection vary with the age and immune competence of the child.

Clinical manifestations of 1° infection with HHV-6B commonly include fever, fussiness, and rhinorrhea; generalized rash occurs in almost one-third of children and roseola (exanthema subitum) occurs in 20 % to 25 %. Acute HHV-6B infection may also be accompanied by cervical and characteristic postoccipital lymphadenopathy, gastrointestinal tract or respiratory tract signs, and inflamed tympanic membranes. Fever may be high (temperature > 39.5 °C) and persist for 3 to 7 days. Approximately 20 % of all emergency department visits for febrile children 6 through 12 months of age are attributable to HHV-6B. Roseola is distinguished by an erythematous maculopapular rash that typically appears once fever resolves and can last hours to days (fig. 15).

Febrile seizures, sometimes leading to status epilepticus, are the most common complication and reason for hospitalization among children with 1° HHV-6B infection. 1° HHV-6B infection has been shown to account for 20 % to 30 % of first-time febrile seizures in young children evaluated in emergency care settings. Other reported neurologic manifestations include a bulging fontanelle and encephalopathy or rarely, encephalitis; the latter more commonly noted in infants in Japan than in the United States or Europe. Hepatitis has been reported as a rare manifestation of primary HHV-6B infection.

In contrast to HHV-6B, primary infection with HHV-6A has not been associated with any recognized disease.

Congenital infection with HHV-6B and HHV-6A, which occurs in approximately 1 % of newborn infants, has not been linked to any clinical disease, and most cases have been shown to be attributable to inherited chromosomally integrated HHV-6.

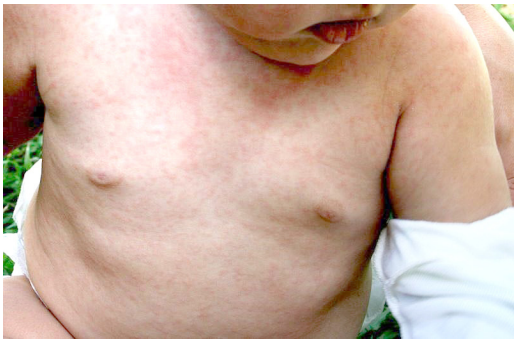

*Fig. 15.* Roseola rash

**Encephalitis** of variable severity can rarely occur as a complication of roseola or as the primary manifestation of HHV-6 infection in otherwise immunocompetent hosts. Panencephalitis is most common, but focal necrotic encephalitis mimicking HSE has been reported. The detection of viral antigens in neural cells suggests that the encephalitis is caused by a direct viral effect, but immune-mediators also may play a role.

HHV-6 has been associated with **mesial temporal lobe epilepsy.** In pathology studies, HHV-6 DNA was recovered more frequently from brain biopsies from patients with mesial temporal lobe epilepsy than from patients without mesial temporal lobe epilepsy, suggesting that HHV-6 has pathologic effects.

HHV-6 has also been reported in association with a **mononucleosis-like syndrome** in infants and adults and with **liver failure** of unknown etiology.

Following infection, HHV-6A/B remains in a latent state and may reactivate. The clinical circumstances and manifestations of reactivation in healthy people are unclear. Illness associated with HHV-6B reactivation has been described primarily among recipients of solid organ and hematopoietic cell transplants.

Clinical findings associated with HHV-6B **reactivation** include fever, rash, hepatitis, bone marrow suppression, acute graft-versus-host disease, graft rejection, pneumonia, delirium, and encephalitis. The best characterized of these is posttransplantation acute limbic encephalitis, a specific syndrome associated with HHV-6B reactivation in the CNS characterized by anterograde amnesia, seizures,

insomnia, confusion, and the syndrome of inappropriate antidiuretic hormone secretion. It is estimated that approximately 2 % of allogeneic hematopoietic cell transplant recipients will experience HHV-6B encephalitis, with cord blood transplant recipients being at highest risk. Significant morbidity and mortality has been attributed to this complication.

**Diagnosis.** In immunocompetent children with typical presentations of HHV-6 (e.g., acute illness with high fever, with or without rash, and nonspecific symptoms), laboratory confirmation of HHV-6 is seldom necessary and is unlikely to affect management. In these children, HHV-6 generally resolves spontaneously without adverse effects.

Laboratory confirmation of HHV-6 may be necessary in immunocompromised children or immunocompetent children with atypical presentations or complications (e.g., meningoencephalitis). In such patients, diagnosis of HHV-6 may affect management (e.g., antimicrobial therapy, immunosuppressive therapy) or facilitate monitoring of the clinical course and/or therapy.

