EDUCATIONAL COMMENTARY – INFECTIOUS MONONUCLEOSIS

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Learning Outcomes
Upon completion of this exercise, the participant will be able to:
- Name the causative agent of infectious mononucleosis
- Discuss the transmission, symptoms and course of disease.
- Describe and compare the laboratory tests used in the diagnosis and treatment of infectious mononucleosis.

Infectious mononucleosis (IM) is an acute lymphoproliferative disease caused by the Epstein-Barr virus. Epstein-Barr virus (EBV) is a herpes virus that is common throughout the world and may play a role in other disorders such as chronic fatigue syndrome, Burkitt’s lymphoma, and nasopharyngeal carcinoma. Burkitt’s lymphoma and nasopharyngeal carcinoma are malignant conditions rarely seen in the United States. Ninety to ninety-five percent of the world’s adult population has been exposed to Epstein-Barr virus. Infants are susceptible as soon as the mother’s protective antibodies have disappeared from the child’s circulation (at about 6 months of age). Infections in children are usually asymptomatic or produce symptoms indistinguishable from common childhood infections. Often in well-developed countries, individuals are not infected until adolescence or young adulthood. If EBV infection occurs at this age, infectious mononucleosis develops in 35% to 50% of the cases. The patient may present clinically with symptoms that range from asymptomatic to severe. Spontaneous recovery usually occurs and rarely is the disease life threatening. Most commonly transmission occurs through exposure to infected saliva, hence, the name “kissing disease”. The virus may be found in the saliva of patients with or without symptoms. The incubation period is approximately 4 to 7 weeks. Infectivity lasts for several weeks or months after infection. Symptoms include fever, sore throat, and swollen lymph nodes. While symptoms usually resolve within two months, the virus remains dormant and the patient becomes a carrier for life. Though the virus may reactivate at a later time, recurrence of symptoms is rare.

The Paul-Bunnell and Davidsohn differential tests for IM are labor intensive assays for the presence of heterophile antibodies and have a high specificity for the infection. These tests are rarely performed in today’s high tech laboratories. Rapid slide tests also detect the presence of heterophile antibodies but have higher false-positive rates. There are several available rapid slide tests based on a variety of principles. Some are differential red cell agglutination assays and others are latex agglutination procedures. In addition to slide agglutination assays, there are membrane-based immunoassays. In the differential red cell agglutination assay, patient serum is mixed with extracts of guinea pig or horse kidney cells in a well on one side of a slide. This mixture is called kidney cell-absorbed serum. The patient’s serum is also mixed with extracts of beef erythrocytes in a well on the other side of the slide. This mixture is called beef red cell-absorbed serum. Next, horse red cells are added to both mixtures. The test is positive if agglutination occurs in the kidney cell-absorbed serum and no agglutination or less agglutination occurs in the beef red cell-absorbed serum. The test is negative if no agglutination occurs in either well or if equal agglutination occurs in both wells. Appropriate controls must be run along with the testing of the patient serum. Red cell agglutination tests are more sensitive than the latex agglutination assays described below.

The rapid latex agglutination test for heterophile antibodies does not involve differential agglutination as described in the procedure above. The patient serum is added to bovine erythrocyte antigens that are attached to latex particles. If heterophile antibodies for infectious mononucleosis are present, agglutination will occur.

The newest rapid tests are enzyme immunoassays for heterophile antibodies. This CLIA designated moderately complex test consists of ox erythrocytes impregnated into a membrane contained in a test device. Patient serum or plasma and an anti-human globulin-enzyme complex (reagent conjugate) are added to the sample well. These components migrate along the membrane to the antigen where color development occurs if IM heterophile antibodies are present. The test device also contains internal positive and negative controls. Recently a CLIA waived test based on the enzyme immunoassay principle has been introduced. The procedure is performed on whole blood and all other reagents are contained in the test device. After addition of a developer solution, a color change in the test area and in the control area indicates a positive test. The sensitivity and specificity of the moderately complex serum or plasma procedure and the waived whole blood procedure are comparable. The waived whole blood test is a qualitative procedure resulting in either a positive or negative result. Moderately complex red cell agglutination, latex agglutination, and enzyme immunoassay tests are quantitative and provide the ability to approximate the concentration or titer of the heterophile antibodies present. Though increased concentration does not correlate with intensity of disease in these tests, increases or decreases in concentration may be used by the physician to assess the stage of disease. If the titer increases significantly, it indicates that the patient is in the early phase of IM. Decreasing titer indicate that the patient is recovering.

False-positive and false-negative results may occur with heterophile antibody testing. Some individuals infected with IM, especially children, do not produce heterophile antibodies and will have false-negative results when these tests are performed. Also when heterophile antibody tests are negative and symptoms persist, it is necessary to differentiate EBV infection from other infections, such as cytomegalovirus, adenovirus, or Toxoplasma gondii. EBV-specific tests must be performed in these situations to aid in diagnosis. These procedures are performed by immunofluorescence or immunoassay. EBV-specific antibody assays detect antibodies to components of the Epstein-Barr virus including antibodies to early antigen, viral capsid antigen, and nuclear antigen. Presence of antibodies to EBV early antigen indicates active infection with levels declining to undetectable in 3 to 6 months for most patients. IgG antibodies to viral capsid antigen appear within 2 to 4 weeks and persist for life. Antibodies to nuclear antigen appear 2 to 4 months after onset and remain for life. Interpretation of EBV-specific tests may be difficult and should be interpreted along with the patient’s clinical condition. These tests are more expensive and labor intensive and may not be required for the diagnosis of IM.

Laboratory testing is very important in the diagnosis and treatment of infectious mononucleosis. Careful attention to quality assurance and technique guarantee reliable results and provide a valuable aid in appropriate diagnosis.