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† It is with great regret that we report that J.G.P. Sissons died on 25 September, 2016.

8.5.2 Herpesviruses (excluding Epstein–Barr virus) 735 and surviving infants have mental, visual, and hearing impairment. (2) Infection in patients who are immunosuppressed patients—the most serious forms are pneumonitis in bone marrow transplant re- cipients and retinitis in HIV/AIDS patients. Specific treatment for HCMV is usually with ganciclovir, which requires intravenous ad- ministration and has limiting side effects including myelotoxicity; valganciclovir has higher oral bioavailability and is particularly used for prophylaxis. Human herpesvirus 6 and 7 (HHV-6 and 7) These are β-herpesviruses, genetically related to HCMV and most probably transmitted via maternal saliva. Unlike any other herpes- virus family members, HHV-6 genome DNA can be found cova- lently integrated into the cell chromosomes in about 1% of the population. Primary infection with HHV-6 in young children is associated with roseola infantum (exanthem subitum, sixth disease), and also with a febrile illness without rash. More than 90% of children are seroposi- tive for HHV-6 by 2 years of age. HHV-6 reactivation may occur in immunosuppressed solid organ and bone marrow transplant recipi- ents, but it is not clear that HHV-6 causes disease in these patients. HHV-6 sensitivity to antiviral drugs corresponds with that of HCMV, but no treatment is usually required. HHV-7 has been associated with some cases of roseola, but there is no other evidence for its being pathogenic. Human herpesvirus-8 (HHV-8) This member of the rhadinovirus (γ 2-herpesvirus) family is the most recently discovered human herpesviruses, having been iso- lated from Kaposi's sarcoma tissue in 1994. The mechanism of transmission is probably by saliva and sexual contact; reported seroprevalence is around 50% or more in many African adult popu- lations, but 5% or less in blood donors in the United Kingdom and the United States of America, with intermediate rates in Italy and other Mediterranean countries. HHV-8 (as other γ-herpesviruses such as Epstein–Barr) is potentially oncogenic: it is clearly associated with (1) Kaposi's sarcoma—HHV-8 can be detected by PCR in the blood of nearly all cases. Manifests clinically as purplish-brown macules, papules and
plaques, and is described in four clinical settings: (a) the classic form—typically presents in elderly Mediterranean or Jewish men with lesions on the extremities and an indolent course; (b) the endemic African form—accounts for 10% of cancer in equatorial Africa and is similar clinically to the classic form of the disease; (c) in patients with immunodeficiency states such as transplant recipients—lesions are more widespread and rapidly progressive, but visceral involvement is unusual; and (d) the AIDS-associated form—with widespread cutaneous lesions, involvement of the oral mucosa, visceral lesions in the lungs or gastrointestinal tract, and sometimes rapid progression. Kaposi's sarcoma lesions may regress with antiretroviral treatment, withdrawal of immuno- suppression, and the disease can also be treated with radiation therapy and (for widespread cutaneous or visceral disease) with chemotherapy. (2) Primary effusion lymphoma—HHV-8 is pre- sent in the tumour cells of all cases of this rare and aggressive type of B-cell lymphoma that presents in patients with AIDS. (3) Multicentric Castleman's disease (angiofollicular lymph node hyperplasia)—HHV-8 is present in most cases of this condition, es- pecially those associated with HIV. Cercopithecine herpesvirus 1 This α-herpesvirus (formerly named herpes B virus) is closely re- lated to HSV, and found in Old World monkeys, its natural host. Transmission to humans from monkey bites results in a high inci- dence of severe disease, with progressive encephalitis. Treatment is with aciclovir or ganciclovir, but morbidity and mortality are high. Human herpesviruses The Herpesviridae family is widely distributed in the animal kingdom. More than 100 have been isolated from humans, pri- mates, and other mammals, and from reptiles and fish. Comparative sequence analysis suggests they have been coevolving with their in- dividual hosts for millions of years. Eight human herpesviruses have been identified to date (Table 8.5.2.1). Shared genomic and bio- logical properties divide the herpesviruses into three

subfamilies, the α-, β-, and γ-herpesvirinae. All the herpesviruses have a linear double-stranded DNA genome contained inside an icosahedral capsid that is surrounded by a protein tegument. The outer lipid envelope contains virus glycoprotein spikes. These large viruses have genomes consisting of unique segments of DNA flanked by inverted repeats, and en- code most of the proteins needed for replication. All herpesviruses share an important biological feature, their capacity to produce la- tent infection in their natural host, during which the viral genome persists in cells, usually as a closed circle (episome), expressing only a limited subset of virus genes. This property results in their ability to produce lifelong infection in different types of cell, depending on the individual virus, and thus to persist in the popu- lation. Herpesvirus disease may result from primary infection, or reactivation of the virus from latency, and tends to be more severe in immunosuppressed patients. The γ-herpesviruses can induce cell transformation, and are associated with specific tumours. Herpes simplex virus infections Historical background ‘Herpes’ derives from the Greek, meaning to creep or crawl, ap- parently used since antiquity to describe the evolution of the skin lesions caused by herpes simplex virus (HSV) and varicella-zoster virus. HSV was the first of the herpesviruses to be isolated, in the 1930s, although the transmission of infection to animals had been demonstrated in 1919. The serological distinction between the two types, HSV-1 and HSV-2, and the association of HSV-2 with genital herpes, was made in the 1960s. HSVs are now some of the most in- tensively studied human viruses. Aetiology HSV has a genome size of 150 kbp, and codes for about 80 pro- teins. The genomes of HSV-1 and HSV-2 are largely colinear, but

 have only about 50% genomic homology. Gene expression occurs in three temporally regulated phases: immediate-early, early, and late. Immediate-early proteins are largely regulatory proteins that prepare the cell to produce further virus. The early genes code particularly for enzymes involved in the replication of virus DNA, and the late genes for the structural proteins of the virion. Antigenic differences in the surface glycoprotein G are used to distinguish between HSV-1 and HSV-2. The release of progeny virus is normally accompanied by cell death (i.e. the infection is lytic). The virus infects a relatively wide range of cells in vitro, and can also infect experimental animals, allowing studies of its pathogenesis. Epidemiology HSV is a ubiquitous virus, widely distributed in populations throughout the world. Although animals can be infected experi- mentally, there are no natural animal hosts, and humans are the only reservoir. Transmission occurs when a susceptible person has direct contact with infected secretions from an HSV carrier, usually from oral, genital, or skin lesions, to mucous membranes or abraded skin of the recipient. HSV carriers can excrete virus asymptomatically, and 1–15% of adult carriers excrete HSV at any one time. Conventionally, the prevalence of infection is assessed by demonstrating antibody to HSV-1 or HSV-2. The prevalence of HSV-1 increases with age, although the time of acquisition of HSV-1 antibody varies depending on socioeconomic factors. Seroprevalence in early life is higher among lower socioeconomic groups, 70–90% of children having antibodies by the age of 10, whereas only about 30% of children in higher socioeconomic groups have antibodies by this time. By mid-life, 80–90% of people are HSV-1 seropositive. HSV-2 infection is usually acquired through sexual contact; consequently, seroconversion correlates with the onset of sexual activity, and a progressive increase in seroprevalence to HSV-2 begins in adolescence. The number of sexual contacts is a major risk factor for the acquisition of HSV-2. Cumulative seropreva- lence rates in adults vary from 10 to 80%, depending on the popu- lation and risk factors. HSV can be transmitted to neonates by infection (usually HSV-2) from maternal genital secretions at the time of delivery. The mothers are most often asymptomatic excretors of the virus who have no his- tory

of genital herpes. Pathogenesis HSV infects and replicates in epithelial cells at the site of inoculation onto mucous membranes or abraded skin, with an incubation period of 4–6 days before clinical lesions appear. There is a marked local inflammatory response, but viraemia and dissemination may occur in the immunocompromised host. Following local epithelial replication, HSV enters the peripheral sensory nerves innervating the site of replication, and ascends the axons by retrograde trans- port to reach the dorsal root ganglia, or the trigeminal ganglion in the case of oral or conjunctival inoculation. The virus then becomes latent in the sensory ganglia, but despite extensive study, the mech- anism of virus latency remains uncertain. Latent HSV DNA is largely in an inactive state, with minimal gene expression. RNA species called latency-associated transcripts, and their processed microRNAs (miRNAs), are the only detectable tran- scripts. These have no detectable protein product, and their dele- tion from the genome does not prevent the establishment of latency, although reactivation is impaired. These transcripts are believed to help globally suppress viral gene expression to maintain latency. Latent HSV is carried for the lifetime of the host, but may be re- activated in response to certain stimuli, including stress, menstru- ation, ultraviolet light, and immunosuppression. Upon reactivation, infectious virus is produced, travels down the peripheral nerves by anterograde axonal transport, and replicates in the epithelial cells at the nerve ending. The neuronal latency of HSV and varicella-zoster virus is an ex- tremely effective method of virus persistence. Latent virus in neur- onal cells appears to be inaccessible to the immune response, and as it does not replicate is not susceptible to the action of antiviral drugs. In normal HSV carriers, reactivation at local sites is thought to be controlled by a specific effector T-lymphocyte response. However, HSV DNA encodes proteins that interfere with antigen processing by the class I MHC pathway, and are presumed to help the virus evade the T-cell immune response. There is no good evidence that the immune response to HSV of people who have symptomatic reactivation episodes differs from that of asymptomatic carriers. Clinical features Primary infection with HSV is often asymptomatic; among sexu- ally active subjects, only 60% of primary infections with HSV-1, and 40% with HSV-2, are symptomatic. HSV-1 is the predominant cause Table 8.5.2.1 The human herpesviruses Common name Designation Subfamily Genome size (kbp) Site of latency and persistence Herpes simplex virus 1 Human herpesvirus 1 α 152 Neurons (sensory ganglia) Herpes simplex virus 2 Human herpesvirus 2 α 152 Neurons (sensory ganglia) Varicella zoster virus Human herpesvirus 3 α 125 Neurons (sensory ganglia) Epstein–Barr virus Human herpesvirus 4 γ 172 B lymphocytes (oropharyngeal epithelium) Human cytomegalovirus Human herpesvirus 5 β 235 Blood monocytes (and possibly epithelial cells) HHV6 Human herpesvirus 6A and 6B β 170 Monocytes, T lymphocytes HHV7 Human herpesvirus 7 β 145 – Kaposi’s sarcoma-associated herpesvirus Human herpesvirus 8 γ 230 Uncertain

 of orofacial infections, whereas HSV-2 is the usual cause of genital HSV infection, but the clinical manifestations overlap. Gingivostomatitis This is the most common clinical form of primary infection with HSV-1. It is most often seen in children, following an incubation period of 2–12 days. Primary infection may be associated with a considerable systemic reaction, involving fever, sore throat, pharyngeal oedema, and redness. Painful vesicles appear a few days later on the pharynx and oral mucosa, the lips, and the skin around the mouth (Fig. 8.5.2.1). There may be cervical lymphadenopathy. Affected pa- tients may have difficulty in eating, and the lesions last from 3 days to 2 weeks. The differential diagnosis includes other causes of pha- ryngitis, including bacterial pharyngitis and herpangina (from Coxsackie A virus infection). Anterior vesicles and ulceration af- fecting the lips and skin around the mouth are more suggestive of HSV infection. Stevens–Johnson syndrome and severe aphthous ul- ceration

