-

Yale NewHaven Health
Yale New Haven Hospital

Laboratory Updates: Clinical Virology and Microbiology

Vol 34 (1) **May 2025**

Immunoglobulin M (IgM) for Acute Infection: True or False?

Immunoglobulin M (IgM) tests have proven valuable for the diagnosis of some acute infectious diseases. However many clinicians and laboratorians are unaware that false positive results are more common with IgM assays than with other diagnostic methods. False positive IgM results may occur as a result of polyclonal B cell activation, which can produce **less specific antibodies** during the early immune response**;** these antibodies may nonspecifically bind to antigens in multiple serologic tests.

Other common causes of false positive IgM results include: cross-reactive antibodies among similar viruses, subclinical reactivation of latent viruses, autoimmune disease, rheumatoid factor, naturally occurring biotin IgM antibodies, test cutoffs set too low, and inappropriate test ordering in low risk patients. False negative results occur when blood samples are collected in the first week of illness when pathogen titers may be high but before antibodies develop, if patients are severely immunocompromised and unable to mount an immune response, or in secondary or reactivation infections which may not trigger a detectable IgM response.

Table 1: Selected case examples of erroneous IgM results:

False positive IgM for:	True etiology	Clinical
EBV[a], Lyme, WNV	Primary CMV[a]	26 year old with >2 weeks of fever, chills, headache, fatigue, diarrhea, poor appetite, and weight loss
EBV[a], Lyme, Toxoplasma	Primary CMV[a]	23 year old with 3 weeks night sweats, low grade fever, poor appetite, weight loss, diarrhea
EBV[a]	Primary CMV[a]	39 year old with headache, fever, and hepatitis
HBV [anti-HBc IgM] [a]	Primary EBV[a]	20 year old with jaundice, hepatitis and mononucleosis
HSV-2	Primary HSV-1	23 year old with oral vesicles and hepatitis
WNV	Primary HSV-2	20 year old with genital herpes
Hantavirus [Sin Nombre]	Adenovirus	26 year old with pneumonia, rapid onset ARDS, and renal failure
EEE	POW	61 year old deer hunter with fever and encephalitis
Mycoplasma	WNV	45 year old with meningoencephalitis in August
Measles	Sulfa allergy	28 year old with morbilliform rash after starting a sulfa drug
HAV[a]	CHF	78 year old with cardiovascular disease, volume overload, and congestive heart failure
EBV[a], CMV[a], Parvovirus B19, Lyme; ANA, cardiolipin	Monoclonal IgM gammopathy	81 year old with pancytopenia, splenomegaly, and weight loss
False negative IgM		
WNV	WNV	48 year old on Rituxan presenting in August with acute flaccid myelitis
Measles	Secondary Measles	59 year old with cough, fever, rash; had one vaccine dose as a child
Mumps	Secondary Mumps	26 year old nurse with bilateral neck swelling; had two MMR doses as a child

a, False positive IgM results are especially common with these pathogens. The false positive results above were obtained using commercial FDA cleared assays either in reference labs or in the YNHH Virology Lab.

Recognition of false positives:

False-positive IgM test results tend to come to light in three situations: 1) multiple tests are performed for the same clinical syndrome and multiple positive results are generated, e.g. in infectious mononucleosis, rash illness, acute CNS disease, fever with headache and myalgia in tick season, or after return from tropical regions; 2) a different etiology is confirmed by another method; or 3) the IgM test result clearly does not match the clinical situation.

However, if an IgM test is done for a single pathogen with no confirmatory testing and the clinical syndrome is compatible, a misdiagnosis may go undetected.

The risks of accepting a false-positive IgM as a true result include delays in appropriate therapy, unnecessary tests and therapies, premature closure of an investigation of etiology, erroneous counseling or a lack of counseling of the patient, and inappropriate public health and infection control interventions.

Improving accuracy:

In most cases, tests for the pathogen itself, such as PCR, are preferred. However, in some cases, PCR is not available, is insensitive because the organism is tissue associated and not in an accessible sample, disease is immune mediated, or patient presents late in illness.

