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Epstein–Barr Virus

Hal B. Jenson, MD*

Objectives   After completing this article, readers should be able to:

1. Describe the epidemiology and transmission of Epstein–Barr virus (EBV) among children, adolescents, and adults.
2. Describe the pathogenesis and natural course of EBV infection and the spectrum of clinical diseases in healthy and immunocompromised persons.
3. Interpret serologic test results to diagnose acute and past EBV infections.
4. Describe the appropriate management of infectious mononucleosis and the role of corticosteroids for treatment of complications.
5. Discuss the relationship of EBV to human malignancies.

Introduction

Epstein-Barr virus infection results in a spectrum of diseases, with the host immune response playing a key role in shaping the clinical manifestations. Infectious mononucleosis is the prototype EBV infection and is characterized by fever, sore throat, cervical and generalized lymphadenopathy, hepatosplenomegaly, and somatic complaints of fatigue and malaise. This condition generally is a benign, self-limited illness in healthy persons. In this article, the term "infectious mononucleosis" refers to the disease caused by primary EBV infection, although other agents can cause "infectious mononucleosis-like" disorders that are clinically similar to the EBV-associated disease.

Aggressive, nonmalignant EBV-associated proliferations, such as virus-associated hemophagocytic syndrome, posttransplant lymphoproliferative syndrome (PTLS), lymphoid interstitial pneumonitis, and oral hairy leukoplakia, occur in immunocompromised persons. EBV also contributes to human malignancies, including nasopharyngeal carcinoma, Burkitt lymphoma, Hodgkin disease, and leiomyosarcoma.

The history of the discovery of EBV as the cause of infectious mononucleosis began with the first clinical description of a subacute febrile illness by Filatov in 1885 and the description of "glandular fever" by Pfeifer in 1889. In 1920, Sprunt and Evans described the finding of atypical lymphocytes and aptly coined the name "infectious mononucleosis" for this disease. The discovery of EBV also was the first identification of a human tumor virus. In 1964, Epstein, Achong, and Barr identified herpesvirus particles in tissues of jaw sarcomas collected by Burkitt from children in Africa. In 1968, Gertrude and Werner Henle linked this virus with a single case of infectious mononucleosis and, along with Niederman, confirmed the epidemiologic association. EBV was the first virus to be linked to human cancer and became the first recognized human tumor virus. (For complete information, see Tselis and Jenson, 2006.)

Abbreviations

AIDS:	acquired immune deficiency syndrome
EA:	early antigen
EA–D:	early antigen-diffuse
EA–R:	early antigen-restricted
EBNA:	EBV nuclear antigen
EBV:	Epstein-Barr virus
HIV:	human immunodeficiency virus
Ig:	immunoglobulin
NK:	natural killer
PTLS:	posttransplant lymphoproliferative syndrome
VCA:	viral capsid antigen
XLP syndrome:	X-linked lymphoproliferative syndrome

Epidemiology

EBV is a γ-herpesvirus that has a double-stranded DNA genome of 184-kb pairs in length, encoding nearly 100 proteins. Two distinct types, type 1 and type 2 (also called type A and type B), share 70% to 85% sequence homology. EBV-1 is more prevalent worldwide than EBV-2, which is

found more frequently in Africa. The primary cellular target of EBV is the B-lymphocyte. EBV-1 induces in vitro growth transformation of B-cells more efficiently then EBV-2, but both types result in lifelong infection, with no identified type-specific differences in disease. Multiple as well as dual infections with both EBV types have been documented in immunocompromised persons.

Because EBV establishes lifelong infection, the prevalence of EBV infection increases with age. Greater than 95% of the world's adult population is seropositive and chronically infected. No symptoms are recognized from the persistent, latent EBV infection that follows the primary infection.

EBV is transmitted primarily by oral contact with saliva, most commonly by exchange of saliva among young children directly or through the handling of toys or by kissing among adolescents, accounting for infectious mononucleosis commonly being called "kissing disease." EBV is shed in oral secretions consistently and at high concentrations for more than 6 months following acute infection and intermittently at lower concentrations for life. Thus, the risk of transmission is greater from recent cases, with some risk of transmission from anyone who has ever been infected. At any given time, as many as 20% to 30% of healthy adults who were infected with EBV, even years previously, shed EBV in low concentrations in oral secretions. Immunosuppression facilitates reactivation of latent EBV, and the proportion of EBV-infected immunosuppressed persons shedding virus in oral secretions increases to 60% to 90%. EBV is found also in male and female genital secretions and can be transmitted by sexual contact.

The epidemiology of the clinical entity of infectious mononucleosis is related to age of acquisition of EBV infection. Although infectious mononucleosis may be seen at all ages, it is rarely recognizable in children younger than 4 years of age, when most EBV infections are asymptomatic. It is rare in adults older than 30 to 40 years of age, when most individuals are already infected with EBV.