may appear similar, and staphylococcal impetigo affects the skin around the mouth, but is not associated with oral ulceration. Reactivation of HSV may give rise to recurrent orolabial lesions, appearing as intraoral mucosal ulcers, but more frequently as the classical cold sore on the lips or skin around the mouth. A tingling sensation in the area of impending ulceration may precede the ap- pearance of vesicles by 1 to 2 days. The lesions usually recur at the same site in individual patients. Around 25% of HSV-1 seroposi- tive people develop recurrent orolabial lesions. The majority have only one or two reactivation episodes per year, although a minority (<10%) have more than one attack per month. The episodes are not associated with systemic symptoms, and diagnosis is usually straightforward. Infection at other cutaneous sites Herpetic whitlow HSV infection of the finger, herpetic whitlow, may complicate pri- mary oral or genital herpes by autoinoculation of virus, or may occur through occupational exposure (e.g. in nursing, medical, and dental staff). There is oedema, erythema, and local tenderness of the infected finger. Lesions at the fingertip may be confused with pyo- genic bacterial paronychias and incised, which is contraindicated for herpetic whitlow, and may even spread infection. Herpes gladiatorum This is mucocutaneous HSV infection occurring by transmission of virus via skin trauma resulting from wrestling or other contact sports. Eczema herpeticum HSV infections of the skin are more severe in patients with pre- existing skin disease. In patients with eczema, burns, or other blis- tering skin diseases, HSV infection may become disseminated. Cutaneous HSV infection can be confused with herpes zoster, although the latter is usually easy to diagnose by its unilateral dermatomal distribution. Herpes simplex and erythema multiforme About 15% of all cases of erythema multiforme are preceded by a symptomatic attack of recurrent herpes simplex, and in susceptible people the characteristic rash can be induced by the intradermal in- oculation of inactivated herpes simplex virus antigen. The rash of erythema multiforme starts several days after the onset of the her- petic vesicles, and in severe cases can involve the mucous mem- branes (Stevens–Johnson syndrome). The frequency of these attacks can be reduced by aciclovir prophylaxis. Keratitis HSV keratitis is characterized by the acute onset of pain, blurred vi- sion, conjunctival injection, and dendritic ulceration of the cornea (Fig. 8.5.2.2). It can cause corneal blindness, and treatment is ur- gent. Topical aciclovir is the drug of choice; topical steroids may make the infection worse. HSV can also cause an acute necrotizing retinitis, usually only seen in immunosuppressed people, including those with HIV infection. Genital herpes Primary genital HSV infection is sexually transmitted, and may be associated with systemic symptoms such as fever, headache, and myalgias. Symptoms tend to be more severe in women than men. There is local pain and itching, dysuria, vaginal discharge, and in- guinal lymphadenopathy, with vesicles and ulcers on the vulva, peri- neum, vagina, and cervix, and sometimes on the skin of the buttocks (Fig. 8.5.2.3). In males, primary HSV lesions are vesicles on the shaft or glans of the penis, and there may be associated urethritis. HSV-2 causes most genital infections, with a variable smaller pro- portion resulting from HSV-1. Only 40% of primary HSV-2 genital infections are symptomatic. In patients who have had prior HSV-1 infection, the symptoms of primary genital herpes tend to be less severe. HSV has been isolated from the urethra in 5% of women with urethral syndrome, in the absence of obvious genital lesions. (a) (b) Fig. 8.5.2.1 Herpes simplex gingivostomatitis: (a) and (b).

 Other manifestations of genital tract disease resulting from primary HSV infection are, rarely, endometritis and salpingitis in women, and prostatitis in men. HSV proctitis may follow rectal intercourse. There is anorectal pain and discharge, with ulcerative lesions visible on sigmoidos- copy. Perianal lesions are seen in immunosuppressed patients, and spreading perianal HSV infection and HSV proctitis occur in HIV- infected patients. Recurrent

genital herpes is frequent in the first year after primary genital disease (90% for HSV-2 and 55% for HSV-1). Thereafter, the recurrence rate tends to decrease with time, to around three to four attacks per year for HSV-2, but fewer for HSV-1. Severe recurrent genital herpes is particularly troublesome to women. The complications of primary genital HSV infection include sa- cral radiculomyelitis, with urinary retention and hyperaesthesia of the perineal area, which usually resolves over several weeks. Aseptic meningitis requiring admission to hospital occurs in up to 7% of women and 2% of men, although suggestive symptoms are more common. Occasionally, and more seriously, transverse myelitis may occur. HSV encephalitis (See also Chapter 24.11.2.) Encephalitis is the most serious type of disease produced by HSV in the immunocompetent host, and has an estimated annual inci- dence of two to three cases per million. It is the most commonly iden- tified cause of acute sporadic encephalitis in Western countries. The great majority of cases are caused by HSV-1. A biphasic age incidence is reported, with higher rates between the ages of 5 and 30 years, and in those older than 50 years. The clinical features are of focal enceph- alitis, with acute onset of fever, confusion, and unusual behaviour, impaired consciousness, and possibly focal neurological abnormal- ities. However, there are no specific features, and the diagnosis of HSV should be considered in any patient with possible encephalitis. The cerebrospinal fluid shows lymphocytic pleocytosis, although neutrophils and red cells may also be present, with a raised protein level. CT scans of the brain may show changes in the temporal lobe; MRI is a more sensitive method of detection. The electroenceph- alogram classically shows spike and slow-wave activity localized in the temporal lobes. The definitive way of establishing the diagnosis is brain biopsy. In the original trial of aciclovir for the treatment of HSV encephalitis, brain biopsy was an entry criterion, but confirmed the diagnosis in only 50% of clinically suspected cases. Since the ad- vent of effective nontoxic chemotherapy for HSV, brain biopsy is very rarely used. There is good correlation between a positive poly- merase chain reaction (PCR) test for HSV DNA in the cerebrospinal fluid, and a diagnosis of HSV encephalitis by brain biopsy and virus isolation. Evidence of intrathecal production of specific HSV anti- body is also diagnostic, but as it is usually not detectable until 1 week after onset, PCR-based diagnosis is more useful. Serum or cerebro- spinal fluid titres of antibodies to HSV do not usually increase in the first week of the illness. In practice, the diagnosis is established by a compatible clinical picture, evidence of characteristic temporal lobe involvement on CT or MRI, and electroencephalogram (EEG), and by PCR-based detection of HSV DNA in the cerebrospinal fluid. The pathological features are of focal haemorrhagic necrotizing encephalitis affecting the temporal lobes. The pathogenesis of HSV encephalitis remains uncertain. Up to one-half of patients have Fig. 8.5.2.3 Genital herpes in the natal cleft. Courtesy of the late Dr B. E. Juel-Jensen. (a) (b) Fig. 8.5.2.2 Herpes simplex keratitis: (a) disciform, and (b) dendritic. Courtesy of the late Dr B. E. Juel-Jensen.

 primary infection, and in the rest the disease is presumed to result from reactivation. However, where HSV has been isolated from the brain and mouth simultaneously in the same patient, the two isolates differ by restriction endo nuclease analysis in about 30% of cases, suggesting a new exogenous virus infection in an already seroposi- tive patient. HSV DNA can be detected at autopsy in the brains of normal virus carriers, and the factors precipitating HSV encephal- itis are not known. Immunosuppression is not usually associated with HSV encephalitis, which predominantly affects apparently immunocompetent adults, and very rarely patients with advanced HIV infection. However, rare mutations affecting the Toll-like re- ceptor 3 signalling pathway causing autosomal recessive UNC-93B and TLR3 deficiencies and autosomal dominant TLR3 and TRAF3 deficiencies have been associated with

primary HSV encephalitis in children. Treatment with intravenous aciclovir should be started immedi- ately if HSV encephalitis is clinically suspected, without waiting for confirmation of the diagnosis (in doses as described next; see ‘CNS infections’). The untreated mortality from HSV encephalitis is more than 70%, and very few survivors make a full neurological recovery. Intravenous aciclovir was established to be more effective than the previous best therapy of vidarabine in a randomized trial reported in 1986. Mortality in the aciclovir-treated group was 28%, although a lower Glasgow coma score on entry carried a higher risk of mor- tality. However, only 38% of those who received aciclovir had fully recovered at 6 months. There is still a high incidence of permanent neurological sequelae, particularly seizures, defects of memory, and personality changes, and the prognosis of HSV encephalitis remains poor. Meningitis HSV can cause aseptic meningitis, which is quite independent of, and not associated with progression to, HSV encephalitis. It is most commonly associated with primary genital HSV-2 infection, in which the incidence of proven HSV meningitis is 7% in women and 2% in men. There is pleocytosis, usually lymphocytic, but neu- trophils may predominate in early meningitis. HSV may be isolated from the cerebrospinal fluid by culture, but is now more reliably de- tected by PCR for HSV DNA. In a high proportion of patients with Mollaret’s meningitis (recurrent aseptic meningitis of unknown aetiology; Chapter 24.11.2), HSV DNA is reported to be detectable in the cerebrospinal fluid by PCR. The role of HSV in this syndrome remains uncertain. Neonatal HSV infection and pregnancy The incidence of neonatal HSV infection is approximately 1 in 3500 deliveries per annum in the United States of America, but appears to be lower in the United Kingdom, at 1 in 6600 live births. About 70% of cases are caused by HSV-2, and result from fetal acquisition of HSV-2 from maternal genital secretions during delivery. Most infants with neonatal HSV are born to mothers without clinically evident HSV infection. The risk of transmission from women with symptomatic primary HSV or clinically evident recurrent HSV- 2 infection is about 50 and 20%, respectively. A small proportion (c.10%) of infections is acquired postnatally through contact with people with active lesions. Neonatal HSV infection may appear as lesions on the skin, eye, and mouth, or as encephalitis or disseminated visceral infection. Although initial superficial infection may progress to visceral infec- tion, visceral infection can present without cutaneous lesions, and the diagnosis should be considered in severely ill neonates. Untreated, visceral infection has a high mortality (around 60%). Primary infec- tion in early pregnancy can lead to congenital HSV infection, which is rare, but can produce serious congenital abnormalities. HSV in immunosuppressed patients HSV infections in immunosuppressed people are usually because of reactivation, rather than primary infection. They tend to be more severe, are more likely to progress, and take longer to heal than in the immunocompetent host. Clinical manifestations in patients with HIV infection include severe perineal, orofacial, and oesophageal infection. HSV pneumonitis, hepatitis, and colitis are also described in immunosuppressed patients. Pathology The histological appearance of HSV infection remains the same, whether it is primary or recurrent. There is ballooning of infected cells, with condensed chromatin in the cell nuclei; intranuclear inclusion bodies (Cowdry type A bodies) may be seen; and multinucleated giant cells form. Varicella-zoster virus produces a similar appearance. Laboratory diagnosis Definitive diagnosis is made by virus isolation. Swabs from ves- icular fluid or other body fluids in virus transport medium can be inoculated into tissue culture, producing typical cytopathic effects. Electron microscopy of negatively stained vesicle fluid is rapid, but will not differentiate HSV from varicella-zoster virus. The use of PCR-based techniques to detect viral DNA is becoming more wide- spread. It is particularly applicable to the detection of HSV DNA in cerebrospinal fluid. Serological tests for antibody to HSV are useful only for making a retrospective diagnosis. Seroconversion provides proof of primary infection, and the absence of antibody to HSV-

1 or HSV-2 rules out a diagnosis of recurrent HSV infection. However, making a diag- nosis of reactivation by demonstrating rising antibody titres is of limited value. Treatment The introduction of aciclovir heralded a new era of specific anti- viral drugs, and superseded the drugs previously used for the treatment of HSV infections, such as vidarabine and idoxuridine. Aciclovir is an acyclic nucleoside that is preferentially phosphor- ylated to the monophosphate in HSV-infected cells by the virus- encoded thymidine kinase. Cellular kinases then phosphorylate the monophosphate to the triphosphate, which is incorporated into nas- cent HSV DNA, where it acts as a chain terminator; aciclovir also directly inactivates the HSV DNA polymerase. Two newer, related drugs with the same mechanism of action are famciclovir, a prodrug of penciclovir, and valaciclovir, the valyl ester of aciclovir, which has greater bioavailability and less frequent dosage. All these drugs are relatively free of side effects, although intravenous aciclovir can crystallize in the renal parenchyma and produce renal impairment; it should be given by infusion over an hour, and patients should be adequately hydrated. The doses should be reduced in patients with renal impairment.