Confirmation of HHV-6 as a causative pathogen is complicated by the high seroprevalence of HHV-6 in individuals older than three years, the persistence of HHV-6 DNA after primary infection, and the possibility of integration of HHV-6 DNA into chromosomes. In addition, reactivation of HHV-6 may occur in healthy children without apparent illness. A combination of laboratory tests may be necessary. Viral replication indicates active infection (1° infection or reactivation). Viral replication in patients with negative serology suggests primary infection rather than reactivation.

Among the available tests, quantitative real-time PCR provides the most useful information. It is typically performed on whole blood, serum, plasma, and CSF. It is highly sensitive and specific and permits HHV-6 speciation. High HHV-6 viral load in the CSF supports HHV-6 as the causative pathogen, particularly in an immunocompromised child. Quantitative PCR of whole blood, as well as plasma, serum and peripheral mononuclear cells, may facilitate preliminary categorization of infection according to levels of HHV-6 DNA.

Qualitative real-time HHV-6 PCR does not differentiate between latent infection, active infection, and chromosomally integrated DNA.

**Treatment.** In immunocompetent children, HHV-6 infection usually is a benign disease that resolves spontaneously and does not require specific therapy.

Antiviral therapy may be warranted for HHV-6 infections associated with increased morbidity (e.g., encephalitis, myocarditis) in both immunocompetent and immunocompromised hosts. When treatment of HHV-6 infection is necessary, ganciclovir or foscarnet generally is preferred to cidofovir, because cidofovir is nephrotoxic. Response to therapy is determined by improvement in clinical symptoms and decreased viral load (if viral load was measured at diagnosis).

## HUMAN HERPESVIRUS 7

HHV-7 belongs to the *Roseolovirusgenus* of the *Betaherpesvirinae* subfamily.

**Epidemiology.** HHV-7 is ubiquitous. More than 95 % of adults are seropositive. Infection with HHV-7 generally occurs during childhood but peaks at a later age than infection with HHV-6, usually around three years of age. HHV-7 appears to be shed throughout life in saliva. HHV-7 DNA has been detected in human milk, peripheral blood mononuclear cells, cervical secretions, and other body sites. Congenital HHV-7 infection has not been demonstrated. For HHV-7, the incubation period is not known.

The **clinical manifestations** occurring with HHV-7 infection are less clear than with HHV-6B. Most primary infections with HHV-7 presumably are asymptomatic or mild and not distinctive. Some initial infections can present as typical roseola and may account for second or recurrent cases of roseola. Hepatitis and a mononucleosis-like syndrome have been reported during HHV-7 with or without concurrent EBV infection.

**Neurological manifestations** associated with HHV-7 have been described in primary infection in children, and very occasionally in immunocompromised adult patients. Several reports describe an association between HHV-7 and febrile seizures, hemiconvulsion and hemiplegia syndrome, encephalopathy and acute myeloradiculoneuropathy. Isolated cases of limbic encephalitis, hemorrhagic brainstem encephalitis, and Guillain-Barré syndrome have been reported during HHV-7 infection.

A few cases of CNS symptoms have been reported in association with HHV-7 reactivation in immunocompromised hosts, but clinical findings generally have been reported much less frequently with HHV-7 than with HHV-6B reactivation.

An association of HHV-7 with **pityriasis rosea** has been suggested by the presence of HHV-7 DNA in cell-free plasma, seroconversion to the virus, and viral particles suggestive of HHV-7 on electron microscopy

**Drug reaction with eosinophilia and systemic symptoms** (DRESS; also known as drug-induced hypersensitivity syndrome) has been associated with reactivation of HHV-7 as well as HHV-6, EBV, and CMV, although a causal link between these viruses and drug reaction with eosinophilia and systemic symptoms has not been demonstrated. One hypothesis is that the rash could be mediated by increased activated CD8 T-lymphocytes directed against these viruses.

**Diagnosis.** PCR assays have been developed, and real-time PCR assays can quantify and differentiate HHV.

**Treatment.** No clinical settings in which treatment for HHV-7 infection is warranted have been identified. In vitro, foscarnet and cidofovir inhibit HHV-7 replication by achievable concentrations. The virus is relatively resistant to acyclovir, penciclovir, and ganciclovir.

## HUMAN HERPESVIRUS-8 INFECTION

HHV-8, also known as Kaposi sarcoma-associated herpesvirus, belongs to the gamma herpesvirus family. Its closest known relative is EBV.

HHV-8 is now established as the cause of several human tumors arising from distinct cells types, including Kaposi sarcoma (KS), primary effusion lymphoma, and, in the setting of HIV, almost all cases of multicentric Castleman disease (MCD). Patients can manifest more than one of these tumors. It has also been implicated in an inflammatory syndrome distinct from HHV-8-associated MCD, the Kaposi sarcoma inflammatory cytokine syndrome (KICS).

