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Infectious Mononucleosis
John Peter, MD* and C. George Ray, MD†

IMPORTANT POINTS
1. The etiologic agent for infectious mononucleosis is Epstein-Barr virus, although a mononucleosis-like syndrome can be caused by other viral agents, most notably cytomegalovirus.
2. The classic physical findings of infectious mononucleosis include fever, lymphadenopathy, pharyngitis, and splenomegaly.
3. Although the presence of heterophil antibodies is considered diagnostic of infectious mononucleosis, children younger than 4 years of age develop an antibody response less than 20% of the time.
4. The primary route of transmission for infectious mononucleosis is saliva; it rarely is spread via aerosol or fomites.
5. Treatment for infectious mononucleosis is generally supportive, with glucocorticoids indicated only for patients exhibiting evidence of airway obstruction.

History
Infectious mononucleosis (IM) was first described in the Russian medical literature in 1885. Epstein-Barr virus (EBV), the viral agent responsible for IM, is a ubiquitous herpesvirus first described by Epstein, Achong, and Barr in continuous cell lines derived from African Burkitt lymphoma tissues. The Henles first observed development of antibodies to EBV in a patient who had acute IM. Subsequent serologic surveys in 1967 confirmed EBV as the major cause of IM.

Epidemiology
EBV preferentially infects B lymphocytes and is transmitted primarily in saliva or, less commonly, by blood transfusion. It is not likely to be transmitted by aerosol or fomites. After an incubation period of 2 to 7 weeks following exposure, as many as 20% of the circulating B lymphocytes of adolescents or young adults developing IM are infected, although the number usually is closer to 1%. There is a subsequent increase in suppressor T lymphocytes during the acute phase of the infection, which produces a low or “inverted” T4/T8 (helper/suppressor) lymphocytic ratio. EBV is shed from the oropharynx for up to 18 months following the primary infection and is shed intermittently in 15% to 25% of healthy EBV-seropositive individuals for years. Immunosuppressed individuals shed the virus more frequently. Most adults throughout the world (>80%) are EBV-seropositive.

The age of initial infection varies in different cultural and socioeconomic settings. In some poor urban settings or in developing countries, 80% to 100% of children are seropositive by 3 to 6 years of age. The majority of primary infections in such groups are subclinical or only mildly symptomatic. In economically privileged communities and developed countries, primary infection occurs later in life, often between the ages of 10 and 30 years. These cases are associated more often with clinical symptoms, usually a mononucleosis syndrome.

Given the widespread rate of infection in the general population, it may be assumed that EBV spreads relatively efficiently. However, in one family study, only 35% of nonimmune siblings developed EBV antibodies over 5.6 contact months after identification of the index case. Mononucleosis-like infections may occur more than once in immunocompetent individuals, but a confirmed case of symptomatic, acute reactivation of EBV disease never has been reported.

Clinical Aspects
Primary EBV infection in young children usually is asymptomatic or presents with such mild, nonspecific symptoms as upper respiratory tract infection, tonsillopharyngitis, or prolonged febrile illness with or without lymphadenopathy. Older children are more likely to develop the typical signs and symptoms of IM. After an incubation period of 2 to 7 weeks, prodromal symptoms of malaise, anorexia, and chills frequently precede the onset of the classic signs and symptoms of IM: fever, sore throat, malaise, and fatigue accompanied by tonsillopharyngitis and lymphadenopathy. Most patients also complain of headache. Periorbital edema may be seen. Fever may reach 39° to 40°C (102.2° to 104°F) and last 1 to 2 weeks. Adenopathy typically is nontender and involves both the anterior and posterior cervical lymph nodes, but diffuse adenopathy may be present. The pharyngitis is usually diffuse, and often there is a thick tonsillar exudate. Palatal petechiae also may be present. Splenomegaly develops in the first 3 weeks of illness in at least 50% of cases and hepatomegaly in about 30% to 50%. Mild hepatic tenderness may be present. In 5% of patients, a macular, petechial, scarlatiniform, urticarial, or erythema multiforme-like rash may appear. Administration of ampicillin- or amoxicillin-containing antibiotics can result in a pruritic, maculopapular eruption in 90% to 100% of patients, usually commencing 7 to 10 days after the first dose.