740 section 8 Infectious diseases Primary mucocutaneous infection In primary oral and genital infection, aciclovir 200 mg 5 times daily given orally for 10 to 14 days from the onset reduces the severity of infection, the duration of symptoms, and the duration of viral shed- ding. There is little evidence that the treatment of primary infec- tion reduces the incidence of subsequent symptomatic reactivation episodes. If swallowing is difficult, intravenous aciclovir (5 mg/kg 8 hourly) may need to be given. Famciclovir 250 mg 3 times daily or valaciclovir 500 mg twice daily are alternatives. Symptomatic reactivation of mucocutaneous infection The treatment of recurrent infections in immunocompetent hosts is often unnecessary, as the symptoms are usually very mild. However, aciclovir can shorten the duration of symptoms if it is given very early in the course of the recurrence, prefer- ably during the prodrome before vesicles appear. Oral aciclovir is effective, and anecdotal reports suggest that topical aciclovir is effective symptomatically. The same dosage as desribed for pri- mary infection can be given for 5 days. Patient-initiated courses of single-day famciclovir (1 g twice daily) or 3-day valaciclovir (500 mg twice daily) have been shown to be effective for recur- rent genital HSV. Long-term suppressive therapy This can be considered in immunocompetent patients with genital herpes who have frequent reactivation episodes. Trials of aciclovir in recurrent genital herpes have shown that a dose of 400 mg twice daily significantly reduces the frequency of attacks. However, pa- tients may be able to find a lower effective dose, and in some, 200 mg daily prevents attacks. Because there is some evidence that resistant virus is a problem in this population, it is advisable to stop treat- ment for a month every 6 to 12 months. Valaciclovir 500 mg daily or famciclovir 250 mg twice daily are alternatives. CNS infections For HSV encephalitis, intravenous aciclovir (10 mg/kg 8 hourly for 14–21 days) should be given to any patient in whom the diagnosis is clinically suspected (see ‘HSV encephalitis’ earlier). For HSV men- ingitis, intravenous aciclovir 5 mg/kg 8 hourly can be used, with conversion to oral valaciclovir 1 g twice daily when improvement occurs, for a total of 10 days. Systemic infection in the immunosuppressed Oral treatment, as for primary HSV, can be used for mild mucocutaneous infection, but for more severe and for visceral in- volvement, intravenous aciclovir 5 mg/kg 8 hourly should be used. After resolution, continued prophylaxis is usually necessary until immunocompetence is restored, particularly in patients with HIV. Aciclovir resistance Resistance of HSV to aciclovir develops readily in vitro, but is clinically rare; it results from mutations in the HSV thymidine kinase or DNA polymerase genes. It is seen almost exclusively in immunocompromised patients who have received prolonged aciclovir prophylaxis, especially those with HIV infection,

and is manifest as unresponsive or worsening HSV disease despite treat- ment with aciclovir. There is usually cross-resistance to famciclovir and valaciclovir, and intravenous foscarnet is the most useful alternative drug in severe infection caused by resistant HSV, al- though it is more usually used for human cytomegalovirus (see ‘Human cytomegalovirus’, next). Prevention and control No vaccine is licensed for HSV, although a gD (glycoprotein D) based vaccine reduced new HSV2 infection in seronegative women, and other candidates are approaching phase III trials. There is par- ticular interest in the use of vaccines for postinfective immunization to reduce the frequency of recurrent genital HSV attacks. This has proved possible in guinea pigs. Special problems in pregnant women Prevention of neonatal HSV infection is best achieved by preventing genital HSV infection late in pregnancy. There is no reason to give aciclovir prophylactically to women with a history of recurrent genital herpes who are asymptomatic, as the incidence of neonatal HSV infection is low in their children. However, women with clin- ically apparent genital herpes in the last trimester (and probably at any other time in pregnancy) can be treated with aciclovir, although the drug is not licensed for treatment in pregnancy. Women with no clinical lesions may have a vaginal delivery, but the presence of active lesions at the time of labour is an indication for Caesarean section. Babies born to mothers with clinically apparent genital HSV infec- tion, or with a history of recurrent genital HSV infection, should be screened for HSV by cultures from the nasopharynx and eyes after birth. Proven neonatal HSV infection should be treated with high-dose intravenous aciclovir (20 mg/kg per day every 8 h for 21 days). Varicella-zoster virus infection Historical background There are clinical descriptions of varicella (chickenpox) and herpes zoster (shingles) in very early medical literature, although the skin lesions of herpes simplex and herpes zoster were grouped together under the term herpes. The similarities between the exanthematous rashes associated with smallpox and varicella meant they were not distinguished until the late 19th century. The characteristic clin- ical appearance of shingles, in a dermatomal distribution, was rec- ognized as a discrete entity in the early Greek literature. The term zoster is derived from the Greek word for a girdle, and shingles from the Latin cingere meaning to encircle. In 1892 von Bocquet observed that children developed vari- cella after contact with adults with herpes zoster, and in 1925 it was shown that vesicular fluid from patients with zoster, inoculated into susceptible people, produced chickenpox. The idea that zoster re- sulted from the reactivation of latent virus remaining in the tissues following childhood varicella was put forward by Garland in 1943, and strengthened by the work of Hope-Simpson, a British general practitioner. Varicella-zoster virus (VZV) was isolated in 1958, and Weller and colleagues showed the similarity between viral isolates from varicella and zoster patients. Restriction endonuclease ana- lysis showed that the isolates from chickenpox and from later zoster in the same immunocompromised patient were identical. The long interval between the two illnesses has prevented such studies in im- munocompetent people.

8.5.2 Herpesviruses (excluding Epstein–Barr virus) 741 Aetiology VZV is structurally similar to other members of the herpesvirus family. The genome is a linear double-stranded DNA of 125 kbp. VZV is an α-herpesvirus, and encodes sets of genes that are largely colinear to those of HSV, and are also expressed in immediate-early, early, and late phases. The virus is closely cell associated, and spreads from cell to cell in tissue culture. Epidemiology VZV infects only humans, which are thus the only reservoir. The virus is presumed to spread by the respiratory route. Varicella is pre- dominantly a disease of childhood, affecting both sexes; and 90% of cases occur in children under the age of 13 years. The incubation period is about 2 weeks (with a range of 10–20 days); patients are infectious for about 48 h before the vesicles appear, and remain so for 4 to 5 days afterwards, until all the vesicles have crusted over. The secondary attack rate in susceptible contacts with an

index case in the household is 70 to 90%. The prevalence of VZV varies in dif- ferent ethnic groups. In Europe, about 10% of the population over 15 years old is seronegative, and consequently susceptible to infec- tion, although in tropical countries only 50% of young adults may be seropositive. Varicella in adults is uncommon in Europe, and less than 2% of all cases occur in patients older than 20 years. Subclinical infection is unusual, and accounts for less than 5% of all infections, but the disease may be mild, and in some surveys only 10% of people with a negative history were in fact seronegative for VZV. One attack of chickenpox usually confers lifelong immunity. After primary infection, VZV becomes latent in dorsal root ganglia. Reactivation appears clinically as herpes zoster, which is a common disease affecting all age groups, but particularly older and immunosuppressed people; about 20% of the population will ex- perience an attack. There is no evidence that exposure to people with active VZV infection predisposes to herpes zoster in their contacts, but a seronegative person may catch varicella from contact with the vesicles of a patient with shingles. Nosocomial varicella infection is well recognized, and the isolation of patients with varicella, and im- munocompromised patients with herpes zoster, should be ensured in hospitals. Local unidermatomal zoster is less likely to cause infec- tion, and consequently to need isolation. Pathogenesis During primary infection, initial virus replication probably occurs in the epithelial cells of the upper respiratory tract mucosa, followed by a phase of viraemia during which VZV can be isolated from leucocytes, and the disseminated rash appears. In the skin, the virus infects capillary endothelial cells, and adjacent fibroblasts and epi- thelial cells. During the viraemic phase, virus may spread to visceral organs, including alveolar epithelial cells, and transient subclinical hepatitis is probably a normal feature of varicella. VZV encephal- itis may be a feature of primary infection, particularly affecting the cerebellum. Patients usually recover completely from encephalitis (unlike that associated with HSV), and it has been suggested its pathogenesis may be immune mediated. Following recovery from primary infection, the virus persists for life in a latent state in dorsal root ganglia. VZV reaches the ganglia by retrograde axonal trans- port from the skin lesions during primary infection, and all dorsal root ganglia and the trigeminal ganglion can potentially carry latent VZV in neurones and possibly in satellite cells. As with other herpesviruses, the host response is critical in con- taining the initial infection. Cellular immunity is important, since varicella may be progressive in patients with severely impaired T- cell immunity. Both CD4 and CD8 cytotoxic T lymphocytes spe- cific for VZV are present in normal people carrying latent VZV. The cellular immune response presumably plays a part in controlling reactivation, since impaired T-cell immunity increases the risk of developing zoster, and of having vesicles in multiple dermatomes, and cutaneous dissemination of reactivated virus. The increasing incidence of herpes zoster with age may reflect waning cellular im- munity to VZV. Clinical features Primary infection and varicella The most striking feature of varicella is the rash, which is centripetal (mainly on the trunk). The lesions are initially present on the face and scalp, before progressing to the trunk and later to the limbs (Fig. 8.5.2.4). A macular erythematous rash, papules, and vesicles may all be present together. Individual lesions progress from being papules to vesicles to pustules, and then crust over. The scabs nor- mally separate after 10 days, without scarring. The systemic symp- toms associated with varicella vary considerably. In most children there is a mild illness with fever. Adults characteristically have a more severe illness, with myalgia, headache, arthralgia, malaise, and higher fever, with the complications listed next. Symptoms may precede the rash by 1 to 2 days. (a) (b) Fig. 8.5.2.4 Severe chickenpox: (a) and (b). Copyright D. A. Warrell.