In developing countries and among socioeconomically disadvantaged populations of developed countries, transmission of EBV occurs almost universally during infancy and early childhood. In central Africa, almost all children are infected with EBV by 3 years of age, resulting in asymptomatic infection or mild disease that is indistinguishable from many other childhood infections. Thus, infectious mononucleosis as a disease is practically unknown in undeveloped regions of the world.

In contrast, in industrialized countries and among affluent populations, infection during childhood occurs less frequently, presumably because of higher standards of hygiene, with approximately one third of EBV infections occurring during adolescence and young adulthood. Primary EBV infection in adolescents and adults results in symptoms in more than 50% of infections, demonstrating the classic infectious mononucleosis triad of fatigue, pharyngitis, and lymphadenopathy. The incidence of infectious mononucleosis in the United States is estimated to be 20 to 70 per 100,000 persons annually; among young adults, the incidence increases to about 100 per 100,000 persons annually.

Pathogenesis

Following acquisition via the oral cavity, EBV initially infects oral epithelial cells with viral replication, cell lysis, and release of virions that spread to contiguous structures, including the salivary glands. Local replication in oral epithelial and lymphoid cells may be the basis of the symptoms of pharyngitis. Viremia ensues, with infection of the primary cellular target of EBV, the B-lymphocytes in the peripheral blood and the entire lymphoreticular system, including the liver and spleen. Of note, the atypical T-lymphocytes in the peripheral blood that are characteristic of infectious mononucleosis are mature $CD8^+$ T-lymphocytes, which have both suppressor and cytotoxic functions. These atypical lymphocytes are antigenically activated and are part of the immune response to the EBV-infected B-lymphocytes. The absolute increase in $CD8^+$ lymphocytes results in a transient reversal of the normal 2:1 $CD4^+/CD8^+$ (helper-suppressor) T-lymphocyte ratio. This pattern is distinguished from the reversal of the $CD4^+/CD8^+$ ratio seen in human immunodeficiency virus (HIV) infection by the normal absolute concentrations of $CD4^+$ T-lymphocytes.

The host immune response reduces the circulating EBV burden in the peripheral blood to less than 1 copy/10^5 circulating B-lymphocytes, equivalent to less than 10 copies/μg of DNA in whole blood. In immunocompromised persons, the EBV burden usually is much higher and can be greater than 4,000 copies/μg of DNA.

EBV also infects T-lymphocytes and natural killer (NK) cells, although at a reduced efficiency of infection compared with the ease with which EBV infects B-lymphocytes. EBV appears to infect epithelial cells of the uterine cervix, although local symptoms have not been described after sexual transmission. However, EBV also has been shown to infect smooth muscle cells in leiomyosarcomas that develop in immunocompromised people.

Following primary infection, EBV, like all herpes-

viruses, establishes persistent latent infection for the life of the host. Latent EBV infection harbors locally in oropharyngeal epithelial cells and systemically in memory B-lymphocytes. Latent EBV produces a few viral proteins, primarily the EBV nuclear antigens (EBNAs). These proteins maintain the virus during the latent state as multiple circular copies, or episomes, in the nucleus that are separate from the cell's chromosomes. EBV persists because the viral episomes replicate with cell division and migrate to both daughter cells during mitosis. In contradistinction, in cases of Burkitt lymphoma, EBV integrates into the cell chromosome with a reciprocal translocation that involves the *MYC* allele.

For unclear reasons, some latently infected B-lymphocytes enter the viral replicative, or lytic, cycle that begins with EBV early antigens (EAs) production; proceeds to viral DNA replication followed by structural glycoprotein production, including the manufacture of viral capsid antigens (VCAs); and culminates in cell death with release of mature virions that are shed through secretions and systemically infect other B-lymphocytes. Reactivation apparently is asymptomatic.

Clinical Aspects

The incubation period of infectious mononucleosis in adolescents and adults is 30 to 50 days and may be shorter in children. Primary EBV infection in young children usually is asymptomatic or produces symptoms that do not distinguish EBV as the cause from the many other febrile infections that occur during childhood. Among adolescents and adults, the clinical syndrome of infectious mononucleosis is characteristic. The onset of illness usually is insidious over 1 to 2 weeks, with nonspecific systemic complaints of malaise, fatigue, and low-grade fever accompanied by sore throat, lymphadenopathy, and often headache, nausea, abdominal pain, and myalgias. Complaints of sore throat and fever gradually increase and prompt medical attention. Sometimes the presenting complaints can be upper quadrant abdominal discomfort and tenderness due to rapidly developing splenomegaly.

