Infectious Mononucleosis

The Virus
- A member of the Herpesvirus family
- Infects human B lymphocytes
- Herpes viruses contain double-stranded DNA, and they have an icosahedral capsid and a glycoprotein-containing envelope. They are relatively fragile and do not survive long outside the human host fluids.
- EBV is transmitted via intimate contact with body secretions, primarily oropharyngeal secretions.
- EBV is ubiquitous. It is estimated that more than 90% of adult humans demonstrate serologic evidence of a prior infection with EBV.
- Most cases of IM are due to EBV, but the vast majority of EBV infections do not result in IM.

Pathophysiology:
- EBV infects the B cells in the oropharyngeal epithelium.
- Circulating B cells spread the infection throughout the entire reticular endothelial system (RES), ie, liver, spleen, and peripheral lymph nodes.
- EBV infection of B lymphocytes results in a humoral and cellular response to the virus.
- The T-lymphocyte response is essential in the control of EBV infection; NK cells and predominantly CD8+ cytotoxic T cells control proliferating B lymphocytes infected with EBV.
- EBV infection of B lymphocytes results in permanent latent infection, and a subset of EBV-infected lymphocytes become immortalized. This permanent infection underlies the potential life-threatening complications of EBV infection in the immunocompromised patient.
- A rapid and efficient T-cell response results in control of the primary EBV infection and lifelong suppression of EBV.
- Ineffective T-cell response may result in excessive and uncontrolled B-cell proliferation, resulting in B-lymphocyte malignancies, eg, B-cell lymphomas.
- The immune response to EBV infection is fever, which occurs because of cytokine release consequent to B-lymphocyte invasion by EBV.
- Lymphocytosis observed in the RES is caused by a proliferation of EBV-infected B lymphocytes.
- Pharyngitis observed in EBV infectious mononucleosis is caused by the proliferation of EBV-infected B lymphocytes in the lymphatic tissue of the oropharynx.

Age:
- Although primarily a disease of young adults, EBV infectious mononucleosis may occur from childhood to old age.

History:
- The incubation period of EBV infectious mononucleosis is 1-2 months
- Most patients with EBV infectious mononucleosis are asymptomatic and, therefore, have few if any symptoms.
- The classic presentation of EBV infectious mononucleosis in children and young adults consists of the triad of:
  1. fever,
  2. lymphadenopathy,
  3. pharyngitis.

Fever.
Temperatures may reach 103-104°F but are usually less than 102°F. Chills are relatively uncommon. Virtually all patients report fatigue and prolonged malaise. Low grade fever lasts 1-2 weeks, but it may persist for 4-5 weeks.

Lymphadenopathy
Bilateral posterior cervical adenopathy is most highly suggestive of EBV infectious mononucleosis. Generalized adenopathy also may occur.
Pharyngitis
The pharyngitis may be exudative or nonexudative. Exudative pharyngitis is commonly confused with group A streptococcal pharyngitis or may present with a pseudomembrane resembling Corynebacterium diphtheriae.

Nausea and anorexia, without vomiting, are frequent symptoms.

Maculopapular generalized rash. The rash is faint, evanescent, nonpruritic and rapidly disappears. A morbilliform or papular erythematous eruption of the upper extremities or trunk accompanies IM in approximately 5% of cases.

A macular erythematous rash may occur in IM patients who are treated with ampicillin. Administration of beta-lactams after resolution of the infection does not result in rashes.

Arthralgias and myalgias occur but are less common than in other viral infectious diseases.

Hepatomegaly. An early, transient, mild increase in serum transaminases is characteristic. High elevation of the serum transaminases should suggest other viral or drug-induced hepatitis. The serum alkaline phosphatase and gamma-glutamyl transpeptidase (GGTP) levels are not usually elevated.

Jaundice. The incidence of jaundice is less than 10% in young adults, but as many as 30% of elderly individuals.