 Complications of varicella The principal complications of varicella in immunocompetent pa- tients are pneumonitis and encephalitis. Pneumonitis In a prospective

study, 6% of young adults with chickenpox had respiratory symptoms, although 16% had changes on chest radiography, but the rate of admission to hospital for pneumonia in adults with varicella is only about 0.3%. Patients present with dyspnoea, cough, hypoxia, and bilateral infiltrates on the chest radiograph, occurring 1 to 6 days after the appearance of the rash. Hypoxia may be more severe than expected from the physical signs or the chest radiograph. The interstitial pneumon- itis can progress to respiratory failure requiring artificial ventila- tion and intensive care (Fig. 8.5.2.4a), but it is more commonly transient, resolving completely within 2 to 3 days. Varicella pneu- monia is said to be more common in smokers. Fatalities are rare, and VZV pneumonia is not associated with long-term respiratory problems. Benign nodular calcification throughout the lung occa- sionally follows. Encephalitis Central nervous system involvement during varicella most commonly presents as acute cerebellar ataxia within 1 week of onset of the rash, although it may appear up to 21 days after the rash. It resolves completely over 2 to 4 weeks. A frequency of 1 in 4000 children aged less than 15 years has been quoted. The cerebrospinal fluid of these patients shows lymphocytosis and elevated protein concentration. More serious encephalitis can occur in 0.1 to 0.2% of cases of varicella. This begins earlier in the course of infection than cere- bellar ataxia, with headache, vomiting, confusion, and impaired consciousness. There is evidence of diffuse cerebral oedema, but no defined pattern of CT or MRI abnormality. The encephalitis may be progressive, and the mortality is between 5 and 20%, with neuro- logical sequelae in up to 1% of survivors. Varicella meningitis can occur. Other rarely reported neuro- logical complications include optic neuritis, transverse myelitis, and Reye’s syndrome. Other complications Primary VZV infection may be compli- cated by acute thrombocytopenia, with petechiae, purpura, haem- orrhage into vesicles, and other haemorrhagic manifestations. The platelet count can remain low for weeks after the illness has resolved. Secondary infection of the skin lesions with Staphylococcus aureus or Streptococcus pyogenes may occur. Purpura fulminans is a rare complication associated with arterial thrombosis and haemorrhagic gangrene (Fig. 8.5.2.5). Nephritis and arthritis have been reported as occasional complications, and myocarditis, pericarditis, pancrea- titis, and orchitis are even more rare. Special problems in pregnant women Varicella in pregnant women can be severe, with a maternal mortality of 1%. Varicella in the first trimester can cause varicella embryopathy. Affected infants may have a scarred, atrophic limb, microcephaly, cortical atrophy, and eye defects including chorioretinitis, microophthalmia, and cataracts. The autonomic nervous system may be damaged. Varicella embryopathy is rare; in recent reported series the risk was about 1 to 2% in mothers with varicella in the first 20 weeks of pregnancy. Varicella-zoster immunoglobulin should be considered for pregnant women in contact with varicella, and varicella in pregnancy should be treated with aciclovir on a named-patient basis. Neonatal vari- cella occurs in babies whose mothers contract varicella just before or after delivery, and is most severe when maternal disease appears from 2 to 7 days after delivery. Herpes zoster The clinical syndrome caused by the reactivation of VZV from sen- sory ganglia is herpes zoster. Typical prodromal localized pain or paraesthesia is followed by erythema and vesicular lesions occurring in a dermatomal distribution. The thoracic dermatomes, especially T4 to T12, are involved in about 50% of cases (Fig. 8.5.2.6); the lumbosacral dermatomes in about 16%; and the cranial nerves (mainly the Vth) in 14 to 20% of patients (Fig. 8.5.2.7a). The first symptoms are usually paraesthesia and shooting pains in the af- fected dermatome, which precede the eruption of vesicles by several days, occasionally 1 week or more. Erythematous maculopapular lesions then appear and quickly evolve into a vesicular rash, nearly always in a unilateral dermatome, with no vesicles beyond the Fig. 8.5.2.5 Varicella purpura fulminans. Courtesy of the late Dr B. E. Juel-Jensen. Fig. 8.5.2.6 Herpes zoster (shingles) of the T4 dermatome. Copyright D. A. Warrell.

8.5.2 Herpesviruses (excluding Epstein–Barr virus) 743 midline. The vesicles usually form scabs after 3 to 7 days, and these separate after 2 weeks or so, but there is sometimes a more severe locally necrotic reaction (Fig. 8.5.2.8). There is a risk of secondary infection, particularly with Staphylococcus aureus. There may be malaise and low-grade fever, but laboratory investigations usu- ally show no abnormalities, although up to 40% of patients with uncomplicated zoster may have lymphocytes and elevated protein in the cerebrospinal fluid. Involvement of the mandibular branch of the Vth cranial nerve can give intraoral lesions on the palate (Fig. 8.5.2.7b), floor of the mouth, and tongue. Involvement of the geniculate ganglion results in Ramsay Hunt syndrome, with pain and vesicles in the external auditory meatus, a loss of taste in the anterior two-thirds of the tongue, and a lower motor neurone VIIth cranial nerve palsy. Complications of zoster Ophthalmic zoster VZV reactivation from the trigeminal ganglion can affect the ophthalmic division of the trigeminal nerve, resulting in ophthalmic zoster (Fig. 8.5.2.7a). The features include conjunctivitis, anterior uveitis, keratitis, and sometimes iridocyclitis, with sec- ondary glaucoma and panophthalmitis. However, these latter sight- threatening complications of ophthalmic zoster are unusual. A rare association with ophthalmic zoster is granulomatous cerebral angiitis, which can be associated with arterial thrombosis; cerebral angiog- raphy shows segmental narrowing in the cerebral arteries on the side of the ophthalmic zoster occurring weeks after the rash. CT may show cerebral infarcts, particularly in the middle cerebral artery territory, and contralateral hemiparesis can occur. (a) (b) Fig. 8.5.2.8 Herpes zoster of the Vth cranial nerve, showing severe necrotic effects: (a) acutely, and (b) after recovery. Courtesy of the late Dr B. E. Juel-Jensen. (a) (b) Fig. 8.5.2.7 Herpes zoster of the Vth cranial nerve: (a) ophthalmic division, and (b) lesions on the palate. Courtesy of the late Dr B. E. Juel-Jensen.

744 section 8 Infectious diseases Motor zoster Weakness or paralysis can sometimes be associated with zoster, and results from the involvement of the anterior horn cells in the same segment of the spinal cord as the involved dorsal root ganglion. Depending on the segment involved, this can lead to a monoparesis affecting the upper or lower limb, or to diaphrag- matic palsy (with the involvement of C5/6). Paralysis usually re- covers completely, although the outlook for the recovery of facial nerve palsy is more variable. It is suggested VZV may be responsible for some cases of idiopathic VIIth nerve (Bell’s) palsy. Autonomic zoster Lumbosacral herpes zoster can be associated with neurogenic bladder, and acute retention of urine. This may be accompanied by haemorrhagic cystitis resulting from vesicles on the bladder wall. Intestinal ileus and obstruction may occur. Zoster meningoencephalitis Meningoencephalitis may accom- pany zoster at any site, and is heralded by impaired consciousness, headache, photophobia, and meningism. The interval from the onset of skin lesions to symptoms is around 9 days, but may be as long as 6 weeks. Symptomatic encephalitis usually lasts around 2 weeks, and is nearly always followed by full recovery without neurological sequelae. Transverse myelitis, although rare, can occur at any level of the spinal cord. Postherpetic neuralgia The incidence of postherpetic neuralgia rises with the increasing age of the patient. It is uncommon in young people, but can occur in 50% of patients older than 50 years. It is characterized by pain in the affected dermatome persisting for 1 month or more after the acute attack of zoster has resolved. The pain may be steady and burning, or paroxysmal and stabbing in na- ture; it may occur spontaneously, or be triggered by stimuli such as temperature or touch. Zoster sine herpete This term refers to radicular pain similar to that experienced in zoster, but without the antecedent skin lesions of zoster. It was originally applied to patients who did have ob- vious zoster, but had dermatomal pain in areas distinct from those where there was rash. However, it is more commonly applied to patients with radicular pain and no

rash at all. There have been reports describing the use of PCR testing for the detection of VZV DNA in the cerebrospinal fluid of patients with presumed zoster sine herpete. The literature is anecdotal, and it is difficult to regard zoster sine herpete as a diagnostic entity unless there is good evidence for VZV involvement (e.g. by the detection of VZV DNA in cerebro- spinal fluid and/or blood mononuclear cells). It should be included in the differential diagnosis of radicular pain of unknown cause. Any possible mechanism is speculative. VZV infection in immunosuppressed patients In patients with immunosuppression, particularly of cellular immunity, vari- cella can be much more severe. The skin lesions are more diffuse (Fig. 8.5.2.9), and can take up to 3 times as long to heal. There may be visceral dissemination to the lungs, liver, and central nervous system. Patients with lymphoma undergoing chemotherapy are particularly susceptible. Herpes zoster in immunosuppressed patients is also more severe than in healthy subjects. Before effective antiviral therapy was avail- able, skin lesions were more extensive and could take several weeks longer to heal. Dissemination, presumably because of viraemic spread, with widespread skin lesions as in varicella, occurs in 10 to 40% of patients. Cutaneous dissemination is more likely to be asso- ciated with visceral dissemination to the same sites as those associ- ated with varicella. Patients with HIV infection or AIDS are prone to multidermatomal zoster, which can be one of the defining features of AIDS. VZV retinitis This is a combination of pain and blurred vision in one eye, with progressive necrotizing retinitis seen on ophthalmos- copy. Adjacent cutaneous zoster indicates the diagnosis, but occa- sionally VZV retinitis occurs in immunocompetent patients as the sole manifestation of VZV reactivation. VZV retinitis may be diffi- cult to distinguish from cytomegalovirus (CMV) retinitis. A severe form of the disease, seen particularly in patients with HIV infection, and named progressive outer retinal necrosis, is associated with a high incidence of retinal detachment, and may require treatment with ganciclovir, as aciclovir is often ineffective. Differential diagnosis Varicella is usually recognized relatively easily. Other causes of a vesicular rash are generalized herpes simplex in the immunosup- pressed patient, and enteroviral disease, particularly hand, foot, and mouth disease caused by Coxsackie virus infection, but the rash on the hands and feet is unlike that of varicella, which has a centripetal distribution (Chapter 8.5.8). Human cases of infection with animal pox viruses (monkey pox and camel pox) have rarely been described (Chapter 8.5.4). Localized pain before the appearance of shingles or in zoster sine herpete may be severe enough to suggest myocardial ischaemia, or lung or intra-abdominal pathology if it involves the thoracic dermatomes. Pathology The histological appearance of VZV infection is similar or indistin- guishable from that of HSV infection. Fig. 8.5.2.9 Herpes zoster varicelliformis. Courtesy of the late Dr B. E. Juel-Jensen.