The physical examination typically reveals pharyngitis that often is accompanied by moderate-to-marked tonsillar enlargement, occasionally with exudates that cannot be distinguished from streptococcal pharyngitis. Petechiae at the junction of the hard and soft palate are common. The reticuloendothelial system usually is affected, as evidenced by generalized lymphadenopathy (90% of cases), splenomegaly (50% of cases), and hepatomegaly (10% of cases). Lymphadenopathy is most common in the anterior and posterior cervical lymph nodes, the submandibular lymph nodes, and sometimes the axillary and inguinal lymph nodes. Epitrochlear lymphadenopathy traditionally is suggestive of infectious mononucleosis because this finding is an uncommon part of generalized lymphadenopathy. Splenomegaly to 2 to 3 cm below the left costal margin is typical, although massive enlargement is very uncommon.

Rashes occur in 3% to 15% of patients and usually are maculopapular. Up to 80% of patients in whom infectious mononucleosis is treated with ampicillin experience an "ampicillin rash," which occurs less frequently with amoxicillin and other beta-lactam antibiotics. This copper-colored, pruritic maculopapular eruption probably is immune-mediated and requires no specific treatment other than discontinuation of the antibiotic, after which the eruption resolves. EBV also is associated with Gianotti-Crosti syndrome, a symmetric rash that has the appearance of atopic dermatitis. Multiple erythematous papules on the cheeks, extremities, and buttocks may coalesce into plaques, and the rash persists for 15 to 50 days.

Nonneoplastic EBV-associated proliferative diseases occur in immunocompromised people, such as HIV-infected individuals and organ transplant recipients. Lymphoid interstitial pneumonitis occurs primarily in children who have acquired immune deficiency syndrome (AIDS) and causes mild respiratory distress. Oral hairy leukoplakia occurs primarily in adults who have AIDS and is characterized by white patches along the lateral margins of the tongue. Biopsy of these lesions reveals extremely high levels of EBV replication.

Diagnosis

The presence of typical clinical symptoms accompanied by atypical lymphocytosis in the peripheral blood suggests the clinical diagnosis of infectious mononucleosis. The diagnosis should be confirmed by serologic testing, either for heterophile antibody or specific EBV antibodies.

The white blood cell count in infectious mononucleosis is either normal or reveals mild leukocytosis of 10 to $20 \times 10^3 / \mu L$ (10 to $20 \times 10^9 / L$), with the lymphocytes accounting for at least two thirds of the white blood cells. Atypical lymphocytes often account for 20% to 40% of the total white blood cells. Atypical lymphocytes appear larger overall, with larger, eccentrically placed, indented, and folded nuclei that have a lower nuclear-to-cytoplasm ratio. Although atypical lymphocytosis may be seen with many infections causing lymphocytosis, the highest concentrations of atypical lymphocytes classically are seen with EBV infection. Atypical lymphocytosis occurs with

acquired cytomegalovirus infection (in contrast to congenital cytomegalovirus infection), toxoplasmosis, viral hepatitis, rubella, roseola, mumps, tuberculosis, typhoid, *Mycoplasma* infection, and malaria as well as with some drug reactions.

Mild thrombocytopenia (100 to $200 \times 10^3/\mu L$ [100 to $200 \times 10^9/L$] platelets) occurs in 25% to 50% of patients and rarely is associated with symptoms. Severe thrombocytopenia ($<20 \times 10^3/\mu L$ [$20 \times 10^9/L$] platelets) rarely occurs.

Mild elevation of hepatic transaminases is seen in approximately 50% of uncomplicated cases, but liver involvement usually is asymptomatic without jaundice.

Heterophile Antibody Test

Heterophile antibodies are defined by their property to agglutinate cells from species different from those of the source serum. The transient heterophile antibodies seen in infectious mononucleosis, also known as Paul-Bunnell antibodies, are immunoglobulin M (IgM) antibodies detected by the Paul-Bunnell-Davidsohn test for sheep red blood cell agglutination. The heterophile antibodies of infectious mononucleosis agglutinate sheep but not guinea pig kidney cells. Horse red blood cells are now used frequently instead of sheep red blood cells and have greater sensitivity. Heterophile antibody titers of more than 1:40, depending on the dilution system used, or of more than 1:28 after absorption with guinea pig cells, are considered positive. The absence of agglutination of guinea pig kidney cells differentiates the EBV heterophile response from the heterophile response of serum sickness and rheumatic diseases.

Heterophile antibody testing responses using sheep red blood cells often stay positive for several months after infectious mononucleosis, and testing with horse red blood cells can yield positive results for up to 2 years after infection. The most widely used method for detecting heterophile antibodies is the qualitative rapid slide test using horse erythrocytes. This test detects heterophile antibody in 90% of cases of EBV-associated infectious mononucleosis that occurs among older children and adults but in only up to 50% of cases among children younger than 4 years of age because these children typically develop lower titers. For this reason, the heterophile test is not recommended for diagnostic testing for infectious mononucleosis among children younger than 4 years of age.

