by the third day of TAC in patients with hematologic disorders; these antibodies remain detectable for ~3 months. B19V IgG is detectable by the seventh day of illness and persists throughout life. Quantitative detection of B19V DNA should be used for the diagnosis of early TAC or chronic anemia. Although B19V levels fall rapidly with the development of the immune response, DNA can be detectable by PCR for months or even years after infection, even in healthy individuals; therefore, quantitative PCR should be used. In acute infection at the height of viremia, $>10^{12}$ B19V DNA IU/mL of serum can be detected; however, titers fall rapidly within 2 days. Patients with aplastic crisis or B19V-induced chronic anemia generally have $>10^5$ B19V DNA IU/mL.

TREATMENT PARVOVIRUS B19 INFECTION

No antiviral drug effective against B19V is available, and treatment of B19V infection often targets symptoms only. TAC precipitated by B19V infection frequently necessitates symptom-based treatment with blood transfusions. In patients receiving chemotherapy, temporary cessation of treatment may result in an immune response and resolution. If this approach is unsuccessful or not applicable, commercial immune globulin (IVIg; Gammagard, Sandoglobulin) from healthy blood donors can cure or ameliorate persistent B19V infection in immunosuppressed patients. Generally, the dose used is 400 mg/kg daily for 5–10 days. Like patients with TAC, immunosuppressed patients with persistent B19V infection should be considered infectious. Administration of IVIg is not beneficial for erythema infectiosum or B19V-associated polyarthropathy. Intrauterine blood transfusion can prevent fetal loss in some cases of fetal hydrops.

PREVENTION

No vaccine has been approved for the prevention of B19V infection, although vaccines based on B19V virus-like particles expressed in insect cells are known to be highly immunogenic. Phase 1 trials of a putative vaccine were discontinued because of adverse side effects.

PARV4/5

DEFINITION

The PARV4 viral sequence was initially detected in a patient with an acute viral syndrome. Similar sequences, including the related PARV5 sequence, have been detected in pooled plasma collections. The DNA sequence of PARV4/5 is distinctly different from that of all other parvoviruses, and this virus is now classified as a member of the newly described genus *Tetraparvovirus.*

EPIDEMIOLOGY

PARV4 DNA is commonly found in plasma pools but at lower concentrations than levels of B19V DNA found before in plasma pools prior to screening. The higher levels of PARV4 DNA and IgG antibody in tissues (bone marrow and lymphoid tissue) and sera from IV drug users than in the corresponding specimens from control patients suggest that the virus is transmitted predominantly by parenteral means in the United States and Europe. Evidence for nonparenteral transmission in other parts of the world is limited.

CLINICAL MANIFESTATIONS

To date, PARV4/5 infection has been associated only with mild clinical disease (rash and/or transient aminotransferase elevation).

HUMAN BOCAVIRUSES

DEFINITION

Animal bocaviruses are associated with mild respiratory symptoms and enteritis in young animals. HBoV1 was originally identified in the respiratory tract of young children with lower respiratory tract infections. More recently, HBoV1 and the related viruses HBoV2, HBoV3, and HBoV4 have all been identified in human fecal samples.

EPIDEMIOLOGY

Seroepidemiologic studies with HBoV virus-like particles suggest that human bocavirus infection is common. Worldwide, most individuals are infected before the age of 5 years.

CLINICAL MANIFESTATIONS

HBoV1 DNA is found in respiratory secretions from 2–20% of children with acute respiratory infection, often in the presence of other pathogens; in these circumstances, the role of HBoV1 in disease pathogenesis is unknown. Clinical disease due to HBoV1 is associated with evidence of primary infection (IgG seroconversion or the presence of IgM), HBoV1 DNA in serum, or high-titer HBoV1 DNA ($>10^4$ genome copies/mL) in respiratory secretions. Symptoms are not dissimilar from those of other viral respiratory infections, and cough and wheezing are commonly reported. There is no specific treatment for bocavirus infection. The role of human bocaviruses in childhood gastroenteritis remains to be established.

222 Human Papillomavirus Infections

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Investigation of human papillomavirus (HPV) infection began in earnest in the 1980s after Harold zur Hausen postulated that infection with these viruses was associated with cervical cancer. It is now recognized that HPV infection of the human genital tract is extremely common and causes clinical states ranging from asymptomatic infection to genital warts (*condylomata acuminata*); dysplastic lesions or invasive cancers of the anus, penis, vulva, vagina, and cervix; and a subset of oropharyngeal cancers. This chapter describes the epidemiology of HPV in general and as a pathogen, the natural history of HPV infections and associated cancers, strategies to prevent HPV infection and HPV-associated disease, and treatment modalities.

PATHOGENESIS

Molecular Overview HPV is an icosahedral, nonenveloped, 8000-base-pair, double-stranded DNA virus with a diameter of 55 nm. Like those of other papillomaviruses, HPV's genome consists of an early (E) gene region, a late (L) gene region, and a noncoding region that contains regulatory elements. The E1, E2, E5, E6, and E7 proteins are expressed early in the growth cycle and are necessary for viral replication and cellular transformation. The E6 and E7 proteins cause malignant transformation by targeting the human cell cycle–regulatory molecules p53 and Rb (retinoblastoma protein), respectively, for degradation. Translation of the L1 and L2 transcripts and splicing of an E1^E4 transcript occur later. The L1 gene encodes the 54-kDa major capsid protein that makes up the majority of the virus shell; the 77-kDa L2 minor protein constitutes a smaller percentage of the capsid mass.

More than 125 HPV types have been identified and are numerically designated according to a unique L1 gene sequence. Approximately 40 HPV types are regularly found in the anogenital tract and are subdivided into high-risk and low-risk categories on the basis of the associated risk of cervical cancer. For example, HPV-6 and HPV-11 cause genital warts and ~10% of low-grade cervical lesions and are thus designated low risk. HPV-16 and HPV-18 cause dysplastic lesions and invasive cancers of the cervix and are considered high risk.

HPV targets basal keratinocytes after microtrauma has exposed these cells to the virus. The HPV replication cycle is completed as keratinocytes undergo differentiation. Virions are assembled in the nuclei of differentiated keratinocytes and can be detected by electron microscopy. Infection is transmitted by contact with virus contained in these desquamated keratinocytes (or with free virus) from an infected individual.