Mononucleosis due to cytomegalovirus (CMV) is the illness confused most frequently with EBV-induced IM. Patients who have CMV mononucleosis are, on average, older than those who have EBV-induced disease and exhibit fever and malaise as the major manifestations; pharyngitis and lymphadenopathy are less common than with EBV-induced IM.

Pharyngitis may be caused by a variety of other viral or bacterial
organisms. Group A beta-hemolytic streptococci can be isolated from the throats of up to 30% of patients who have symptomatic IM and in nearly the same percentage of asymptomatic individuals. Therefore, isolation of this organism does not rule out IM. Malignancies or infection with adenoviruses, Toxoplasma gondii, rubella virus, human immunodeficiency virus (HIV), and hepatitis A virus also may produce a mononucleosis-like syndrome (Table 1).

EBV initially was believed to be the etiologic agent of chronic fatigue syndrome, an illness characterized by recurrent malaise, difficulty with concentration, headache, weakness, myalgias, arthralgias, pharyngitis, lymphadenitis, and low-grade fever. However, subsequent studies have not supported such an association. Although fewer than 5% of patients experience malaise and fever for as long as 3 to 4 months, some patients have been reported in whom signs and symptoms persisting for more than 6 months are associated with evidence of ongoing EBV replication. Some have labeled this disorder “chronic mono,” but this is an extremely rare condition, and the etiology of the ongoing viral replication is uncertain.

**Laboratory Evaluation**

Although the classic tube heterophil titer is still performed in some laboratories, the “monospot” slide test is sensitive, specific, easily performed, and used more commonly. The sensitivity and specificity are 85% and 97%, respectively, in children older than 4 years of age. Symptomatic children younger than 4 years most often do not develop a heterophil antibody response to EBV, and the sensitivity in this age group is less than 20%. Up to 15% of patients who have IM may be heterophil-negative initially, then become positive on retesting during the second or third week of illness. Antibody concentrations decline after the acute illness has resolved but may be detectable for up to 9 months after the onset of illness. Therefore, a positive monospot test is not diagnostic of active disease.

Viral-specific serology should be used to diagnose EBV IM in children younger than 4 years of age who exhibit typical presentations and in patients who have atypical clinical presentations or severe, prolonged illnesses with negative heterophil tests (Table 2). Immunoglobulin M antibodies to the EBV capsid antigen (IgM anti-VCA) are produced at the time of the acute infection, persist for weeks to months, and do not reappear (Figure). Comparison of acute and convalescent sera shows a rise, a subsequent fall, and a lifelong persistence of IgG anti-VCA. Antibodies to EBV nuclear antigen (anti-EBNA) usually do not appear until 2 to 4 weeks after the onset of symptoms, so their absence in a previously well person who develops acute illness and is otherwise seropositive suggests an acute, primary EBV infection. Antibodies to EBV early antigens (EA) appear early in the infection, usually persist for several months, and can reappear at any time, either spon-

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**TABLE 1. Conditions and Infections Producing a Mononucleosis-like Syndrome**

- Malignancies
- Adenoviruses
- Toxoplasma
- Rubella
- Human immunodeficiency virus
- Hepatitis A
- Diphtheria

**TABLE 2. Interpretation of EBV Serology**

<table>
<thead>
<tr>
<th></th>
<th>IgG-VCA</th>
<th>IgM-VCA</th>
<th>EBV NUCLEAR ANTIGEN</th>
<th>EBV EARLY ANTIGENS</th>
</tr>
</thead>
<tbody>
<tr>
<td>No evidence of infection</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>&lt;2</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Acute infection</td>
<td>&gt;10</td>
<td>≥10</td>
<td>&lt;2</td>
<td>≥20</td>
</tr>
<tr>
<td>Convalescent infection</td>
<td>&gt;10</td>
<td>Variable</td>
<td>&gt;2</td>
<td>Variable</td>
</tr>
<tr>
<td>Remote past infection</td>
<td>≥10</td>
<td>&lt;10</td>
<td>≥2</td>
<td>≤20</td>
</tr>
</tbody>
</table>