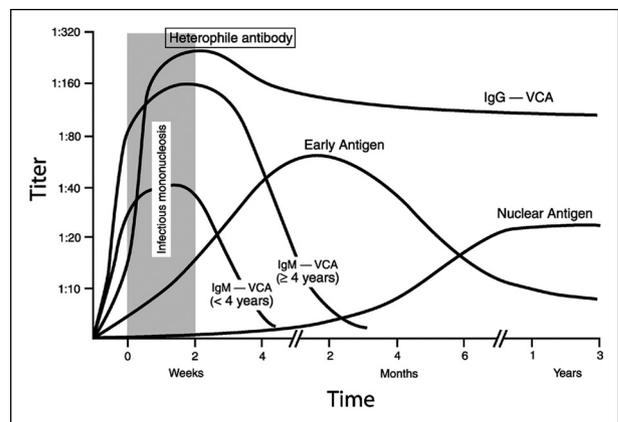Approximately 5% to 10% of cases of apparent infectious mononucleosis are not caused by EBV and do not

Figure. Schematic representation of the development of antibodies to various Epstein–Barr virus antigens in patients who have infectious mononucleosis. Antibody titers are calculated as geometric mean values expressed as reciprocals of the serum dilution. The immunoglobulin M (IgM) response to viral capsid antigen (VCA) is divided because of the significant differences noted according to age of the patient. IgG= immunoglobulin G. Reprinted with permission from Jenson HB. Epstein–Barr virus. In: Detrick B, Hamilton RG, Folds JD, eds. *Manual of Molecular and Clinical Laboratory Immunology.* 7th ed. Washington, DC: American Society for Microbiology; 2006:637–647.

consistently have a heterophile antibody response. The false-positive rate is less than 10%, usually resulting from erroneous interpretation. If the heterophile test result is negative and an EBV infection is suspected, antibody testing for specific EBV antibody tests should be undertaken.

EBV Antibody Tests

Specific antibody tests best confirm EBV infection. These tests help diagnose acute EBV infection (especially if the heterophile test result is negative), confirm past infection, and determine susceptibility to future EBV infection. Several distinct EBV antigen systems based on different EBV genes have been characterized for diagnostic purposes (Figure and Table). The nuclear EBNA, the EA, and the VCA systems are most useful for diagnostic purposes. IgM tests for EA and EBNA are not reliable and are not recommended. The EA antigens include two morphologic components, diffuse (EA-D) and restricted (EA-R), each of which comprises two individual EBV proteins. EA-D and EA-R are distinguished on the basis of their distribution (diffuse or restricted to the cytoplasm) within the cells and by their differential denaturation during the fixation process. The

Table. **Correlation of Clinical Status and Serologic Responses to EBV Infection**

| Clinical Status | Heterophile Antibodies (Qualitative Test) | Serologic Response EBV–Specific Antibody | | | | |
		IgM-VCA	IgG-VCA	EA-D	EA-R	EBNA
Negative reaction	−	<1:8*	<1:10*	<1:10*	<1:10*	<1:2.5*
Susceptible	−	−	−	−	−†	−
Acute primary infection: infectious mononucleosis	+	1:32 to 1:256	1:160 to 1:640	1:40 to 1:160	−†	− to 1:2.5
Recent primary infection: infectious mononucleosis	+/−	− to 1:32	1:320 to 1:1,280	1:40 to 1:160	−†	1:5 to 1:10
Remote infection	−	−	1:40 to 1:160	−‡	− to 1:40	1:10 to 1:40
Reactivation: immunosuppressed or immunocompromised	−	−	1:320 to 1:1,280	−‡	1:80 to 1:320	− to 1:160
Burkitt lymphoma	−	−	1:320 to 1:1,280	−‡	1:80 to 1:320	1:10 to 1:80
Nasopharyngeal carcinoma	−	−	1:320 to 1:1,280	1:40 to 1:160	−§	1:20 to 1:160

Data obtained from numerous studies. Individual responses outside the characteristic range may occur.
*Or the lowest test dilution.
†In young children and adults who have asymptomatic seroconversion, the antibody response to EA may be primarily to the EA-R component.
‡A minority of individuals have the antibody response to EA, primarily to the EA-D component.
§A minority of individuals have the antibody response to EA, primarily to the EA-R component.
EA-D=diffuse staining component of early antigen, EA-R=cytoplasmic restricted component of early antigen, EBNA=EBV-determined nuclear antigens, EBV=Epstein-Barr virus, IgG=immunoglobulin G, IgM=immunoglobulin M, VCA=viral capsid antigen, −=negative, +=positive.
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late antigens are produced after viral DNA synthesis and include the VCAs, the structural proteins of the viral capsid.

Acute EBV infection is uniformly characterized by rapid IgM and IgG antibody responses to VCA and a detectable IgG response to EA in most cases. The IgM response to VCA is transient but can be detected for at least 4 weeks and occasionally as long as 3 months. The IgM-VCA test is the single most valuable and specific serologic test for diagnosing acute EBV infection and generally is sufficient by itself to confirm the diagnosis. Rheumatoid factor, if present, may cause a false-positive IgM-VCA result, thereby necessitating rheumatoid factor absorption before IgM-VCA testing. The IgG response to VCA usually peaks late in the acute phase, declines slightly over several weeks to months, and persists at relatively stable titers for life. Therefore, a positive IgG-VCA result alone cannot distinguish recent from remote infection.

