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REVIEW

# Mononucleosis and Epstein–Barr virus infection: treatment and medication

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**Abstract:** Epstein–Barr virus is a member of the human herpes virus family. Primary infection is usually asymptomatic in childhood; in adolescents and young adults, however, it leads to infectious mononucleosis with symptoms including fever, fatigue, and sore throat that can persist for months. The disease is usually self-limited and resolves over a period of weeks or months but may occasionally be complicated by a wide variety of complications. Symptomatic treatment, the cornerstone of therapy, includes adequate hydration, analgesics, antipyretics, and limitations of contact sports and activities. The role of antiviral treatment and corticosteroids is debatable and not recommended in general, while the development of vaccination is under investigation. This review concentrates on the diagnosis, the potential complications, and the therapeutic strategies in patients with infectious mononucleosis.

**Keywords:** Epstein–Barr virus, infectious mononucleosis, EBV

## Introduction

Epstein–Barr virus (EBV) is a ubiquitous human virus infecting more than 90% of the human population worldwide. Primary EBV infection is usually subclinical and occurs predominantly in early childhood. However, if infection occurs in a young healthy adult it may result in infectious mononucleosis (IM), an acute febrile illness characterized by the classic triad of fever, tonsillar pharyngitis, and lymphadenopathy.[1]

EBV is a gamma-herpesvirus with a 172-kb DNA genome, replicates primarily in B lymphocytes but may replicate also in the epithelial cells of the pharynx and parotid duct.[1] After primary infection the virus persists for life in infected B cells (latent infection).[1,2]

Furthermore, in a minority of infected patients with primary or acquired abnormalities of their immune system, the infection may lead to the development of a number of EBV-associated lymphoid or epithelial cancers.[1]

## Epidemiology

The virus occurs worldwide, and most people become infected with EBV sometime during their lives. The majority of primary EBV infections throughout the world occur subclinically. Seroepidemiological studies have shown that approximately 90%–95% of individuals worldwide are infected with EBV.[3] In lower socioeconomic groups and in areas of the world with lower standards of hygiene (eg, developing countries), EBV tends to infect children at an early age, and symptomatic IM is uncommon. In areas with higher standards of hygiene, infection with EBV is often delayed until adulthood, and IM is more prevalent.[4] In general, IM is considered a disease of young adults.

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## Transmission

EBV transmission occurs predominantly through exposure to infected saliva, often as a result of kissing. The virus has also been reported in both male and female genital secretions, suggesting that sexual transmission may occur.[5] Two recent studies showed that sexual activity is a risk factor for higher EBV seropositivity and IM.[6,7] The incubation period is 4–8 weeks.[8]

## Pathogenesis

EBV is a successful virus that utilizes normal B cell biology to infect, persist, and replicate.[9] The infection is usually self-limited and controlled by the strongly elevated T cell immune response. If the infection occurs in adolescence or adulthood, up to 50% of T cells in the host can be specific to the virus, which may cause the clinical symptom of IM.[10] EBV then persists latently in the host within long-life memory B cells.[11]

## Clinical features

The symptoms occurring after the incubation period are unspecific. A prodrome of fatigue, malaise, and myalgia may last for 1–2 weeks before the onset of fever, sore throat, and lymphadenopathy.[12,13] Fever is most common in the first 2 weeks of illness; however, it may persist for more than 1 month. Lymphadenopathy and pharyngitis are most prominent during the first 2 weeks, while splenomegaly is more prominent during the second and third week. Lymphadenopathy most often affects the posterior cervical nodes, although generalized adenopathy can occur. Lymph nodes are moderately tender and firm, but discrete. The pharyngitis can vary from a mild erythema to a very painful throat that has a thick gray-white exudate. Less common clinical signs including periorbital edema, hepatomegaly, and splenomegaly could also be presented. Most patients have symptoms for 2–4 weeks, but malaise and difficulty concentrating can persist for months.[14,15]

Differential diagnosis of IM includes other causes of pharyngitis such as streptococcal and viral pharyngitis (caused by rhinovirus, coronavirus, influenza virus, adenovirus, para influenza virus). The differential diagnosis between IM and streptococcal pharyngitis is important since this bacterial clinical entity needs antimicrobial therapy not only to shorten the clinical course but also to prevent acute rheumatic fever, reduce potential complications, and reduce infectivity.[16] On the other hand, administration of amoxicillin or ampicillin in patients with IM is associated with morbilliform rash with a high incidence up to 95%. Thus, it is reasonable to screen patients who have suspected IM for group A streptococcal infection with the use of a throat swab and rapid antigen testing or culture.[4]

The differential diagnosis of mononucleosis syndrome includes also primary infection with the human immunodeficiency virus, human herpes virus 6, cytomegalovirus (CMV), or *Toxoplasma gondii*. In case of CMV infection, it may not be possible, or even useful, to distinguish between IM caused by EBV infection and an IM-like syndrome caused by toxoplasmosis or CMV, because the management of these syndromes is the same. If acute human immunodeficiency virus infection is suspected, a quantitative polymerase chain reaction (PCR) test should be performed.