Diagnostic accuracy can be improved by: 1) not testing patients with low pretest probability; 2) assessing the relative strengths of IgM and IgG reactivities for positive results (i.e. IgM reactivity should be higher than IgG in acute primary infection); 3) obtaining serial samples to determine if IgM and IgG levels are rising, 4) using a second and more specific serologic test; 5) documenting seroconversion of IgG in paired sera 2-4 weeks apart; and 6) correlating IgM results with the clinical findings, other laboratory values, and epidemiologic risk factors.

While IgM assays are the test of choice for some infections (e.g. arbovirus neurologic disease, dengue or chikungunya presenting after 7 days of symptoms, EBV mononucleosis, hepatitis A, Fifth disease, Lyme, toxoplasmosis), IgM should avoided when more accurate tests such as PCR are readily available (i.e. HHV-6, HSV, VZV, enteroviruses, anaplasma, ehrlichia and babesia) (**Table 2**).

Table 2: Diagnosis of acute infection

IgM commonly used for diagnosis	Arbovirus neurologic disease: WNV, EEE, POW
	Arbovirus rash illness: Dengue, Chikungunya, Zika viruses Use IgM if >7 days of symptoms. (Use PCR if <7 days of symptoms.)
	Infectious mononucleosis: CMV, EBV
	Acute viral hepatitis A, B, E
	Acute HIV-1 and HIV-2 infections
	Measles, mumps and rubella
	Fifth disease, aplastic crisis, red cell aplasia, hydrops fetalis
	Hantavirus pulmonary syndrome
	Lyme (*Borrelia burgdorferi*)
	Toxoplasma gondii
IgM use should be discouraged[a]	HHV-6
	HSV, VZV
	Enterovirus infections: Coxsackie A and B, echovirus, poliovirus, etc
	Anaplasma, Ehrlichia, Babesia[b]

a, PCR should be used to detect active infection. b, If patients present after 7 days of symptoms, acute and convalescent sera 2-4 weeks later can be obtained to confirm seroconversion of IgG.

Recommendation:

When the diagnosis is important for therapy, prognosis, or public health; when the patient is sick enough to be hospitalized; or when the clinical or epidemiologic findings do not fit; IgM detection should not be accepted as a standalone test. Rather, the diagnosis should be confirmed by testing for the pathogen by PCR if available, comparing antibody titers or documenting seroconversion of IgG in serial samples, and/or the application of additional test methods.

To educate clinicians, the following Interpretive comment is added to all positive IgM results in the YNHH Virology Lab:

"A positive IgM usually indicates acute or recent infection. However, false positive IgM results can occur. Additional testing may be indicated to confirm acute infection. Clinical correlation is essential."

References:

1. Landry ML. Immunoglobulin M for Acute Infection: True or False? Clin Vaccine Immunol. 2016 Jul 5;23(7):540-5. doi: 10.1128/CVI.00211-16. PMID: 27193039; PMCID: PMC4933779.
2. Landry ML, Hassan S, Rottmann BG, Pesak SJ, Ordazzo M, Skrzyniarz M, Deponte S, Peaper DR. Performance of two modified two-tier algorithms for the serologic diagnosis of Lyme disease. J Clin Microbiol. 2024 May 8;62(5):e0013924. doi: 10.1128/jcm.00139-24. Epub 2024 Apr 10. PMID: 38597655; PMCID: PMC11077974.
3. Azar MM, Canterino J, Landry ML. The Brief Case: Secondary Measles and the Pitfalls of Diagnostic Testing. J Clin Microbiol. 2020 Aug 24;58(9):e01938-19. doi: 10.1128/JCM.01938-19. PMID: 32839284; PMCID: PMC7448623.
4. Azar MM, Canterino J, Landry ML2020.Closing the Brief Case: Secondary Measles and the Pitfalls of Diagnostic Testing. J Clin Microbiol58:10.1128/jcm.01939-19.https://doi.org/10.1128/jcm.01939-19