Antibodies to EA are transiently detectable in 80% of patients during the acute phase of infectious mononucleosis, for several months after primary infection, and possibly intermittently at low titers for many years. Antibodies to EA-R emerge transiently during convalescence in healthy people and reach very high titers in patients who have Burkitt lymphoma. Antibodies to EA-D reach very high titers in patients who have nasopharyngeal carcinoma. High titers of antibodies to EA-D or EA-R also may be found in immunocompromised persons who have high EBV replication.

Antibodies to EBNA develop relatively late after EBV infection, gradually appear during the 3 to 4 months following acquisition, and remain at consistently detectable but low titers for life. Absence of antibodies to EBNA when other EBV-specific antibodies are detectable implies recent infection within a few weeks or months. The presence of antibodies to EBNA implies infection occurring at least 3 to 4 months previously, which could be at any time during the life of the individual.

Virus Culture

Culturing EBV by the transformation assay is tedious and usually performed only for research studies. Oropharyn-

geal or genital secretions, peripheral blood (10 to 30 mL), or tumor specimens are cultivated with human umbilical cord lymphocytes, which are especially susceptible to EBV infection, and observed for 4 to 6 weeks for signs of cell transformation. Such transformation can include proliferation and rapid growth, mitotic figures, large vacuoles, granular morphology, and cell aggregation. EBV cultivation with umbilical cord cells immortalizes the cord cells, resulting in cell lines that can be maintained in perpetuity harboring EBV isolated from the patient.

Differential Diagnosis

Approximately 5% to 10% of cases of apparent infectious mononucleosis are EBV-negative. These infectious mononucleosis-like illnesses are caused by primary infection by other pathogens such as cytomegalovirus, *Toxoplasma gondii,* adenovirus, viral hepatitis, HIV, and possibly rubella virus. Cytomegalovirus infection is a particularly common cause of infectious mononucleosis-like illnesses among adults. Streptococcal pharyngitis may cause sore throat and cervical lymphadenopathy that is indistinguishable from that of infectious mononucleosis but is not associated with hepatosplenomegaly. Because the pharyngeal streptococcal carriage rate is approximately 5%, failure of a patient diagnosed with streptococcal pharyngitis to improve within 48 to 72 hours suggests the possibility of infectious mononucleosis and incidental streptococcal carriage. In clinical practice, the cause of most cases of EBV-negative infectious mononucleosis-like illnesses remains unknown because of the expense of confirmatory tests and the lack of clinical imperative to determine the cause of a self-limited illness.

Patients who have clinical findings of infectious mononucleosis in the presence of extremely high ($>30\times10^3/\mu L$ [$30\times10^9/L$]) or low ($<1\times10^3/\mu L$ [$1\times10^9/L$]) white blood cell counts combined with moderate-to-severe thrombocytopenia ($<50\times10^3/mL$ [$50\times10^9/L$] platelets) or hemolytic anemia suggests leukemia and may warrant hematologic consultation and bone marrow examination to exclude this diagnosis.

Management

Observation over time and symptomatic treatment are the mainstays of management. Sore throat is managed with acetaminophen, nonsteroidal anti-inflammatory drugs, and saltwater gargles as well as other symptomatic remedies. Bed rest is indicated if there is debilitating fatigue. Continuation of normal activities or gradated activities leading toward resumption of normal activities is recommended. It is customary to advise against participation in contact sports and any strenuous athletic activities during the initial 2 to 3 weeks of illness or while splenomegaly is present to minimize the risk of splenic rupture.

EBV encodes for a viral DNA polymerase, thereby making it susceptible to acyclovir and its analogs, although the clinical effectiveness of such therapy is minimal. High doses of acyclovir, with or without corticosteroids, decrease viral replication and oropharyngeal shedding during the period of antiviral administration but do not reduce the severity or duration of illness or alter the eventual outcome.

Short courses of corticosteroids for fewer than 2 weeks are indicated for a few specific complications of infectious mononucleosis. There are no controlled data showing efficacy for these indications and their use is off-label. Generally accepted indications include incipient upper airway obstruction, thrombocytopenia complicated by bleeding, autoimmune hemolytic anemia, seizures, and meningitis. A recommended regimen is prednisone 1 mg/kg per day (maximum of 60 mg/d) or an equivalent corticosteroid for 7 days, followed by a tapering regimen over another 7 days. In view of the potential and unknown hazards of immunosuppression for a virus infection that can have oncogenic complications, corticosteroids should not be used routinely in uncomplicated cases of infectious mononucleosis.

