Testing for IgM-class Antibodies to Determine Acute Infection: Clinical and Diagnostic Considerations

Testing for IgM-class antibodies is commonly performed to assist in the diagnosis of acute or reactivated infection. While there are many scenarios in which this practice is clinically useful, there are multiple infections for which IgM testing should be avoided. Below is a brief review of some of the challenges associated with interpretation of IgM antibody results and some examples of when IgM testing should and should not be performed, particularly with respect to frequently ordered tests.

Challenges of IgM antibody testing:

1. Detection of IgM antibodies is often interpreted as an indicator of acute infection. However, false-positive IgM results are common, as a result of cross-reactivity with IgM antibodies to other, closely related microorganisms or other interfering substances. Additionally, IgM antibodies may remain detectable for 2-4 months (or longer) following disease resolution; therefore, a positive IgM result may not necessarily indicate ‘acute’ infection and additional testing (e.g., IgG testing) may be necessary to interpret results.

2. Development of a detectable antibody response for many infections occurs 5-7 days post infection, and therefore, initial IgM test results may be negative if samples are collected prior to antibody development. Additionally, immunosuppressed patients may remain seronegative.

Clinical scenarios for which IgM antibody testing may be clinically useful:

1. Viral infections associated with immune-mediated clinical manifestations. For a number of viral infections, including Epstein-Barr virus (EBV), measles and parvovirus B19, by the time patients present clinically, IgM levels are typically high, whereas viral loads have typically declined below detectable levels. Serologic testing, and specifically testing for IgM-class antibodies, is therefore a routine diagnostic approach for these viruses, particularly for immunocompetent individuals.

2. Arboviral infections. Arboviral infections may be challenging to diagnose for multiple reasons, including non-specific symptomatology and relatively short viremic periods, which typically last ~5-7 days. While nucleic acid amplification testing is preferred during the acute, viremic phase, a negative result does not rule out infection and serologic testing should be pursued. IgM antibodies are typically detectable 5-7 days post symptom onset and frequently remain elevated for 2-4 months following infection. Detection of IgM-class antibodies and/or documentation of seroconversion are preferred methods of diagnosis for most arboviral infections, including, but not limited to, West Nile virus, Zika virus, St. Louis Encephalitis virus, dengue virus, and Chikungunya virus.
3. **Select bacterial infections.** IgM serologic testing is helpful to detect infections caused by certain bacterial agents, especially those that are challenging to culture and are associated with protracted clinical manifestations. These include *Borrelia burgdorferi*, *Bartonella* species, *Coxiella burnetti*, and *Rickettsia* species. For these infections, nucleic acid amplification testing in blood may be insensitive and/or not routinely/readily available. Detection of IgM antibodies against these bacteria may provide preliminary evidence of infection, with convalescent testing showing a 4-fold rise in IgG antibodies and/or IgG seroconversion considered diagnostic.

**Clinical scenarios for which IgM antibody testing is not routinely recommended (in addition to those that are listed in the current Choosing Wisely recommendation):**

1. **Infectious agents for which non-serologic diagnostic tests is/are preferred diagnostic options.** This includes many microorganisms, including but not limited to: herpes simplex virus types 1 and 2 (HSV-1/2), enterovirus, adenovirus, varicella zoster virus (VZV), acute infection (~7 days or less) with tick-borne pathogens (e.g., *Babesia microti*, *Anaplasma phagocytophilum*), *Legionella* species, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Chlamydia* species.
   a. **IgM antibody testing for HSV**
      IgM antibody testing for HSV is frequently inappropriately ordered as a means to diagnose acute HSV infection. For suspected acute HSV infection, lesions should be swabbed and tested by a targeted nucleic acid amplification assay, rather than ordering anti-HSV IgM testing. Anti-HSV IgM testing is not recommended due to the delayed development of antibodies, inability to differentiate IgM against HSV-1 and HSV-2 and overall lack of accuracy of current anti-HSV IgM serologic assays. The Centers for Disease Control and Prevention specifically recommends against performing HSV IgM serologic testing due to the lack of clinical utility associated with this serologic marker.

**References**