## Laboratory diagnosis

Beyond the clinical symptoms and signs that raise the suspicion of IM, numerous laboratory diagnostics tests are available to ensure the diagnosis. Common laboratory findings in patients with IM include marked lymphocytosis (>50% leukocytes) and an increased proportion of atypical lymphocytes. The cut-off point of atypical lymphocytes used alters the sensitivity and specificity for the diagnosis of IM.[14]

An additional tool for the diagnosis of IM is the heterophile antibody test. This test is based on the fact that primary EBV infection induces the activity of a heterogeneous group of circulating immunoglobulin M (IgM) antibodies directed against viral antigens that cross-react with antigens found on sheep and horse red cells.[4] Moderate-to-high levels of heterophile antibodies are seen during the first month of illness and decrease rapidly after week 4.

The diagnosis of IM can be based on typical clinical and hematological findings and confirmed with a positive test for heterophile antibodies.[14,17] However, false-negative results can be found in specific subgroups of patients. Indeed, heterophile antibody tests are less sensitive in patients younger than 12 years, detecting only 25%–50% of infections in this group.[18] False-positive results for heterophile antibodies are fewer than false-negative but they have occasionally been reported, particularly in patients with human immunodeficiency virus-infection, rubella, malaria, systemic lupus erythematosus, pancreatic carcinoma, viral hepatitis, and leukemia.[17]

As a result, in children and in patients with heterophile-negative test, but high clinical suspicion of IM, further serologic tests are needed. Effective laboratory diagnosis can be made by testing for specific IgM and immunoglobulin G (IgG) antibodies against viral capsid antigens (VCA), early

antigens, and EBV nuclear antigen (EBNA) (Table 1). These EBV-specific antibodies tests have the higher sensitivity 97% (95%–99%) and specificity 94% (86%–100%) but are also the most expensive for diagnosing of IM.[19,20] Responses of IgM against VCA commonly appears early in infection and disappears within 4–6 weeks. IgM antibodies are not detected in association with chronic infection, so their presence is virtually diagnostic of primary EBV infection. Appearance of IgG antibodies against VCA takes place at the time of, or shortly after, presentation with IM and persists at reduced levels throughout life. IgG to the early antigen appears in the acute phase and generally falls to undetectable levels after 3–6 months, however, 20% of healthy people may have these antibodies for years.[1,4,17]

Rarely, false-positive VCA antibody titer results have been observed due to cross-reactivity with other herpes viruses, eg, CMV, or with unrelated organisms, eg, *Toxoplasma gondii*. Such patients have high elevations of IgM CMV or toxoplasmosis titers, which help to differentiate between the primary infectious agent and the serological cross-reactivity resulting in a false-positive test result.

IgG antibodies against EBNA are usually not detectable until 6–12 weeks after the onset of IM as they appear only when the virus is becoming latent, and persist throughout life. Their presence excludes acute infection.[4,17]

In summary, the diagnosis of IM based on EBV-antibody tests is confirmed if IgM antibody to VCA is present and antibody to EBNA is absent, or in the case of rising or high IgG antibodies to the VCA and negative antibodies to EBNA after at least 4 weeks of illness.[17]

**Table 1** Laboratory diagnostic tests for infectious mononucleosis

| Test | Comments |
|---|---|
| Heterophile antibody test | Moderate-to-high levels of heterophile antibodies are seen during the first month of illness and decrease rapidly after week 4 |
| IgM VCA | Appears early in infection and disappears within 4–6 weeks |
| IgG VCA | IgG antibodies against appears at clinical presentation of IM and persists at reduced levels throughout life |
| Anti-EA-D | Peaks at 3–4 weeks after onset and persists for 3–6 months |
| Anti-EA-R | Appears 2 weeks to several months after onset and persists for 2 to more than 3 years |
| EBNA | IgG antibodies against EBNA are usually detectable 6–12 weeks after the onset of IM and persist throughout life |
| Quantitative real time PCR | EBV viral load in blood is high at clinical presentation of infectious mononucleosis |

**Abbreviations:** VCA, viral capsid antigens; IM, infectious mononucleosis; EA, early antigens; EBNA, EBV nuclear antigen; PCR, polymerase chain reaction; EBV, Epstein–Barr virus.