Complications

The most compelling reason for developing an EBV vaccine is to reduce the risk of EBV-associated malignancies, although complications in otherwise healthy persons are uncommon. The most feared complication historically was subcapsular splenic hemorrhage or splenic rupture, commonly related to trauma, which may be mild and only rarely fatal. Rupture has been reported most frequently during the second week of the disease, at a rate of less than 0.5% in adults. The rate in children is unknown but is probably much lower.

Tonsillar swelling may be substantial and cause upper airway obstruction, as indicated by drooling, stridor, and difficulty breathing. Airway compromise with progressive symptoms occurs in fewer than 5% of cases of infectious mononucleosis and is a common indication for hospitalization. Airway compromise is managed best by elevating the head of the bed and providing intravenous hydration, humidified air, and systemic corticosteroids. Respiratory distress with actual airway occlusion should be managed with corticosteroids and tonsilloadenoidectomy, followed by endotracheal intubation for 12 to 24 hours in an intensive care setting.

Many uncommon and unusual neurologic conditions have been reported as being associated with infectious mononucleosis. Headache occurs in about 50% of cases, but serious neurologic manifestations, such as seizures and ataxia, occur in only 1% to 5%. An unusual symptom is perceptual distortions of sizes, shapes, and spatial relationships, known as the "Alice-in-Wonderland syndrome" or metamorphopsia. Other neurologic conditions that may occur are meningitis with nuchal rigidity and mononuclear pleocytosis, facial nerve palsy, transverse myelitis, and encephalitis. Guillain-Barré syndrome or Reye syndrome may follow acute illness.

Hemolytic anemia, often yielding a positive direct antiglobulin (Coombs) test result and cold agglutinins specific for red cell antigen i, occurs in 3% of cases. The onset typically is within 2 weeks of illness and lasts for fewer than 4 weeks. Aplastic anemia is a rare complication that usually presents 3 to 4 weeks after the onset of illness, followed by recovery in 4 to 8 days, although some cases do require stem cell transplantation. Mild thrombocytopenia and neutropenia are common, but severe thrombocytopenia ($<20\times10^3/\mu$L [20×10^9/L] platelets) and severe neutropenia ($<1\times10^3/\mu$L [1×10^9/L] neutrophils) are rare.

Myocarditis or interstitial pneumonia may occur, both resolving in 3 to 4 weeks. Additional rare complications include pancreatitis, parotitis, and orchitis.

Fulminant or fatal infectious mononucleosis in healthy persons is rare but may result from an uncontrolled host lymphoproliferative response that usually demonstrates hemophagocytic lymphohistiocytosis, which is the phagocytosis by macrophages of erythrocytes, leukocytes, platelets, and their precursors in bone marrow and other tissues. EBV is considered to be the principal cause of severe cases of virus-associated hemophagocytic syndrome, a nonmalignant but serious generalized histiocytic proliferation associated with marked hemophagocytosis. Fever, lymphadenopathy, and hepatosplenomegaly are complicated further by pulmonary infiltrates, rash, cytopenias, and hepatic dysfunction, with a fulminant course often leading to death. Treatment with etoposide, which reduces both monocyte and macrophage activity, and with corticosteroids, both off-label uses, may be effective.

Immunocompromised Persons

The immune response is essential for controlling EBV replication during the primary infection as well as during lifelong latent infection. The decline in T-cell immunosurveillance of EBV infection parallels the risk and incidence of EBV-associated proliferations. Increased risk for EBV-associated malignancies is associated with acquired immunodeficiency syndromes such as HIV infection and organ transplantation anti-immune therapy, as well as congenital immunodeficiencies, including the X-linked lymphoproliferative (XLP) syndrome, common variable immunodeficiency, ataxia-telangiectasia, Wiskott-Aldrich syndrome, and Chédiak-Higashi syndrome. The tumors associated with EBV are primarily of B-cell lineage, especially primary central nervous system lymphoma, diffuse large-cell B-cell lymphoma, immunoblastic B-cell lymphoma, and Hodgkin disease. The most recent association of EBV with malignancy is the surprising finding of EBV infection in smooth muscle cells of leiomyosarcomas in immunocompromised persons, including HIV-infected patients, organ transplant recipients, and persons who have congenital immunodeficiency. EBV is not found in smooth muscle cells of leiomyomas or leiomyosarcomas that occur in immunocompetent persons.

The prototype of immune system failure to control EBV infection is the XLP syndrome (also known as Duncan syndrome), an X chromosome-linked recessive disorder of the immune system that is associated with severe, persistent, and sometimes fatal primary EBV infection. The defective gene in XLP syndrome, known as *SH2D1A*, is localized to Xq25. SH2D1A is an adhesion molecule that is highly expressed in thymocytes and peripheral blood T-cells and NK cells, with a prevalent expression on Th1-cells. The absence of SH2D1A leads to an uncontrolled cytotoxic T-cell immune response to EBV. Approximately two thirds of affected male patients die at the time of primary EBV infection of disseminated and fulminating lymphoproliferation involving multiple organs. Affected males who survive are at high risk for developing hypogammaglobulinemia, B-cell lymphoma, or both. Most affected males die by 10 years of age.