 Laboratory diagnosis The diagnosis of varicella and herpes zoster is usually made on clin- ical criteria alone. Virus can be seen in vesicular fluid by electron mi- croscopy, or isolated in culture. A serological diagnosis of varicella can be made by demonstrating seroconversion or VZV IgM anti- body. Urgent serology is needed to confirm the seronegative status of contacts at risk of severe VZV infection, to determine the need for VZV immunoglobulin (see ‘Prevention and control’, next). PCR- based tests for the detection of VZV DNA are available, and are of most use in testing cerebrospinal fluid in cases of suspected central nervous system disease. Treatment Pruritus may be alleviated by calamine lotion and antihistamines in patients with chickenpox. Fingernails should be closely cut to min- imize scratching. Skin care is important to prevent secondary bac- terial infection in patients with varicella and zoster. Aspirin should be avoided in children with chickenpox because of the risk of Reye’s syndrome. Strong analgesia may be needed in patients with zoster. VZV is sensitive to the

nucleoside analogues aciclovir, famciclovir, and valaciclovir; as for HSV, VZV encodes a thymidine kinase that preferentially phosphorylates these drugs in infected cells. The median 50% inhibitory concentration of aciclovir against HSV is 0.1 μM, but is 2.6 μM against VZV, so 800 mg orally is necessary to achieve inhibitory concentrations. The treatment recommendations for varicella and herpes zoster are summarized in Box 8.5.2.1. Varicella Whether to treat normal children with varicella (who are the great majority of patients) has been much debated; the argument can be made that the disease is not always mild and it is not possible to predict which child may have a severe case. Therapy with aciclovir is safe, and although it has been suggested that widespread treat- ment with antivirals might result in viral resistance, or failure to develop normal immune responses, there is no evidence of this in controlled trials. Treatment with aciclovir begun within 24 h of the onset of the rash leads to a 25% decrease in the duration and se- verity of chickenpox. The argument for treating all adolescents and adults is easier, as chickenpox is more severe for them than it is for young children. Chickenpox in neonates, children with leukaemia, and transplant recipients should always be treated with aciclovir. Intravenous aciclovir limits the visceral spread of the virus if given immediately on diagnosis. Treatment in these immunosuppressed patients can be changed from intravenous to oral aciclovir once the fever has settled, if there is no evidence of visceral varicella. Herpes zoster The major justification for the antiviral treatment of herpes zoster in immunocompetent patients has been to limit postherpetic neur- algia. Although there are difficulties in accurately and objectively quantifying the pain of postherpetic neuralgia, trial data indicate that aciclovir, valaciclovir, and famciclovir can limit the duration of zoster-associated pain, and that valaciclovir is slightly more ef- fective. All three drugs accelerate the healing of cutaneous lesions by 2 days over placebo; valaciclovir and famciclovir have the advantage of more convenient dosage, as well as probably being slightly more effective. Patients over the age of 50 years with zoster have the highest risk of postherpetic neuralgia, and so should be offered antiviral treat- ment. Younger patients may warrant treatment if they have marked pain. All patients with ophthalmic zoster should be treated urgently with antivirals, even if they present relatively late, as aciclovir re- duces the incidence of keratitis. Immunosuppressed patients with herpes zoster should receive intravenous aciclovir to prevent cuta- neous and visceral dissemination. Valaciclovir and famciclovir may be used if zoster presents in a localized form in less severely im- munosuppressed patients. Corticosteroids have been advocated in patients with herpes zoster, in order to reduce the severity of postherpetic neuralgia. However, the addition of oral prednisone to aciclovir slightly in- creases the rate of healing of skin lesions, but does not affect the incidence of postherpetic neuralgia; a role for corticosteroids thus remains unproven. Established postherpetic neuralgia can be man- aged with analgesics, tricyclic antidepressants, and other agents used for neuropathic pain, such as gabapentin and pregabalin, which were effective for the treatment of postherpetic neuralgia in large placebo-controlled trials. Although the use of opioids for the treat- ment of neuropathic pain is controversial, several studies support their efficacy and safety; oxycodone and tramadol have been shown to be superior to placebo for the treatment of postherpetic neuralgia. Topical agents such as lidocaine 5% patches and topical capsaicin have been useful in ameliorating postherpetic neuralgia, but are un- satisfactory for use as sole agents (see also Chapter 24.12). Prevention and control Varicella-zoster immune globulin, prepared from high-titre immune human serum, has been shown to prevent or ameliorate varicella in seronegative people at high risk, such as immunocompromised Box 8.5.2.1 The use of aciclovir in varicella-zoster infections Indications for intravenous aciclovir (10 mg/kg, 8 hourly) Chickenpox: • Immunocompromised patients • Neonatal chickenpox • Chickenpox with systemic complications • Severe chickenpox in adults and in pregnancy (5 mg/kg, 8 hourly) Shingles: • Severe shingles in immunocompromised patients •

Multidermatomal shingles • Shingles complicated by ocular, motor, autonomic, or systemic involvement • VZV retinitis (severe forms in AIDS may require foscarnet or ganciclovir) Indications for oral aciclovir (800 mg, 5 times daily) • Uncomplicated chickenpox (except for mild chickenpox in children) • Uncomplicated shingles in patients over 45 years • Uncomplicated shingles in immunosuppressed patients • Shingles presenting with severe pain Infections not requiring active antiviral treatment • Uncomplicated mild chickenpox in children • Patients presenting more than 48 h after the appearance of the last le- sion, or when all lesions have crusted • Uncomplicated shingles in patients under 45 years • Postherpetic neuralgia

746 section 8 Infectious diseases people and pregnant women. It should be given to seronegative immunodeficient patients (including those on high-dose cortico- steroid treatment), and pregnant women with definite contact with varicella. It should be administered within 10 days (preferably 2–4 days) of exposure. Neonates whose mothers have had varicella less than 1 week before delivery, or within 28 days after delivery are also recommended to receive varicella-zoster immune globulin. A VZV vaccine is available; a live attenuated vaccine containing the Oka strain of VZV. It confers 90% protection from natural varicella when administered to susceptible immunosuppressed people (such as patients with leukaemia and lymphoma receiving chemotherapy), but it produces rash in up to 40% of these recipients. In immunized healthy children the risk of subsequent varicella after community exposure is reduced to less than 5%, and the vaccine-induced rash is much less common (about 5% of recipients). This vaccine is li- censed in Japan, some European countries, and the United States of America, where it is recommended for the routine immunization of children aged 12 to 18 months. However, in the United Kingdom it is recommended only for use in seronegative healthcare workers and children over 1 year in contact with individuals at high risk of severe varicella. Trials have shown that the postinfective immuniza- tion of subjects aged 60 years or over diminishes the incidence of zoster and postherpetic neuralgia, and the vaccine is now licensed in the United States of America for the prevention of herpes zoster in this age group. The nosocomial transmission of VZV by patients with varicella requiring admission to hospital is a significant risk, as 10% of adults are seronegative. Nursing and managing patients with varicella in hospital should be restricted to those staff known to be seropositive for VZV. Patients with varicella in hospital should ideally be isolated in negative-pressure rooms to prevent airborne transmission. Human cytomegalovirus infection Historical background The syndrome of congenital cytomegalovirus infection, cytomegalic inclusion disease, was described in children with fatal infection in 1904, but the intranuclear inclusions were attributed to a protozoan parasite. In 1921, the pathologist Goodpasture suggested that the inclusions in the parotid glands of infants were caused by a virus, because a filterable agent produced similar histology in guinea pig salivary glands, and the lesions were attributed in 1926 to ‘salivary gland virus’. Human cytomegalovirus (HCMV) was finally isolated in 1956, and so named by Weller for the characteristic owl’s-eye, or cytomegalic inclusions it produces in the nuclei of infected cells. HCMV produces little morbidity in immunocompetent people, but can produce severe disease in the fetus if infection is acquired in utero, and in immunosuppressed patients. Aetiology HCMV is the largest human herpesvirus, with a linear double- stranded DNA genome of 250 kb encoding more than 200 proteins. Mammalian cytomegaloviruses are species specific, and so HCMV cannot be studied in animal models. The most widely studied la- boratory strain, AD169, shows significant genomic variation from recent clinical isolates, which possess an additional 15 kb of DNA. HCMV replicates slowly compared with other herpesviruses, and gene expression occurs sequentially in immediate-early, early, and late phases. Epidemiology Following primary infection, HCMV persists for life as a latent in- fection, with

periodic asymptomatic excretion of virus in saliva, breast milk, urine, semen, and cervical secretions. Infection is spread by close contact with these body fluids. In developing coun- tries, HCMV is usually acquired in childhood, and nearly 100% of young adults are seropositive. In developed countries, serocon- version progresses with age, but seroprevalence is higher in lower socioeconomic groups. Overall, about 50% of adults are seroposi- tive. In childhood, HCMV is acquired from breast milk or con- tact with infected children excreting virus in their saliva or urine. Children in day nurseries transmit the virus to each other, and to susceptible adult carers. Later, sexual transmission becomes a major route of infection, and seroprevalence approaches 100% in homo- sexual men, and sex workers. Blood and blood products from normal seropositive donors can transmit HCMV. Transfusion recipients at risk of HCMV disease now usually receive screened seronegative blood; otherwise the risk of transfusion-related HCMV infection is 2.5% per unit of blood. The virus is carried in leucocytes, and leukodepletion of blood greatly reduces the risk of HCMV transmission. The technique is also being widely adopted as a preventive measure against transmis- sible spongiform encephalopathies. Finally, solid organ and bone marrow transplants from seropositive donors can transmit HCMV, producing particularly severe disease in seronegative recipients. Pathogenesis Current evidence suggests myeloid lineage cells are a principal site of HCMV latency, and that virus may be reactivated from dendritic cells and monocytes as they differentiate. Endothelial cells, possibly epithelial and other cells, may also be sites of latency. The immune response is critical for controlling infection in the normal host. Normal immunocompetent individuals infected with HCMV mount a strong T-cell response, with very high frequencies of cytotoxic (CD8+) T lymphocytes in the peripheral blood targeted particularly at the HCMV major tegument protein pp. 65, and the major immediate-early protein IE1. Impairment of this response is associated with the risk of disseminated infection. HCMV possesses multiple immune-evasion genes, whose products interfere with the class I MHC antigen-processing pathway, and recognition by natural killer (NK) cells, which may help the virus reactivate by delaying T- and NK-cell recognition of infected cells. Antibody probably limits blood-borne dissemination of HCMV, as maternal IgG appears to be especially important in preventing viral transmission to the fetus. Subclinical reactivation occurs frequently in the normal host, but is controlled by the immune response. Immune deficiency, particu- larly of the T-cell response, such as iatrogenic or disease-induced immunosuppression, may allow uncontrolled replication and re- sult in HCMV disease. Pathology is presumably produced by the direct cytopathic effects of the virus, although indirect effects pro- duced by soluble virus-encoded proteins or the host response are also possible. The presence of HCMV in a diseased organ does not necessarily implicate the virus as a cause; reactivation of the virus