Acute EBV infection can also be detected by using quantitative real time PCR assay on blood or plasma. This technique may be useful for making the correct viral diagnosis for patients with atypical clinical features or for young children with heterophile-negative IM.[21] Immunocompetent patients with symptomatic EBV infections have viral loads averaging 5000 copies/mL of whole blood during the first 7–10 days of illness; viral loads during latency are rarely >1000 copies/mL of whole blood.[22] Quantitative PCR could also be useful for monitoring the effect of anti-EBV therapy and in the evaluation of antiviral treatment.[22] The presence of detectable viral load by using PCR should be related to some active viral replication rather than a latent EBV without clinical significance because latent EBV is normally undetectable or near the lower level of detection with PCR.[22]

## Treatment of mononucleosis

To our knowledge, there are no professional-society guidelines for the management of IM. Supportive care, including adequate hydration and nonsteroidal anti-inflammatory drugs or acetaminophen for fever and myalgia, is recommended for those patients.[4,14] Special precautions against transmission of EBV are not necessary, since most people are EBV-seropositive.[4] Contact sports and activities (eg, bike riding) should be avoided, in order to prevent the complication of splenic rupture, for at least 3 weeks or until patients are afebrile, after clinical symptoms and findings have resolved, or when they feel well enough.[23]

The role of antiviral treatment in IM is debatable. The use of acyclovir has been evaluated in five randomized trials. Despite the significant, but transient, reduction in the rate of oropharyngeal EBV shedding observed, no clinical effectiveness was shown.[24] Considering newer antiviral therapies, such as valacyclovir, recent studies with promising results have been published. Indeed, valacyclovir has been found to reduce the EBV excretion and possibly produce a clinical benefit in patients with IM.[25] Moreover, valacyclovir might reduce the transmission of EBV by healthy individuals through decreasing the prevalence of EBV in saliva.[26,27] Recently, lipid esters of cidofovir, an effective therapy for certain human cytomegalovirus infections in immunocompromised patients, have been shown to be active in vitro against EBV, suggesting their potential role in the management of EBV infection.[28] However, the use of antiviral treatment is not recommended in patients with IM but further randomized studies are needed in order to clarify the potential role of newer antiviral agents in IM.

Another point of controversy in the management of IM is the role of corticosteroids. A recent review from Cochrane, including seven randomized trials, concluded that there is lack of evidence to recommend steroids as treatment for the management of symptoms in IM.[29] In addition, no data about long-term side effects from the use of steroids is available. However, clinical experience suggests that corticosteroids may be helpful in the management of more severe complications of IM, including upper-airway obstruction, hemolytic anemia, and thrombocytopenia.[4]

The development of vaccination against EBV is a matter of continuing research. Most vaccine-development efforts have focused on the EBV glycoprotein gp350, which is the principal target of naturally occurring neutralizing antibodies. A phase II randomized study has been published with promising results.[30] Indeed, young adults who were vaccinated were not protected against acquiring infection, but were less likely to have symptoms of IM during primary EBV infection, as compared to patients who were not vaccinated.[30] The development of vaccination against EBV would have a great impact on public health and health economics taking into account the fact that EBV has been associated with a wide range of chronic diseases and malignancies.[31–37]

## Early complications

The majority of patients with IM recover without apparent sequelae. However, early complications can occur in about 20% of patients recently infected with EBV.[15] The hematologic, neurologic, respiratory system, and the liver are involved most frequently.

Hematologic complications, observed in 25%–50% of cases of IM, are generally mild and include hemolytic anemia, thrombocytopenia, and neutropenia.[38] Severe hematological complications such as aplastic anemia,[39] severe thrombocytopenia with hemorrhagic manifestation,[40] and severe neutropenia[41] are extremely rare. EBV-associated hemophagocytic lymphohistiocytosis is a rare hematological complication of EBV that is characterized by prolonged fever, lymphadenopathy, hepatosplenomegaly, rash, hepatic dysfunction, and cytopenia.[42] This disease is a disorder of generalized histiocytic proliferation with marked erythrophagocytosis.[42] Most cases with unfavorable fulminant IM are the consequence of an apparently uncontrolled lymphoproliferative response to EBV.[43]

Neurologic complications occur in about 5% of patients. Meningoencephalitis is the most common severe neurologic manifestation.[38] Quantitative PCR and detection of EBV lytic cycle messenger RNA in cerebrospinal fluid indicates that direct EBV infection of the central nervous system is one mechanism of neuropathology.[15] In addition, immunological mechanisms may also contribute to neurologic syndromes complicating IM.