*Values are expressed in reciprocal titers as measured by standard immunofluorescence methods.*
response to a wide range of stressful stimuli. Immunofluorescence is the most commonly used method for EBV serology, but it is labor-intensive and time-consuming. Several currently available commercial enzyme-linked immunosorbent assays (ELISAs) have varying degrees of sensitivity and specificity. Careful evaluation of the performance of these kits is essential before any are adopted for routine use, but when used correctly, all are equally clinically effective. Approximately 75% of patients who have IM demonstrate an absolute lymphocytosis (>50% lymphocytes, with total leukocytes >5,000/mm³), often with more than 10% atypical lymphocytes, most of which are activated T cells. This lymphocytosis is the most reliable indicator of IM when the monospot slide test is negative and serology is not readily available. Transient neutropenia and thrombocytopenia are noted frequently, as are mild increases in serum IgA, IgG, and IgM and hepatic cellular enzymes. The thrombocytopenia appears to be due to various mechanisms, including increased destruction by an enlarged spleen and the presence of antplatelet antibodies. Frequently, patients develop antibodies to human erythrocyte antigens (anti-i), but significant hemolytic anemia is uncommon. In fewer than 1% of cases is the neutropenia, thrombocytopenia, and increased levels of hepatic cellular enzymes and human erythrocyte antigens of any clinical significance.

Management
Treatment of IM is supportive. Adequate rest is advocated, but there is no evidence that bed rest hastens recovery. Fluids and a soft diet along with acetaminophen or ibuprofen will help ease the symptoms of pharyngitis and fever. Patients who have concurrent streptococcal pharyngitis should receive penicillin or erythromycin for 10 days to prevent poststreptococcal sequelae.

Patients who have splenomegaly should be advised to avoid contact sports to prevent the rare possibility of splenic rupture (estimated to be 0.1% to 0.2%). Interestingly, the majority of documented cases of splenic rupture are not accompanied by significant trauma. Although there is a wide range of recommendations for the timing of a return to contact sports, most experts agree that vigorous sports should be restricted until the spleen has returned to its normal size and protected location within the rib cage. Recovery from IM is often gradual; in some individuals, malaise or fatigue lasts for 3 to 4 months. Glucocorticoids generally are indicated only for those who exhibit symptoms of upper airway obstruction, although some clinicians prescribe them to hasten the resolution of symptoms. Some limited studies suggest that corticosteroids hasten the resolution of fever and tonsillopharyngeal symptoms, but they do not provide significant or reproducible benefit for lymphadenopathy or hepatosplenomegaly. The use of corticosteroids because of sporadic reports of an association between encephalitis or myocarditis in patients who have IM and are treated with steroids. Questions also have been raised about the possible adverse influence steroids might have on the development of long-term immunity to EBV. Most authorities advise against the routine use of corticosteroids in patients who have uncomplicated acute IM. Several antiviral agents have been shown to inhibit the replication of EBV. The efficacy of acyclovir has been assessed in controlled studies of uncomplicated acute IM. Parenteral or high-dose oral acyclovir reduced oropharyngeal shedding of EBV. Despite this reduction in shedding, though, little or no clinical benefit was demonstrated in treating uncomplicated acute IM. The question has been raised about the possible beneficial effects of acyclovir for patients being treated with steroids in an attempt to restrict the potentially enhanced opportunity for the virus to replicate in the setting of steroid-induced immunosuppression. In one study, acyclovir suppressed oropharyngeal shedding of EBV even when steroids were administered. Although the combined regimen appeared to be clinically beneficial, the individual contribution of acyclovir to this effect was not delineated.