PTLS occurs as a consequence of organ transplant immunosuppressive regimens, most notably with the antibody OKT3, which is a potent anti-T-cell agent. The greatest risk factor is pretransplant EBV seronegative status because of the reduced ability of the immune system to control primary EBV infection. As expected, the incidence of PTLS is several times higher among children than adults, who are usually seropositive for EBV. The incidence of PTLS among adults is about 1% following bone marrow and kidney transplants, 2% following liver transplants, 5% following cardiac transplants, and 8% following lung transplants. PTLS presenting early after transplantation usually is polyclonal and almost always associated with EBV, with about 50% of the cases showing *bcl-6* mutations. PTLS presenting late

after transplantation tends to be monoclonal and is associated with EBV in only 15% to 30% of cases. The condition resembles nonHodgkin lymphoma or Hodgkin disease and shows a variety of separate chromosomal abnormalities, including *bcl-6*, *MYC*, and *RAS* mutations.

Nasopharyngeal Carcinoma

Nasopharyngeal carcinoma occurs worldwide but is 10 times more common among males in southern China, where it is the most common malignant tumor among adult men. It also is common among whites in North Africa and Inuits in North America. The carcinoma presents with signs and symptoms of cervical lymphadenopathy, eustachian tube blockage, and nasal obstruction with epistaxis.

Undifferentiated nasopharyngeal carcinoma is characterized by a high copy number of EBV episomes in every cell as well as elevated EBV antibody titers, which can be used both for diagnosis and prognosis. High titers of IgA antibody to EA and VCA may be detected in asymptomatic individuals, and a decrease in titers indicates a favorable response to tumor therapy (Table). In contrast, well-differentiated, keratinizing nasopharyngeal carcinoma is characterized by a low number of or no EBV genomes and EBV serologies that are similar to other EBV-infected persons.

Computed tomography scan and magnetic resonance imaging are helpful in defining masses in the head and neck. The diagnosis is established by biopsy of the mass or an involved cervical lymph node. Surgery is important for staging and diagnosis. Radiation therapy is effective for control of the primary tumor and regional nodal metastases. Chemotherapy with 5-fluorouracil, cisplatin, and methotrexate is effective but not always curative. The prognosis is good if the tumor is small and localized.

Burkitt Lymphoma

Endemic (or African) Burkitt lymphoma is the most common childhood cancer in equatorial East Africa and New Guinea. The median age at onset is 5 years. Tumors most often involve the jaw. The endemic regions are characterized by a high rate of EBV infection early in life as well as infection by *Plasmodium falciparum* malaria. The constant malarial exposure appears to act as a B-lymphocyte mitogen that contributes to the polyclonal B-lymphocyte proliferation associated with EBV infection, impairs the T-lymphocyte control of EBV-infected B-lymphocytes, and increases the risk for development of Burkitt lymphoma. Approximately 98% of cases of endemic Burkitt lymphoma contain the EBV genome compared with only 20% of cases of nonendemic (or sporadic or American) Burkitt lymphoma. Individuals who have EBV-associated Burkitt lymphoma have unusually and characteristically high titers of antibody to VCA and EA that correlate with the risk for developing tumor (Table).

All cases of Burkitt lymphoma, including those that are EBV-negative, are monoclonal and demonstrate chromosomal translocation of the c-*myc* proto-oncogene located on the long arm of chromosome 8 to the constant region of the Ig heavy-chain locus on chromosome 14 [t(8;14)], to the κ constant light-chain locus on chromosome 2 [t(2;8)], or to the λ constant light-chain locus on chromosome 22 [t(8;22)]. These translocations result in the deregulation and constitutive transcription of the c-*myc* gene with overproduction of a normal c-*myc* product that auto-suppresses c-*myc* production on the untranslocated chromosome.

Hodgkin Disease

Several lines of evidence link EBV with some types of Hodgkin disease. Immunohistochemical studies have localized EBV to the Reed-Sternberg cells and their variants, the pathognomonic malignant cells of Hodgkin disease. The incidence of Hodgkin disease is highest during childhood in developing countries and during young adulthood in developed countries. Infection with EBV increases the risk for Hodgkin disease by two- to fourfold. The titers of EBV antibodies are consistently elevated preceding the development of Hodgkin disease, and only a minority of patients who have Hodgkin disease is seronegative for EBV. EBV is associated with more than 50% of cases of mixed cellularity Hodgkin disease and approximately 25% of cases of the nodular sclerosing subtype. EBV is rarely associated with lymphocyte-predominant subtype.