 can sometimes be nonpathogenic, and reflects its being a bystander, coexisting with another pathogenic process. Clinical features of HCMV disease Primary infection in immunocompetent subjects Primary infection in children and adults is asymptomatic in most cases, but HCMV can produce an illness clinically indistinguishable from infectious mononucleosis caused by primary Epstein–Barr virus (EBV) infection, typically with fever, myalgia, cervical lymph- adenopathy, and mild hepatitis. Tonsillopharyngitis is much less common than in primary EBV infection, and lymphadenopathy and splenic enlargement are less prominent features. The fever lasts 2 to 3 weeks, but can persist for up to 5 weeks. In developed countries an increasing proportion of HCMV seroconversion illness is seen in older adults, and the diagnosis should still be considered in patients aged over 50 years. Myocarditis, pneumonitis, and aseptic menin- gitis are rare complications. A proportion (5–10%) of patients with Guillain–Barré

syndrome show serological evidence of primary HCMV infection; they are more likely to have antibodies to the GM2 ganglioside than other patients with Guillain–Barré syndrome, and a causal relationship has been postulated. Primary HCMV infection acquired from blood transfusion re- sults in a similar clinical picture occurring 3 to 6 weeks after transfu- sion, and is usually self-limiting in the normal host. To distinguish between primary HCMV infection and other causes of mononucle- osis syndromes, such as EBV and toxoplasmosis, requires sero- logical testing (the Paul–Bunnell and monospot tests are negative in HCMV mononucleosis). HCMV disease in immunosuppressed patients HCMV infection is most severe in immunosuppressed patients, particularly solid organ and bone marrow transplant recipients, and those with AIDS, all of whom have impaired T-lymphocyte func- tion. This strongly supports the importance of T cells in controlling infection. Solid organ transplant recipients The risk of HCMV disease is 3 to 5 times greater in a seronegative recipient receiving a graft from a seropositive donor, and it causes much more severe infection than in a seropositive recipient who has a reinfection or reactivation of latent virus. Many centres pair seronegative donors with seronegative recipients, although this is often thwarted by organ shortage. Clinically, there may be specific organ involvement, which is not seen in normal patients. Interstitial pneumonitis caused by HCMV is rare, except in bone marrow transplant recipients, and carries a poor prognosis; gastrointestinal disease includes oesophagitis, gastritis and peptic ulceration, and colitis; and HCMV retinitis may occur in severely immunosup- pressed patients. HCMV has been reported to be associated with increased graft rejection and renal artery stenosis in renal trans- plant recipients; with accelerated coronary artery stenosis in heart transplant recipients; and with vanishing bile duct syndrome in liver transplant recipients. However, none of these associations is definitively established as causal. Bone marrow transplant recipients HCMV disease is a major problem in allogeneic bone marrow trans- plant recipients, with a 30 to 50% incidence of clinically significant infection. It is a lesser problem in autologous bone marrow trans- plant. If the donor and/or recipient is seropositive there is a risk of HCMV disease, but if both donor and recipient are seronegative, in- fection can be prevented if solely HCMV-seronegative blood prod- ucts are used to support the patient. Pneumonitis is the most serious manifestation of HCMV infection after bone marrow transplant, occurring in 10 to 15% of allogeneic bone marrow transplant recipi- ents, with a mortality of 80% without antiviral therapy. The clinical presentation is interstitial pneumonitis in the absence of any other identifiable pathogen, with increasing arterial hypoxaemia, and progression to respiratory failure. It is suggested that graft versus host disease may contribute to the lung injury in HCMV pneumon- itis in bone marrow transplant recipients. The relationship between HCMV and graft versus host disease is controversial, with sugges- tions that HCMV may predispose to graft versus host disease, and vice versa. Patients with AIDS HCMV disease is one of the most frequent opportunistic infections in patients with advanced HIV infection, of whom 40% develop sight- or life-threatening HCMV disease. A CD4 count of less than 50/μl carries a high risk of disease, although the widespread use of antiretroviral therapy in developed countries means that relatively few patients now have such low CD4 counts, and the incidence of HCMV disease in patients with AIDS has declined significantly. HCMV retinitis has been seen in up to 25% of patients with AIDS not receiving effective antiretroviral therapy. Haemorrhagic retinal necrosis spreads along retinal vessels, and threatens sight when disease encroaches on the macula (Fig. 8.5.2.10). The clin- ical effect is visual impairment, and the risk of retinal detachment and haemorrhage is increased, hence those with low CD4 counts should have regular fundoscopy to detect retinitis before it be- comes symptomatic. Diagnosis is made by the ophthalmological detection of typical retinal changes, preferably with accompanying evidence of HCMV viraemia. In the absence of treatment, HCMV retinitis almost invariably progresses to affect both eyes and des-

troy vision. HCMV is reported to produce diffuse encephalitis in AIDS patients, but although the virus is sometimes seen in neuronal cells at autopsy, encephalitis attributable to HCMV is relatively rare in clinical practice by comparison with the other causes of encephalitis in AIDS. HCMV can also produce a progressive Fig. 8.5.2.10 CMV retinitis.

 radiculopathy, causing low-back pain that radiates to the area supplied by the affected spinal nerve root, and the development of flaccid paraparesis. In the gastrointestinal tract, HCMV is associated with oesopha- gitis, gastritis, and enterocolitis, and virus can be seen in biopsies from these sites, usually in shallow ulcers. HCMV pneumonitis is rare in patients with AIDS, suggesting that there must be additional factors to account for its frequency in bone marrow transplant recipients. Congenital and neonatal HCMV infection HCMV infection of the neonate may be congenital from intrauterine infection, perinatal from transmission during birth, or postnatal from breast milk. The frequency of congenital HCMV infection in developed countries is around 0.5 to 1% of live births, resulting from either primary maternal infection in pregnancy, or from reactiva- tion of HCMV in a previously infected mother during pregnancy. The risk of primary maternal infection in pregnancy is about 1%, and it carries a 40% risk of congenital infection. Fetal infection is more likely to be severe following primary infection in early preg- nancy, whereas the risk of symptomatic congenital infection is much lower, although not absent, from reactivation of maternal HCMV. Pre-existing maternal immunity limits spread to the fetus. Approximately 5 to 20% of congenitally infected babies are symp- tomatic at birth. In its most severe form, usually in babies of mothers with primary maternal infection, the clinical features of congenital HCMV are: microcephaly; chorioretinitis; nerve deafness; hepa- titis with jaundice and hepatosplenomegaly; and thrombocyto- penia with petechiae. This classical cytomegalic inclusion disease has a high mortality, and 80% of all infants symptomatic at birth who survive have serious sequelae, such as learning, visual, and hearing impairment. However, most congenitally infected babies are asymptomatic at birth, and only 5 to 15% of these subsequently develop sequelae on long-term follow up, the most common being sensorineural deafness, which also occurs in isolation in otherwise normal babies. Perinatally or postnatally acquired HCMV infection is rarely symptomatic or associated with long-term sequelae, if the mother is seropositive. Pathology On light microscopy, typical HCMV-infected cells appear large, with a relative reduction in cytoplasm, and nuclei that contain prominent inclusions surrounded by a clear halo (described as owl’s-eye in- clusions). These cells contain replicating virus, and are associated with active infection and disease; they are diagnostic when seen in biopsies of affected organs. In patients dying of severe disease, histological evidence of HCMV involvement can be found in most organs, whereas it infects a restricted range of cells in vitro. Malignancy Although associations between HCMV and malignancy have been postulated in the past, there is currently no good evidence to asso- ciate the virus with any human malignancy. Laboratory diagnosis Primary infection is usually diagnosed by the detection of IgM anti- body to HCMV in the absence of IgG antibody; there is a marked atypical lymphocytosis (mainly increased CD8+ T cells), but heterophile antibody (as detected in primary EBV infection by the monospot or Paul–Bunnell tests) is absent. IgG antibody is a useful marker of HCMV carriage, but titres do not rise reliably in disease; IgM antibody, a marker of primary infection, is also sometimes found with reactivation in immunosuppressed patients, and serology is of limited use in confirming HCMV disease in these patients. Culture of virus from urine may only indicate asymptomatic reactivation, but culture from the blood buffy coat suggests HCMV disease. The virus can never be cultured from the blood of normal HCMV car- riers, and culture from an organ site (such as bronchoalveolar lavage fluid) may indicate locally active infection. Rapid culture

methods such as DEAFF (detection of early antigen fluorescent foci), which uses a monoclonal antibody against an immediate-early viral protein, or shell vial tests (centrifuging sam- ples onto cell cultures) are now used less often. PCR techniques are increasingly used to detect and quantify the HCMV load in blood or plasma, and this is now the standard assay for detecting HCMV in most laboratories. As virus can never be detected in plasma (as opposed to leucocytes) in normal carriers, the presence of HCMV DNA in plasma indicates active viral replication. Detection of virus in biopsy specimens by histological and immunohistological tech- niques implies active HCMV infection in the relevant tissue. In practice, HCMV disease is usually diagnosed by the combin- ation of an appropriate clinical syndrome, and detection of HCMV DNA by quantitative PCR above a threshold level in blood or plasma, or in biopsies from involved organs, in the absence of any other likely causal microbial pathogen. Treatment Several drugs are now available for the treatment of HCMV disease. Aciclovir has little in vitro activity against HCMV, which does not possess a thymidine kinase (see ‘Herpes simplex virus infections’, earlier), and has no place in therapy (although valaciclovir is used in prophylaxis; see ‘Antiviral prophylaxis’, next). Ganciclovir, another nucleoside analogue, is monophosphorylated in infected cells by the UL97 gene product of HCMV, and is active against HCMV; its most limiting side effect is myelotoxicity, with leukopenia and thrombocytopenia, but it has many other potential side effects, including azoospermia, and intravenous administration is necessary. Valganciclovir, a valyl ester prodrug of ganciclovir, has much higher oral bioavailability, and produces equivalent plasma concentrations to intravenous ganciclovir; it is thus useful for prophylaxis. Resistance to ganciclovir results from a mutation in the HCMV DNA polymerase, or in the UL97 gene, and is seen mainly in immunosuppressed patients in whom prolonged use is necessary. An alternative drug to ganciclovir is foscarnet, a competitive in- hibitor of the viral DNA polymerase, which shows no cross-resistance with ganciclovir. This also must be given intravenously, and its side effects include renal impairment and hypocalcaemia. Cidofovir, a nucleotide analogue acting on the viral DNA polymerase, is highly nephrotoxic (probenecid must be given concurrently to prevent ir- reversible renal damage), and therefore relatively infrequently used. Ganciclovir resistance remains a significant problem, and hence other drugs with in vitro activity against HCMV are currently being studied, and have been used in initial small clinical trials, although none is yet licensed for HCMV infection: these include maribavir, brincidofovir, and letermovir. Interestingly, both leflunomide, and artesunate have been shown to have some anti-CMV activity.