Prognosis
The majority of individuals who have IM experience an uneventful course and recover without residual problems, although complications do occur infrequently and may be dramatic. Hematologic complications include a self-limiting anti-i-mediated autoimmune hemolytic anemia, which resolves over a 1- to 2-month period in greater than 95% of affected individuals who are not treated. A mild thrombocytopenia may occur in up to 50% of patients; profound thrombocytopenia is rare. Similarly, mild granulocytopenia is common, but severe pancytopenia associated with infection and death has been reported. Both the thrombocytopenia and granulocytopenia usually resolve spontaneously in 3 to 6 weeks. Neurologic complications of IM occur in about 1% of patients who have IM and may appear prior to the classic signs, symptoms, and laboratory findings. The most common neurologic complications are cranial nerve palsies and encephalitis. Cerebrospinal fluid findings generally are not helpful, and the clinical presentation in some patients resembles herpes simplex encephalitis. At least 85% of patients who have neurologic symptoms, even when severe, recover spontaneously. An “Alice-in-Wonderland” syndrome, characterized by metamorphopsia (distortion of sizes, shapes, and spatial relations of objects) has been reported. Subclinical hepatitis is common in IM, with mildly to moderately...
elevated aminotransferases reported in 70% to 90% of patients. Chronic liver disease and liver failure are rare complications. Fatal IM occurs in 1 in 3,000 cases, with the usual cause of death being fulminant hepatic failure. Children who have X-linked lymphoproliferative disease (Duncan syndrome) have no obvious manifestation of immunodeficiency until they become infected with EBV and develop hepatic failure. Up to 40% of affected males may die during their primary infection. The mechanism of liver injury appears to be due to abnormal T and natural-killer cell activity rather than to direct EBV infection of hepatocytes.

Despite the development of a significant neutropenia, serious bacterial superinfections are unusual. However, peritonsillar abscess has been observed, probably because up to 30% of patients have throat cultures positive for group A streptococci.

Infection with EBV has been associated with the development of nasopharyngeal carcinoma, a variety of lymphoproliferative disorders, and Burkitt lymphoma. However, IM usually runs a similar course in both immunocompetent and immunocompromised patients, and most EBV infections are clinically silent.

Summary

EBV-induced IM is a generally self-limited infection characterized by fever, pharyngitis, and adenopathy. Management consists of basic supportive measures and treatment of streptococcal pharyngitis when present. Corticosteroids may be considered for individuals who exhibit evidence of significant upper airway obstruction. To date there is little evidence to support the use of antiviral agents in immunocompetent patients. Complications of IM may arise, which can be life-threatening, but these are relatively rare.

**SUGGESTED READING**


**PIR QUIZ**

16. Which one of the following is a typical feature of infections with EB virus?

A. In communities that have good hygiene standards, most infections are asymptomatic.
B. In developing countries, most infections are symptomatic.
C. Most immunocompromised individuals experience severe complications when infected.
D. Primary infection in older individuals is associated with chronic fatigue syndrome.
E. Virus is shed from the oropharynx for a prolonged period after primary infection.

17. Which one of the following clinical findings is most characteristic of infectious mononucleosis?

A. Lymphadenopathy develops in those patients who have splenomegaly.
B. Most patients are afebrile.
C. Most patients develop a pruritic maculopapular skin rash if given ampicillin.
D. The isolation of group A beta-hemolytic streptococci from the throat distinguishes streptococcal pharyngitis from infectious mononucleosis.
E. Virtually all patients develop a skin rash.

18. Which one of the following serologic results is expected during acute infection with EBV in a 4-year-old child?

A. EA <40.
B. EBNA >10.
C. IgG-VCA <10.
D. IgM-VCA <10.
E. Negative monospot.

19. Which one of the following is not recognized as a complication of infectious mononucleosis?

A. A self-limiting hemolytic anemia.
B. Acute hepatic failure.
C. Encephalitis.
D. Streptococcal peritonsillar abscess.
E. Thrombocytopenia with aplastic anemia.

20. The differential diagnosis of infectious mononucleosis syndrome includes which one of the following?

A. Acute infection with hepatitis B virus.
B. Acute infection with measles virus.
C. Infection with Epstein-Barr virus.
D. Reactivated varicella-zoster virus infection.
E. Secondary syphilis.
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