Other Tumors

EBV appears somehow to contribute to other tumors, including carcinoma of the salivary glands, some T-lymphocyte lymphomas (including lethal midline), angioimmunoblastic lymphadenopathy-like lymphoma, thymomas and thymic carcinomas derived from thymic epithelial cells, supraglottic laryngeal carcinomas, lymphoepithelial tumors of the respiratory tract and gastrointestinal tract, and gastric adenocarcinoma.

Prognosis

The prognosis for complete recovery from infectious mononucleosis is excellent, with symptoms typically lasting 2 to 4 weeks, followed by gradual but steady recov-

Summary

- Classic virology testing, confirmed by molecular virology, has clarified the epidemiology of EBV and its association with illness. EBV is a ubiquitous virus that causes infections, primarily among children and adolescents, resulting in a spectrum of disease from asymptomatic infection and self-limited infectious mononucleosis to lymphoproliferations in immunocompromised persons and associations with several malignancies of B-cell and epithelial lineages.
- Diagnosis of EBV infection is established best by serologic testing.
- Observational studies and expert opinion show that management of infectious mononucleosis is primarily supportive, with corticosteroids for selected complications such as upper airway obstruction.
- EBV is associated with several malignancies of B-cell lineage as well as epithelial cell carcinomas and, most recently, leiomyosarcoma.
- At present, the greatest potential benefit for developing an EBV vaccine is to reduce the risk for EBV-associated malignancies.

ery. Some otherwise unremarkable patients experience prolonged signs and symptoms and sometimes debilitating fatigue and malaise that may wax and wane for several weeks to as long as 6 months. No convincing evidence links EBV infection or EBV reactivation to chronic fatigue syndrome. Secondary infections with a different type of EBV (EBV-1 or EBV-2) have been documented in immunocompromised persons, but symptoms or second attacks of infectious mononucleosis caused by EBV have not been documented.

Suggested Reading

Balfour HH Jr, Holman CJ, Hokanson KM, et al. A prospective clinical study of Epstein-Barr virus and host interactions during acute infectious mononucleosis. *J Infect Dis.* 2005;192: 1505–1512

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Jenson H. Acute complications of Epstein-Barr virus infectious mononucleosis. *Curr Opin Pediatr.* 2000;12:263–268

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Sitki-Green DL, Edwards RH, Covington MM, et al. Biology of Epstein-Barr virus during infectious mononucleosis. *J Infect Dis.* 2004;189:483–492

Straus SE, Tosato G, Armstrong G, et al. Persisting illness and fatigue in adults with evidence of Epstein-Barr virus infection. *Ann Intern Med.* 1985;102:7–16

Thompson SK, Doerr TD, Hengerer AS. Infectious mononucleosis and corticosteroids. *Arch Otolaryngol Head Neck Surg.* 2005; 131:900–904

Tselis A, Jenson HB, eds. *Epstein-Barr Virus.* New York, NY and London. Taylor & Francis; 2006

Torre D, Tambini R. Acyclovir for treatment of infectious mononucleosis: a meta-analysis. *Scand J Infect Dis.* 1999;31:543–547

Parent Resources from the AAP at HealthyChildren.org

The reader is likely to find material to share with parents that is relevant to this article by visiting this link: http://www.healthychildren.org/english/health-issues/conditions/infections/pages/mononucleosis.aspx.

PIR Quiz

Quiz also available online at http://www.pedsinreview.aappublications.org.

6. Which of the following statements regarding the epidemiology of EBV is true?

   A. Immunocompetent persons who have been infected shed more virus than immunosuppressed persons.
   B. Infectious mononucleosis caused by EBV occurs most commonly in infants and toddlers.
   C. Most people who become infected with EBV are symptomatic for life.
   D. The risk of transmission is highest from persons who have had recent infections.
   E. The virus is only transmitted through oral secretions.

7. Which of the following signs and symptoms is the *most* commonly seen clinical manifestation of infectious mononucleosis?

   A. Diarrhea.
   B. Headache.
   C. Lymphadenopathy.
   D. Rash.
   E. Splenomegaly.

8. You are evaluating a 2–year–old girl who has had fever for 10 days, pharyngitis, and cervical lymphadenopathy. You suspect that she has an infection caused by EBV. Which of the following tests is *most* likely to confirm your diagnosis?

   A. Complete blood count.
   B. Heterophile antibody.
   C. IgM early antigen test.
   D. IgM viral capsid antigen test.
   E. Viral culture.

9. Your testing confirms the diagnosis of EBV infection in the patient cited in question 8. Her mother asks you how to treat the infection and asks if her daughter is likely to suffer complications. Which of the following is true with respect to these questions?

   A. Acyclovir should be administered for 7 days.
   B. At her age, airway compromise will probably occur, so she should be hospitalized for monitoring.
   C. She would definitely benefit from a trial of corticosteroids.
   D. The mother should treat her daughter's fever and sore throat with acetaminophen or ibuprofen.
   E. Hemolytic anemia is a common complication that she likely will experience.

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