8.5.2 Herpesviruses (excluding Epstein–Barr virus) 749 Primary infection In the immunocompetent host this usually requires no specific anti- viral treatment, although occasionally, severe primary infection may lead to hospitalization and require treatment. HCMV disease in immunosuppressed patients Whether due to primary or secondary infection, or reactivation, this is usually treated with ganciclovir or foscarnet for 2–3 weeks, with full-dose induction intravenous therapy; for ganciclovir this is 5 mg/kg every 12 h and for foscarnet 60 mg/kg every 8 h. Oral valganciclovir 900 mg twice daily is an equivalent dose to intra- venous ganciclovir. Secondary prophylaxis may well be needed if immunosuppression persists (see ‘Prevention and control’, next). HCMV pneumonitis in bone marrow transplant recipients This responds poorly to ganciclovir or foscarnet alone, but the com- bination of full-dose ganciclovir with intravenous immunoglobulin has been reported to reduce mortality. Specific anti-CMV immuno- globulin was initially used, then other trials suggest normal pooled intravenous immunoglobulin was equally effective, and recent re- ports question whether IVIg confers any additional benefit. Many centres monitor bone marrow transplant recipients, especially of allogeneic grafts, for CMV viraemia, and commence preemptive therapy with

ganciclovir if viraemia is detected before the develop- ment of symptomatic or obvious organ disease. HCMV retinitis in AIDS This is treated with an induction course of ganciclovir or foscarnet (both drugs have also been used in combination) or valganciclovir 900 mg twice daily for 21 days. Continued prophylaxis is needed to prevent relapse until significant recovery of the CD4 count can be induced with antiretroviral therapy; valganciclovir 900 mg daily is most convenient. Implantable intraocular devices providing sus- tained release of ganciclovir into the vitreous humour have also been used. The use of combination antiretroviral therapy in HIV-infected patients is associated with much improved long-term control of HCMV infection. However, the syndrome of immune-recovery vitritis, characterized by posterior segment inflammation, can occur in patients with previously treated CMV retinitis when their CD4 count reconstitutes on antiretroviral therapy. Congenital HCMV infection Treating symptomatic congenital HCMV infection with ganciclovir (8 or 12 mg/kg daily for 6 weeks) reduces the excretion of CMV in the urine, but viruria returns to near pretreatment levels after cessation of therapy. Hearing improvement may occur, but the role of antiviral therapy in congenital HCMV infection remains to be established. Prevention and control The problem posed by HCMV in immunosuppressed patients has led to several approaches to prophylaxis. Antiviral prophylaxis There is a definite case for primary prophylaxis in solid organ and bone marrow transplant recipients at high risk of disease (seronega- tive recipients of a seropositive graft, or seropositive recipients), and in AIDS patients with fewer than 100 CD4 cells/μl. Ganciclovir has been widely used, and valganciclovir 900 mg daily is effective in many of these settings. Despite limited in vitro activity against HCMV, and lack of efficacy as therapy, oral valaciclovir has been shown to provide significant prophylaxis against HCMV disease in renal transplant recipients, and is licensed for this use. Passive immunization CMV hyperimmune globulin is reported to reduce the risk of HCMV disease in renal transplant recipients, but is expensive and little used in practice. There are reports that HCMV-specific T-cell immunity can be reconstituted in bone marrow transplant recipients by the adoptive transfer of virus-specific T lymphocytes from the immune donor, but this is still the subject of investigational studies. Active immunization A live laboratory strain (Towne) of HCMV has been tested as an experimental candidate vaccine in renal transplant recipients, with some evidence of protective immunity, perhaps equivalent to having previous natural HCMV infection. A more recent phase II trial of recombinant glycoprotein B based HCMV vaccine in seronegative women showed it has the potential to decrease incident cases of ma- ternal and congenital CMV infection. However, there is currently no available licensed vaccine. Special problems in pregnant women Pregnant women who are seronegative should avoid contact with possibly infected children in day-nursery settings, although this may be impractical. Ganciclovir must not be used in pregnancy. Human herpesvirus 6 and 7 Human herpesvirus 6 Human herpesvirus 6 (HHV-6) was first isolated in 1986 from cul- tured human lymphocyte lines, and named human B lymphotropic virus, a misnomer since it is trophic principally for T cells, al- though replication also occurs in macrophages, glial cells, and EBV-transformed B cells. HHV-6 is widely distributed in humans. Primary infection causes roseola infantum (also known as exanthem subitum or sixth disease), an aetiological association first described in Japanese children in 1988. Unlike any other herpesvirus, HHV- 6 genome DNA can be found covalently integrated into the cell chromosomes in about 1% of the population. Aetiology HHV-6 has typical herpesvirus morphology, and is genetically clas- sified in the β-herpesvirus subfamily. Two types of isolate, HHV- 6A and HHV-6B, are now clearly distinguished by their genetic sequence, and some variation in biological properties. HHV-6B is associated with roseola, whereas HHV-6A has not been associated with disease. Epidemiology There is high seroprevalence of HHV-6 in all populations. More than 90% of children are seropositive at 2 years of age. The virus (usually the HHV-6B variant) can be detected

in peripheral blood

750 section 8 Infectious diseases mononuclear cells by PCR-based tests in nearly all healthy people. It is most probably transmitted via maternal saliva, although intra- uterine and perinatal transmission could occur. There is also evi- dence that chromosomally integrated maternal HHV6 can be transmitted in the germline, although the clinical significance is un- certain. The virus is not detectable in breast milk. Pathogenesis HHV-6 probably replicates in regional lymphoid tissue in the oro- pharynx during primary infection, and can be found in circulating lymphocytes. The virus replicates in vitro in CD4 + T-cell lines, but during persistent infection in the normal adult, virus can be de- tected by PCR in both CD4 + T cells and monocytes/macrophages in peripheral blood, which are probably the principal site of car- riage during persistent infection. The mechanism of viral latency is uncertain. Although HHV-6 cannot usually be isolated by culture from the peripheral blood of normal people, specific DNA is easily de- tected in blood during immunosuppression, indicating reactivation of HHV-6. The mechanism by which HHV6 produces its clinical manifestations remains unclear. Clinical features Primary infection with HHV-6 in young children is associated with roseola, and also with a febrile illness without rash. Roseola infantum (exanthem subitum, sixth disease) Roseola is an acute illness of infants and young children, typically 3 to 5 days of high fever with upper respiratory tract symptoms, and sometimes cervical lymphadenopathy. As the fever subsides, a rash appears and lasts for 1 to 3 days. The rash is diffuse, macular, or maculopapular, and appears similar to that of rubella. There is mild atypical lymphocytosis and there may be neutropenia. Infections may rarely be complicated by febrile convulsions, meningitis, encephal- itis, and hepatitis; the last is usually mild, but occasionally severe. Roseola has been estimated to occur in only 10 to 20% of children, and primary HHV-6 infection is commonly subclinical. Febrile illness Fever without rash is a more usual manifestation of primary HHV-6 infection than roseola. In a North American study, 10% of 1600 fe- brile children under the age of 3 years (including 20% of those aged 6–12 months) presenting with acute febrile illness were diagnosed as primary HHV-6 infection, but only 17% of them had clinical roseola. Febrile convulsions It is suggested HHV-6 may have a particular association with febrile convulsions in young children. Primary HHV-6 infection was re- ported to account for one-third of all the febrile seizures in children up to the age of 2 years; however, there were no seizures in 81 chil- dren with primary infection in a prospective cohort. HHV-6 DNA can be detected in the cerebrospinal fluid of children with primary infection, and any association may be because HHV-6 specifically infects the nervous system, rather than solely because of high fever. HHV-6 infection in immunosuppressed patients Several studies have shown increases in antibody titres to HHV- 6, and increased HHV-6 DNA levels in the peripheral blood of immunosuppressed solid organ and bone marrow transplant recipients. In bone marrow transplant recipients, HHV-6 has been associated with fever, rash, graft versus host disease, encephalitis, delayed engraftment, marrow suppression, and pneumonitis. It is not clear whether HHV-6 plays a specific aetiological role in all these syndromes; the evidence is perhaps stronger for a causal role in encephalitis. There is also good evidence that HHV-6 reactivates in patients with advanced HIV infection and AIDS, but again there is less firm evidence that this is associated with disease. Other disease associations Studies of chronic fatigue syndrome and multiple sclerosis have not provided convincing evidence of any significant aetiological associ- ation with HHV-6. Differential diagnosis Primary HHV-6 infection may be confused with many febrile child- hood illnesses accompanied by a rash. Roseola may also be misdiag- nosed as a sensitivity reaction to recent antibiotic treatment. Other virus infections (EBV, HCMV) may also be associated with atypical lymphocytes and a mononucleosis syndrome. Pathology HHV-6 replicates in vitro in

cells originating from the central ner- vous system, particularly glial cell lines. HHV-6 DNA can be de- tected in the brains of apparently normal people, suggesting viral persistence in the central nervous system. No distinctive histopath- ology has yet been attributed to HHV-6. Malignancy HHV-6 DNA has been detected in the blood of patients with sev- eral lymphoproliferative disorders, but this probably reflects re- activation rather than any causal association with the tumour. HHV-6 DNA has been reported in some tumour tissues, including the nodular sclerosis variant of Hodgkin's disease, but without a convincing aetiological association between the virus and any tumour. Laboratory diagnosis Most assays for HHV-6 antibody do not distinguish between anti- body to HHV-6A and HHV-6B, and may cross-react with anti- bodies to HHV-7. Seroconversion is evidence of primary infection. IgM assays for HHV-6 antibody are not reliable indicators of pri- mary infection, as some HHV-6 carriers may periodically have IgM antibody. Although HHV-6 can be cultured from peripheral blood mono- nuclear cells during acute primary infection, few laboratories will undertake this. PCR-based techniques for the detection of HHV-6 DNA in plasma and cerebrospinal fluid are the method of choice for clinical diagnosis, and are becoming more widely available. Treatment HHV-6 sensitivity to antiviral drugs corresponds with that of cytomegalovirus. Thus, HHV-6 replication is inhibited in vitro by ganciclovir and foscarnet, but not aciclovir; however, there are no controlled clinical trials of these drugs. Their use may be considered for immunosuppressed patients with suspected HHV-6-associated pneumonitis.

8.5.2 Herpesviruses (excluding Epstein–Barr virus) 751 Prevention and control There are no preventive measures for HHV-6 transmission. It seems unlikely that there will be a case for the development of a vaccine because infants may be infected so early in life, while they still have maternal antibody. Special problems in pregnant women Nearly all pregnant women will be carriers of HHV-6. There is no evidence that HHV-6 infection harms the fetus or the neonate. Human herpesvirus 7 Human herpesvirus 7 (HHV-7) was isolated in 1990, and is a β-herpesvirus similar to, but distinct from, HHV-6. HHV-7 pre- dominantly infects CD4+ T cells and can be reactivated from latency by T-cell activation. Although there is serological crossreactivity between HHV-6 and HHV-7, data indicate that HHV-7 infects nearly all children, but later than HHV-6, with more than 90% being infected by the age of 5 years. The virus is excreted in saliva. HHV-7 has been associated with some cases of roseola, which it was reported to cause in Japanese infants with a previous episode of roseola proven to be caused by HHV-6. There is no further evidence of pathogenicity. The best method of diagnosis is PCR-based testing of serum or cerebrospinal fluid. Laboratory tests for HHV-6 often detect HHV- 7 by multiplex PCR. There is no reason to consider any treatment for HHV-7. Human herpesvirus 8 Human herpesvirus 8 (HHV-8) is the most recently isolated of the human herpesviruses; Chang and colleagues reported the detection of novel DNA sequences with homology to herpesviruses in Kaposi's sarcoma tissue in 1994. Initially named Kaposi's sarcoma-associated herpesvirus, it was subsequently designated HHV-8. It is genetic- ally most closely related to a well characterized simian herpesvirus (herpesvirus saimiri), and less so to EBV; it has consequently been assigned to the rhadinovirus (γ2-herpesvirus) subfamily. Current culture techniques are unreliable, but the virus can be detected by PCR. Serological assays depend on the use of infected cell lines or synthetic antigens from predicted open reading frames. The seroepidemiology, biology, and disease associations of the virus are still being analysed, but HHV-8 is clearly associated with Kaposi's sarcoma, a tumour that has long been suspected of having a viral aetiology; with primary effusion lymphoma; and with multicentric Castleman's disease. Reported associations with multiple myeloma and other cancers are unconfirmed. Aetiology HHV-8 has the characteristic morphology of a herpesvirus. The viral genome is composed of a 141 kbp