Splenomegaly. Splenomegaly is a late finding in EBV infectious mononucleosis. Splenic enlargement returns to normal or near normal usually within 3 weeks after the clinical presentation. Severe abdominal pain is uncommon in patients with IM, and it should prompt immediate attention to a possible splenic rupture.

Early and transient bilateral upper lid edema.

Uvular edema. Uvular edema is an uncommon finding in infectious mononucleosis, but if present, it is a helpful sign in distinguishing EBV infectious mononucleosis from other causes of viral pharyngitis or from group A streptococcal pharyngitis.

EBV infectious mononucleosis rarely may result in a variety of unusual clinical manifestations, including:

- aseptic meningitis, encephalitis, optic neuritis, transverse myelitis, cranial nerve palsies
- pancreatitis, acalculous cholecystitis,
- myocarditis,
- mesenteric adenitis,
- myositis,
- glomerular nephritis,
- anemia

Mortality/Morbidity:

- Patients with EBV infection who present clinically with infectious mononucleosis invariably experience accompanying fatigue. Fatigue may be profound initially but usually resolves gradually in 3 months.
- Mortality and morbidity from an uncomplicated primary EBV infectious mononucleosis are low. The primary mortality, which is infrequent, usually is entirely related to spontaneous splenic rupture.
- Most cases of EBV infectious mononucleosis are subclinical, and the only manifestation of EBV infection is serological response to EBV surface proteins with EBV serological tests.
- Selective immunodeficiency to EBV, which occurs in X-linked lymphoproliferative syndrome, may result in severe, prolonged, or even fatal infectious mononucleosis.
- EBV is the main cause of malignant B-cell lymphomas in patients receiving organ transplants. Most instances of posttransplant lymphoproliferative disorder (PTLD) are EBV related.
- EBV-related lymphogranulomatosis usually occurs in patients with immunodeficiency, whereas lymphogranulomatosis occurring in healthy hosts is usually not EBV related. Depending upon the intensity, rapidity, and completeness of the T-lymphocyte response, malignancy may result if EBV-induced B-lymphocyte proliferation is uncontrolled. Hodgkin disease and non-Hodgkin lymphoma (NHL) may result. Other EBV-induced malignancies include oral hairy leukoplakia
in HIV patients, leiomyomas and leiomyosarcomas in children, nasopharyngeal (NP) carcinoma, and Burkitt lymphoma.

**Lab Studies:**

- **Leukocytosis**
  Most patients with EBV infectious mononucleosis have a mild-to-moderate increase in their peripheral WBC count, usually in the range of 12-20,000 cells/mL.

- **Lymphocytosis**
  Lymphocytosis (≥60%) plus atypical lymphocytosis (≥10%) are the characteristic findings of EBV infectious mononucleosis. Lymphocytosis increases during the first few weeks of illness, and then gradually returns to normal. The appearance, peak, and disappearance of atypical lymphocytes follow the same time course as lymphocytosis.

- **Thrombocytopenia**
  Mild transient thrombocytopenia is not uncommon in EBV infectious mononucleosis. Severe or persistent thrombocytopenia should suggest an alternate diagnosis.

- **Erythrocyte sedimentation rate**
  Erythrocyte sedimentation rate (ESR) elevations occur in virtually all patients early in the course of EBV infectious mononucleosis.

EBV infection induces specific antibodies to EBV and a variety of unrelated non-EBV heterophile antibodies.

- **Heterophile test antibodies** are sensitive and specific for EBV mononucleosis, they are present in peak levels 2-6 weeks after primary EBV infection, and they may remain positive in low levels for up to a year. The heterophile antibodies react to antigens from animal RBCs. Monospot is qualitative and heterophile antibody test is quantitative.
  - Sheep RBCs agglutinate in the presence of heterophile antibodies and are the basis for the Paul-Bunnell test.
  - Agglutination of horse RBCs on exposure to heterophile antibodies is the basis of the Monospot test. Sensitivity is 85%, and specificity is 100%.
  The causes of false-positive heterophile test antibodies results include toxoplasmosis, rubella, lymphoma, and certain malignancies, particularly leukemias and/or lymphomas, pancreatic cancer.