While HHV-8 associated tumors are most common in individuals with HIV, they have also been reported in other immunosuppressed and older individuals, and occasionally in patients with congenital immunodeficiencies. Additionally, hemophagocytic syndrome has been reported after HHV-8 infection in infants with heterozygous mutations in perforin alleles.

HHV-8 can infect a variety of cells, including those of endothelial lineage, monocytes, and B cells. Thus, HHV-8-associated cancers derive from different cells of origin among the range of cells infected by HHV-8.

Like all HV, HHV-8 infection exhibits both latent and lytic phases, distinguished by their viral gene expression patterns. During the latent phase of infection, only a few viral genes are expressed, while during the lytic phase, the full viral genetic program involving multiple genes is expressed and viral replication occurs along with destruction of the host cell.

HHV-8-associated tumors are estimated to account for just under 1 % of all cancers occurring worldwide. Although HHV-8 infection is necessary to cause the associated tumors, the tumors require other cofactors (e.g., untreated HIV infection, immunosuppression) in order to develop. The risk of developing HHV-8-associated diseases among individuals with HHV-8 without any contributing cofactors is low: only about 1 in 400 to 1 in 1500 individuals with HHV-8 develop KS, with the incidence increasing with age (likely due to waning cellular immunity). In contrast, as many as one half of patients with HIV and HHV-8 coinfection will develop KS in the absence of effective antiretroviral treatment.

**Epidemiology.** Serologic surveys show that HHV-8 is not ubiquitous. Significant variations in prevalence occur geographically and across different behavioral groups. HHV-8 infection is very common in sub-Saharan Africa with seropositivity rates of over 50 %; moderately prevalent in Mediterranean countries (20–30 %); and much less common (well under 10 %) in most of Europe, Asia, and the United States. The reasons for this geographic variation remain unclear. HHV-8 prevalence also is elevated in certain behavioral groups regardless of geography. Most strikingly, its prevalence is greatly elevated in men who have sex with men, independent of the increase in HIV prevalence also seen in that group.

The mechanisms for this variation remain unclear but could relate to specific sexual practices.

HHV-8 is primarily transmitted by saliva but can also be transmitted via organ donation or rarely, via blood transfusion.

**Associated clinical syndromes.** In most cases, 1° infection with HHV-8 is either asymptomatic or minimally symptomatic. However, symptomatic primary infection syndrome has been described in immunocompetent children, immunocompetent adults, and immunocompromised individuals.

In some *immunocompetent children,* primary HHV-8 infection may be associated with fever and a maculopapular rash, appearing on the face and spreading gradually to the trunk and extremities. The median duration of the rash is 6 days (range 3 to 8 days), and the median duration of fever is 10 days (range 2 to 14 days).

In *immunocompetent adults,* studies in men who have sex with men without HIV describe transient lymphadenopathy in association with HHV-8 seroconversion. In a minority of cases, the lymphadenopathy was associated with a mild systemic illness including fatigue, diarrhea, and localized rash.

In *immunocompromised adults,* including solid organ transplant recipients and individuals with HIV, case reports describe significant systemic symptoms with primary infection. Features include fever, splenomegaly, lymphoid hyperplasia, pancytopenia, and in some cases rapid-onset KS. These features resemble the inflammatory symptoms seen with HHV-8-associated MCD and with KICS, but the great majority of cases were transient and self-limited.

**Kaposi sarcoma.** KS is a multifocal angioproliferative tumor with four epidemiologic forms: Classic KS, endemic or African KS, AIDS-related KS, and organ transplant-associated KS. Regardless of these epidemiologic categories, the pathology of KS is similar, and with some exception, the clinical course is similar as well. KS usually manifests as red, purple, or brown papules or plaques on the skin or mucous membranes (fig. 16). Lesions may occur at any site, but there is a predilection for the extremities, ears, nose, and palate for reasons which remain unclear. KS involvement of visceral organs such as the lungs or gastrointestinal tract and effusions in serous body cavities are other manifestations of advanced disease and may be life threatening.

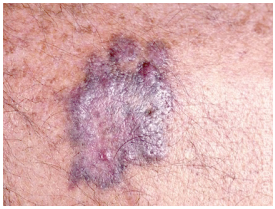

*Fig. 16.* A violaceous plaque representing Kaposi sarcoma is shown

**Multicentric Castleman disease.** HHV-8 is the etiologic agent of a plasmablastic form of MCD that is most common in the setting of HIV but can also arise in transplant recipients and in other patients without HIV. HHV-8 associated MCD is a polyclonal B-cell disorder characterized clinically by intermittent flares of inflammatory symptoms and signs, including fevers, night sweats, fatigue, and cachexia, and edema, together with lymphadenopathy and hepatosplenomegaly. Common laboratory abnormalities include anemia, thrombocytopenia, hypoalbuminemia, hyponatremia, and elevated inflammatory markers, most notably C-reactive protein.