Airway obstruction (less than 5% of all patients) is resulting from the virus-induced B cell proliferation and reactive T cell expansion which leads to nasopharyngeal tonsil hypertrophy and inflammatory edema of surrounding soft tissues; this can be life-threatening and is one of the most common reasons for hospital admission.[44]

Hepatic involvement is exceedingly common in EBV related IM, demonstrating a moderate and transitory raise of liver enzymes in 80%–90% of cases.[1,45] A recent study has found that abnormalities of transaminases occurred from the first week after the onset of illness with a peak during the second week, and returned to normal 3 weeks later, while more than half of the patients in this study had an anicteric form of cholestatic liver disease with predominant biochemical abnormalities in the elevation of alkaline phosphate and γ-glutamyl transpeptidase.[46] Hepatomegaly and hepatic tenderness are present in 10%–15% of cases. However, clinical jaundice is rare.

The risk of splenic rupture, due to splenomegaly, is estimated at 0.1%–0.5%.[47] Patients should be recommended to avoid athletic activities which increase the risk of splenic rupture.

An overview of early complications of EBV infections that have been reported is presented in Table 2. It is crucial to mention that for many of these rare complications there are few detailed cases reported. The rarity of some reported complications might reflect only coincidental association with IM. However, the clinician should be aware of the described complications of EBV infection so as to be prepared to treat them should they occur.

Since IM is a self-limited disease, admission is rarely necessary in patients with uncomplicated IM. Circumstances that warrant inpatient treatment include serious complications, as described above.

Patients with uncomplicated IM should be advised to avoid participation in contact sports or vigorous exercise for at least 3 weeks due to the potential for splenic rupture.[23] Clinical examination is not recommended as a tool for evaluation of splenomegaly due to the low sensitivity, while ultrasound might be of value in some cases.[23]

Routine follow-up care with primary care physicians is recommended to monitor symptomatic improvement over time and to watch for the development of complications.[48] Follow-up should include serial blood counts and liver

**Table 2** Early complications of Epstein–Barr virus infection

| System/organ | Complication |
|---|---|
| Cardiac[48] | Myocarditis |
| | Pericarditis |
| Hematological[15,38–43] | Hemolytic anemia |
| | Thrombocytopenia |
| | Neutropenia |
| | Hemophagocytic |
| | Lymphohistiocytosis |
| Liver[38,45,46] | Self-limited hepatitis |
| | Clinical jaundice |
| | Fulminant hepatitis |
| Neurological[38] | Encephalitis |
| | Acute cerebellar syndrome |
| | Aseptic meningitis |
| | Guillain-Barré syndrome |
| | Cranial nerve palsy especially VII |
| | Transverse myelitis |
| | Seizures |
| | Mononeuritis |
| | Optic neuritis |
| | Cerebral hemorrhage |
| Psychiatric[38] | Anxiety |
| | Depression |
| Renal[38] | Haematuria |
| | Interstitial nephritis |
| | Glomerulonephritis |
| Respiratory[38,44] | Airway obstruction |
| | Pneumonia |
| | Rhabdomyolysis[38] |
| Secondary infections[38] | Streptococcal infection |
| | Sepsis due to neutropenia |
| Spleen[38,47] | Splenic rupture |

function tests. Normalization of liver function tests is expected after 3 weeks.[46] Patients with positive heterophile tests should not be monitored with serial testing because the heterophile test may remain positive for as much as 1 year after infection.

Considering the fact that in patients with IM, the chronic symptom of fatigue is reported by up to one half of patients, regular follow-up assessment visits for all patients might be useful.[49] When chronic fatigue syndrome is diagnosed a variety of interventions such as graded exercise or cognitive behavior therapy should be considered as treatment options.[50]

## Conclusions

IM is a clinical entity with several points that deserve attention. The diagnosis should be based on clinical examination including the classic triad with fever, lymphadenopathy, and pharyngitis, and laboratory findings including the presence of atypical lymphocytosis and heterophile antibodies. In case of uncertainties, EBV-antibody tests should be performed. The disease is largely self-limited and only supportive care is recommended in the first place. The role of antiviral treatment and steroids remains questionable. However, IM has been associated with a variety of early complications and late diseases. Clinicians should be aware of those complications in order to individualize and optimize patient's follow-up in an effort to prevent and, if complications occur, to treat them.

## Disclosure

The authors report no conflicts of interest in this work.

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