- **Testing for EBV-specific antibodies** in Enzyme-linked immunosorbent assay (ELISA) rapid diagnostic tests is as follows:
  - Antibodies directed against the VCA (viral capsular antigen) of EBV IgM and IgG are useful in confirming the diagnosis of acute EBV infection. EBV IgM VCA titers decrease in most patients after 3-6 months but may persist in low titer for up to 1 year. EBV IgG VCA antibodies rise later than the IgM VCA antibodies but remain elevated with variable titers for life.
    - False-positive VCA antibody titer results may occur on the basis of cross-reactivity with other herpes viruses, eg, CMV, or with unrelated organisms, eg, Toxoplasma gondii.
  - Antibodies to EBV early antigens (anti-EBEA) appear early in the infection, usually persist for several months, and can persist lifelong.
  - EBV nuclear antigen (EBNA) appears after 1-2 months and persists throughout life. The presence of elevated EBNA titers has the same significance as elevated IgG VCA titers. The presence of these antibodies suggests previous exposure to the antigen (past infection) and excludes EBV infection acquired in the previous year.

- As with heterophile antibody responses, specific EBV antibodies may not be present in children younger than 2 years.

**Interpretation of Anti-EBV Serologic Test Results**

<table>
<thead>
<tr>
<th>Stage</th>
<th>IgG-VCA</th>
<th>IgM-VCA</th>
<th>Anti-EBNA</th>
<th>Anti-EA</th>
</tr>
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<tbody>
<tr>
<td>No evidence of infection</td>
<td>-</td>
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Further Outpatient Care:
- Monitor patients to be sure that the infection is improving over time. Serial CBC counts should document the increase in lymphocytes as well as atypical lymphocytes, and this may be monitored on a weekly basis until these values normalize.
- 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.
- Serial specific EBV antibody testing is usually not necessary in patients with acute infection. Caution patients that increased IgG, VCA, and EBNA levels persist for life. Also, inform patients that titers vary and that IgG titers have no relationship to disease activity or to how the patient feels.
- Patients should be advised that fatigue may take some time to resolve, and some patients may develop a state of chronic fatigue that is induced, but not caused by, EBV infectious mononucleosis.

Treatment
- The treatment of uncomplicated EBV-IM is supportive.
- Nonsteroidal anti-inflammatory agents or acetaminophen can be used for pain and fever.
- Bed rest can be recommended during the febrile phase of the illness.
- Aspirin should be avoided, since it has been associated with rare cases of Reye’s syndrome in acute EBV.
- Patients should avoid vigorous activity for 3 to 4 weeks to allow splenomegaly to resolve and avoid the risk of splenic rupture.
- Acyclovir and other available antiviral drugs are not currently recommended for treatment of acute EBV-IM because they have not been shown to significantly improve outcomes, despite their suppressant effects in vitro and on oral EBV shedding.

Corticosteroids for Complications of Epstein-Barr Virus Infection

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<thead>
<tr>
<th>Condition</th>
<th>Drug</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Impending airway obstruction</td>
<td>Prednisone, 60-80</td>
<td>Response is usually rapid. Dosage can be tapered over 1-2 weeks.</td>
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<tr>
<td></td>
<td>mg/day given in a</td>
<td>For severe or prolonged prostration, a</td>
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<td></td>
<td>split daily regimen</td>
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<tr>
<td>Severe thrombocytopenia</td>
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<tr>
<td>Disorder</td>
<td>Treatment</td>
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<tr>
<td>Hemolytic anemia</td>
<td>short, tapering course of lower prednisone doses may be beneficial (initial dose equivalent to 40 mg of prednisone is usually sufficient).</td>
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<tr>
<td>Central nervous system involvement</td>
<td></td>
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<td>Myocarditis</td>
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<tr>
<td>Pericarditis</td>
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