**Kaposi sarcoma inflammatory cytokine syndrome.** KICS is a syndrome characterized by severe inflammatory symptoms and elevated HHV-8 viremia. The clinical manifestations are similar to those of MCD, and include fevers, night sweats, fatigue, and cachexia, and edema. Hepatosplenomegaly is common whereas lymphadenopathy is not. Laboratory abnormalities include anemia, thrombocytopenia, hypoalbuminemia, hyponatremia, and elevated inflammatory markers including C-reactive protein.

**Primary effusion lymphoma.** Primary effusion lymphoma is a rare variant of B-cell non-Hodgkin lymphoma notable for its unusual presentation and aggressive clinical course. The great majority of reported cases occur in people with HIV, although it may also be seen following solid organ transplantation, in older adults, and in chronic hepatitis C virus infection. Primary effusion lymphoma usually presents as a lymphomatous effusion in serous body cavities, with pleural involvement seen in 60–90 % of patients, followed by involvement of other body cavity membranes, including peritoneal (30–60 %), pericardial (up to 30 %), joint spaces, and rarely meninges.

**Diagnosis.** HHV-8 infection should be suspected when an immunocompromised patient presents with symptoms or signs that are consistent with one of the HHV-8 associated clinical tumor syndromes. Since primary HHV-8 infection is transient and self-limiting, even in immunocompromised individuals, diagnosis and treatment is not necessary. There is no clinical role for screening asymptomatic individuals for HHV-8 infection.

Available tests to detect HHV-8 include immunohistochemistry on body tissue/fluid, blood PCR, and serology. HHV-8 associated tumors are typically diagnosed by immunohistochemistry of body tissue samples or cells from body cavity effusions. In contrast, KICS is typically diagnosed by detecting HHV-8 viremia by PCR in peripheral blood.

**Treatment.** Several antiviral agents such as ganciclovir, foscarnet, and cidofovir inhibit HHV-8 replication in vitro. However, direct antiviral therapy of HHV-8 infection in patients has a very limited role. Primary HHV-8 infection is usually asymptomatic and if symptomatic, self-limited without treatment. HHV-8 infection cannot be eradicated although long-term remissions of the associated clinical syndromes are possible with reduction in immunosuppression in immunocompromised patients.

## SELF-CONTROL TASK

**1. Select the virus, which belongs to Alphaherpesvirinae Subfamily:**

a) CMV; c) VZV;
b) EBV; d) HHV-6.

**2. Select the virus, which belongs to Betaherpesvirinae Subfamily:**

a) HSV 1; c) VZV;
b) EBV; d) CMV.

**3. Select the virus, which belongs to Gammaherpesvirinae Subfamily:**

a) HSV-1; c) EBV;
b) HSV-2; d) VZV.

**4. A 17-year-old college girl with an extremely sore throat and high fever who develops a rash upon administration of ampicillin. Match the disease with the associated organism:**

a) rubivirus; d) HHV-7;
b) VZV; e) EBV.
c) measles virus;

**5. The appearance of an evanescent, erythematous, maculopapular rash following the rapid defervescence of several days of high-grade fever in a 9-month-old boy. Match the disease with the associated organism:**

a) rubivirus; c) measles virus;
b) VZV; d) HHV-6.

**6. In what case atypical lymphocytes can appear in CBC?**

a) scarlet fever;
b) infectious mononucleosis;
c) herpes zoster;
d) erythema infectiosum.

**7. What result of specific EBV serology indicates an acute infectious mononucleosis?**

a) IgG anti-viral capsid antigen positive;
b) IgM anti-viral capsid antigen positive;
c) anti-EBNA (Epstein–Barr virus nuclear antigen) positive;
d) IgM anti-viral capsid antigen negative.

**8. Select the effective antiviral medicine for the treatment of varicella infection:**

a) Oseltamivir; c) Acyclovir;
b) Prednisolon; d) Ganciclovir.

**9. Evolution of the elements of rash in chickenpox:**

a) vesicle – spot – pimple – crust;
b) spot – papule – vesicle – crust;
c) spot – vesicle – papule – crust;
d) spot – crust.

**10. EBV is associated with:**

a) Kaposi's sarcoma;
b) Burkitt's lymphoma;
c) Hepatocellular carcinoma;
d) Neuroblastoma.

**Answer key: 1** — c; **2** — d; **3** — c; **4** — e; **5** — d; **6** — b; **7** — b; **8** — c; **9** — b; **10** — b.

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