

Serologic Diagnosis of Infectious Mononucleosis and Epstein-Barr Virus Infection

Background Information:

The clinical syndrome of infectious mononucleosis (fever, pharyngitis, lymphadenopathy, atypical lymphocytosis, etc.) is caused by Epstein-Barr virus (EBV) infection in 80% of patients. The differential diagnosis includes other non-streptococcal etiologies such as 5-10% CMV, 2% toxoplasmosis, 2% HHV6, 2% HIV and 5-10% where no etiology can be found. Under the age of 10 years and in older adults, acute EBV infection is more likely to be subclinical or clinically atypical. Classical EBV infectious mono syndrome is accompanied by demonstrable heterophile antibodies in approximately 80% of patients. However, patients younger than 4 years infrequently develop heterophile antibodies and patients 4-12 years of age have a lower incidence of heterophile antibodies. At any age, the antibodies may be transient. Thus the sensitivity and specificity of the heterophile test depends on the population tested (age, symptoms, repeated tests) as well as the skill and training of the technical personnel.

Heterophile tests measure IgM antibody directed toward bovine, sheep or horse erythrocytes. This is a nonspecific antibody classically generated by teenagers and young adults in response to an acute, primary EBV infection. The antibody appears during the first week after exposure, may be very transient, or may remain positive up to 6-12 months. The original heterophile test (Paul-Bunnell) has been modified several times to improve performance characteristics (MonoCard, MonoSpot, MonoTest, etc.). Currently our lab is doing a rapid heterophile test using red cell extracts.

Specific EBV serology tests measure antibody against various antigens associated with EBV infection. IgM and IgG antibody against viral capsid antigen (VCA), antibody against early antigen (EA) and IgG antibody against Epstein-Barr nuclear antigen (EBNA) are frequently reported. The pattern of antibody response successfully identifies the type of EBV infection in 96% of patients, however, occasional patients have atypical reactions and immunodeficient patients may not develop antibody. EBV serology is more time-consuming and more expensive than heterophile tests. Attempts to devise EBV tests to replace the heterophile for rapid screening have been unsuccessful so the heterophile test is still preferred for rapid diagnosis in typical patients. See attached interpretive chart. Currently EBV serology is performed by EIA methodology.

Clinical Stage	Heterophile Ab	VCA-IgM	VCA-IgG	EBNA
Susceptible	Neg	Neg	Neg	Neg
Established infection	Pos	Pos	Pos	Neg
Past (remote) infection	Neg	Neg	Pos	Pos

(continue on reverse)

When to do heterophile tests?

Patients with typical clinical symptoms of infectious mononucleosis syndrome and with a CBC showing lymphocytosis and >10% atypical lymphocytes should have a screening heterophile test performed by a reliable laboratory. If positive, you have a presumptive diagnosis of EBV infection and confirmation by specific EBV serology is generally not necessary. Under these limited clinical circumstances and in teenagers and young adults, the heterophile test has a high positive predictive value over 90%. If the patient has a negative heterophile, especially in infants or with atypical presentations, you must do a specific EBV serology to rule out EBV as a cause.

When to do specific EBV serology tests?

1. When the heterophile is negative and the clinical findings do not fit the negative result **OR**
2. When a serious complication or an unusual clinical syndrome requires a confirmed diagnosis **OR**
3. When the patient is under 4 years of age **OR**
4. When the clinical findings are not classical and a specific etiologic diagnosis is important clinically.

REFERENCES:

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