unique segment flanked by mul- tiple 801 bp direct repeats. Sequence analysis suggests that HHV-8, like other herpesviruses, is an ancient human virus; comparative analysis of the variable genes ORF-K1 and K15 indicates there are at least four virus subtypes, A to D, reflecting the migrationary di- vergence of modern human populations. HHV-8 contains genes homologous to mammalian genes encoding cell-cycle regulatory proteins (the cyclins), chemokines, and inhibitors of apoptosis. On the evidence to date, the normal cellular site of latency of HHV-8 almost certainly includes the B cell. Epidemiology The emerging epidemiology of HHV-8 suggests it is less ubiqui- tous than other human herpesviruses. Initial serological assays de- tected antibodies to a latent nuclear antigen; assays using lytic-cycle antigens gave higher rates of seroprevalence, and newer assays using multiple HHV-8 antigens are currently being applied. Current data suggest a seroprevalence of 90% or more in patients with Kaposi's sarcoma, and 40% in HIV-positive homosexual men without Kaposi's sarcoma. Seroprevalence in healthy adults is reported as being more than 50% in African adults in West Africa, 20% in black South African blood donors, and 53% in HIV-positive and -negative adults in Uganda. Seroprevalence is 5% or less in blood donors in the United Kingdom and the United States of America, with inter- mediate rates in Italy and other Mediterranean countries. HHV-8 can be detected by PCR in nearly all cases of Kaposi's sarcoma, but is less easy to detect in the blood of normal carriers. The usual route of transmission is probably saliva and sexual con-tact, but intravenous drug use, blood transfusion, and organ trans- plantation also transmit the virus. A latent nuclear antigen-based assay detected seroconversion to HHV-8 in HIV-infected homo- sexual men at a median of 33 months before they subsequently de- veloped Kaposi's sarcoma. HHV-8 infection in children correlates with seropositivity in their mothers, but whether this reflects ver- tical or horizontal transmission is uncertain. Pathogenesis There has been much uncertainty over the cell of origin of Kaposi's sar- coma, but the spindle cells of which the tumour is largely composed are thought to be of lymphatic endothelial origin. In Kaposi's sarcoma tumour tissue, HHV-8 DNA and latent nuclear antigen are present in every spindle cell, suggesting an aetiological role for the virus. In HIV-associated Castleman's disease, the HHV-8 latent nuclear antigen is present in immunoblasts in the mantle zone of the tu- mour. HHV-8 is present in the tumour cells of all cases of primary effusion lymphoma so far studied (although so is EBV), and HHV-8 latently infected cell lines derived from these tumours can be in- duced to release infectious virus. These clear associations of virus DNA with tumour cells suggest a definite oncogenic role for HHV- 8. HHV-8 latent transcripts, including latency-associated nuclear antigen, viral cyclin, viral FLIP, and virus-encoded microRNAs, promote cell proliferation and prevent apoptosis, whereas lytic proteins, such as viral G protein-coupled receptor, K1, and virus- encoded cytokines (viral interleukin-6 and viral chemokines) con- tribute to the characteristic angioproliferative and inflammatory Kaposi's sarcoma lesions through a mechanism known as paracrine neoplasia. It has been suggested that HHV-8 may be involved in the patho- genesis of multiple myeloma, but this association is unproven, as is an association with primary pulmonary hypertension. The individual HHV-8 subtypes are not associated with any distinct pathology. Clinical features Apart from these malignancies, the only reported clinical syndrome accompanying primary or reactivated HHV-8 infection is fever

associated form. In the classical and African forms there are lesions on the extremities; systemic and mucosal involve- ment is rare, and the disease is indolent. In immunosuppressed pa- tients (other than those with AIDS) the lesions are more widespread and more rapidly progressive, although visceral involvement is still unusual, and lesions may regress if immunosuppressive drugs are stopped. AIDS-associated Kaposi's sarcoma is seen predominantly in homosexual men in Western countries, but is commonly associated with heterosexually acquired HIV infection in African countries. The clinical signs are widespread cutaneous lesions, with involvement of the oral mucosa (see Chapter 8.5.23, Figs. 8.5.23.12 and 8.5.23.13), and visceral lesions may occur in the lungs or gastrointestinal tract. Progression can be much more rapid than the other forms. HHV-8 has been isolated from all four types of Kaposi's sarcoma. Primary effusion lymphomas Previously known as body-cavity based lymphomas, these are a rare and aggressive type of B-cell lymphoma in patients with AIDS. They present as lymphomatous effusions of the peritoneal, pleural, or pericardial spaces, usually without any identifiable tumour mass. HHV-8 is present in the tumour cells of all cases so far studied, al- though so also is EBV. Castleman's disease or angiofollicular lymph node hyperplasia This can be localized, and is amenable to curative excision. However, a multicentric form is seen particularly in HIV-infected patients, and is more aggressive. HHV-8 is found in a high proportion of these multicentric cases, especially those associated with HIV. Pathology No distinctive histopathology has been identified for HHV-8 inde- pendent of the pathology of the tumours with which it is associated. Laboratory diagnosis HHV-8 can best be detected by PCR-based tests. The antibody assays described earlier may become commercially available in the near future. Treatment In vitro assays in HHV-8-infected lymphoma cell lines indicate that HHV-8 replication is moderately sensitive to foscarnet, ganciclovir, and cidofovir. AIDS patients treated with foscarnet and ganciclovir may be less likely to develop Kaposi's sarcoma. Antiviral drugs are not an established treatment for HHV-8 tumours. Kaposi's sarcoma confined to the skin can be treated with radio- therapy or intralesional α-interferon. More widespread cutaneous or visceral disease can be treated with single-agent or combination chemotherapy. The treatment of Kaposi's sarcoma in AIDS pa- tients is discussed in Chapters 8.5.23 and 8.5.24. Kaposi's sarcoma lesions may regress with antiretroviral treatment, possibly because of improved cellular immunity resulting from the reduction in HIV load. Prevention and control Given the uncertainty around the epidemiology and disease associ- ations of HHV-8, prevention and control are not yet possible. No spe- cial problems of infection have been identified in pregnant women. Cercopithecine herpesvirus 1 (herpes B virus) Cercopithecine herpesvirus 1 is the formal name now given to herpes B virus (replacing the previous term, herpesvirus simiae), the natural hosts of which are members of the Macaca genus of Old World monkeys. It produces minimal disease in its natural hosts, but its transmission to humans results in a high incidence of severe dis- ease. Although more than 30 other herpesviruses have been isolated from nonhuman primates, none of these has been unequivocally associated with a disease in humans. The virus was first isolated in 1932 from the brain of Dr W B, who died of encephalitis after a bite from a macaque (hence the name herpes B virus). There have since been about 45 cases of human infection resulting from accidental transmission from captive monkeys. Aetiology Herpes B virus is an α-herpesvirus closely related to HSV, and appears to behave in an analogous manner to HSV in its natural pri- mate host. Herpes B virus can also infect and produce disease in other nonhuman primates and small mammals. Epidemiology Herpes B virus is enzootic in Old World monkeys of the Macaca genus, principally rhesus (M. mulatta) and cynomolgus (M. fascicu- laris) macaques. The epidemiology in its primate host is similar to that of HSV in humans, with 80% or more of natural and captive adult monkeys being infected. Infected monkeys may develop ves- icular oral lesions, and can shed virus

intermittently from oral, con- junctival, and genital secretions. Rhesus and cynomolgus macaques have been quite widely used in medical research, particularly for the development of polio vaccine in the mid-1950s, and in the late 1980s following the AIDS epidemic, for studies of retroviruses. Nearly all the reported human cases re- sulted from occupational exposure through bites and scratches in workers handling monkeys, but transmission from needlestick in- juries and a splash in the eye have also been reported. One case of human-to-human transmission apparently occurred by inoculation onto inflamed skin. Two clusters of infection have been described in the United States of America (in 1987, involving the case of human-to-human transmission, and 1989). A seroprevalence study of more than 300 monkey handlers showed that none was seropositive, and asymp- tomatic infection documented by seroconversion appears to be ex- tremely uncommon. Clinical features The incubation period, from occupational exposure to the devel- opment of symptoms, has usually been 3 to 5 days, but can range

 from 3 to 30 days. Cutaneous vesicles may occur at or near the site of inoculation, accompanied by regional lymphadenitis. In the first 2 weeks, fever, malaise, headache, and abdominal pain are common, but the dominant and characteristic features are progressive multi- focal haemorrhagic myelitis, and encephalitis. Visceral spread of herpes B virus is recorded in fatal cases. The untreated mortality is 80%. The history of monkey bite may lead to a suspicion of rabies (Chapter 8.5.10). It is not clear whether herpes B virus in humans can become latent and then be reactivated. Viral shedding has recurred when antiviral treatment was stopped relatively early, so most patients have been maintained on antivirals for long periods. Laboratory diagnosis As herpes B virus is a category 4 pathogen, viral culture and isolation are only attempted in a few designated laboratories: in the United Kingdom at the Central Public Health Laboratory, Colindale, London; and in the United States of America at Georgia State University, Atlanta. Monkeys with suspected infection should have serum antibody tests. Serodiagnosis in humans is difficult because of antigenic crossreactivity between herpes B virus and HSV. The inoculation site should ideally be biopsied for culture and analysis. PCR-based methods are available in specialized centres, and are the standard for definitive diagnosis. Treatment Although injuries from macaques carry the risk of herpes B virus in- fection, most captive macaque colonies are now maintained free of the virus. A suspected contaminated wound should be debrided and cleaned with chlorhexidine or iodine soap. Postexposure prophy- laxis may be initiated if the monkey is suspected to be positive for herpes B virus, and there is skin puncture or mucosal exposure. There may be a case for initiating immediate antiviral treatment if infection in the monkey is suspected, or for a deep wound. Aciclovir and ganciclovir both inhibit herpes B virus replication in vitro. For postexposure prophylaxis, valaciclovir 1 g 8 hourly is re- commended for at least 2 weeks. If symptomatic disease is suspected or proven, intravenous aciclovir is recommended if CNS symptoms are absent (15 mg/kg 8 hourly), and ganciclovir if CNS symptoms are present (5 mg/kg every 12 h). Treatment has been associated with the limitation of disease, and recovery, in some patients, but pro- longed oral therapy with aciclovir or valaciclovir is advised to limit the risk of reactivation. Prevention and control Those working with macaques should follow standard procedures to avoid infection. The screening of newly imported monkeys, and the creation of colonies of macaques free of herpes B virus, are now becoming standard practice.

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Revision #1
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Updated 2026-01-22 16:45:20 UTC by Omar Ayman