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The Pitfalls in Diagnosing and Treating Mono

Mononucleosis is no stranger to most clinicians, who know it is most often caused by Epstein-Barr virus. Still, it presents diagnostic and management difficulties.

Consider a 12-year-old with 4 days of fever, headache, severe sore throat, and fatigue. Your exam detects bilateral, mildly tender, swollen (greater than 1 cm) anterior cervical lymph nodes and white tonsillar exudate, but no splenomegaly, which you know is only present in about 50% of children with EBV. Other EBV signs, such as supraorbital edema or maculopapular rash are absent, although they are seen in about 15%-20% of cases. A negative rapid streptococcal antigen and throat culture point to a virus (although 5%-25% of patients with EBV can have concomitant group A streptococcus). Now, how do you go about confirming EBV?

BY CHRISTOPHER J. HARRISON, M.D.

► **Pitfall 1.** Laboratory confirmation is unlikely until at least the second week of EBV illness. It is tempting to order serology (monospot-like test or EBV-specific serology) plus a CBC when the patient feels lousy and parents want answers. But keep in mind that in the first week negative serology doesn't rule out EBV and complete blood count results are usually nonspecific.

Not until the second week (or maybe even later), after illness onset, does the picture become clearer. At this point, nonspecific viral illnesses will usually have resolved and EBV infection becomes more likely if fever, sore throat, and cervical adenopathy continue (although they may be diminished), while fatigue is increasing. Splenomegaly also may develop in the interim with more generalized symmetrically bilateral adenopathy (groin, axilla, or posterior cervical).

Now, a CBC could suggest EBV mono via lymphocytosis (greater than 50% lymphocytes), and more than 10% atypical lymphocytes. In the case above, this result would allow a correct clinical diagnosis of EBV even without serology 90% of the time. However, not all patients with EBV will have this CBC result.

► **Pitfall 2.** Monospot-like tests have limitations. When the CBC is not sufficiently consistent with EBV but the clinical picture still suggests EBV mono in the second week of illness or later, then it's time for a nonspecific but quick and inexpensive serology—a monospot-like test. Contrary to what its name suggests—and to what one might believe—it does not detect EBV-specific antibody. Rather, it detects heterophile antibody, a low-affinity, highly cross-reactive IgM produced when EBV infects uncommitted B cells. Some of this nonspecific antibody cross-reacts with membrane antigens on mammalian red blood cells. ("Heterophile" refers to the cross-species affinity).

Monospot-like tests may not turn positive for up to 4 weeks. Moreover, children younger than 8 years are less likely to ever produce heterophile antibody, so the test isn't useful in that age group. In addition, a positive monospot isn't always caused by currently active mononucleosis. A rare individual can have persistent heterophile antibody years after recovery.

Also, some individuals who had EBV mono in the past may have a positive monospot because of amnestic responses while ill with an alternative virus, such as rubella. Other causes of false-positive monospots include malaria, autoimmune hepatitis, systemic lupus erythematosus, leukemia, pancreatic cancer, or, rarely, primary HIV infection (Am. J. Med. 2001;111:192-4). Of course, primary HIV is far less common than EBV, but should be kept in mind.

Still, EBV mono is the most likely diagnosis in a patient with a positive monospot who has had the classic symptoms.

► **Pitfall 3.** Specific EBV serology panels can be confusing. An EBV-specific antibody panel is the next step in the persistently ill patient with a negative monospot test. It not only nails down the diagnosis but also can tell us where the patient is in the course of infection. Depending on the laboratory, either three or four antibodies are included in the EBV panel:

The first is IgM to viral capsid antigen (VCA). It is initially positive in the second or third week of infection. It usually wanes by 2-4 weeks and may not develop at all in young children.

Next is IgG to VCA. It is initially positive in second to fourth week of infection and detectable for life.

Third is an antibody to early antigen (EA). It is usually present during EBV replication. (This is the one that some labs omit.)

Fourth is an antibody to EBV nuclear antigen (EBNA). Its presence coincides with recovery and arises beyond 6 weeks.

A positive IgM to only VCA confirms that the patient is early in course of EBV mono. A positive IgG to VCA, with or without a positive IgM to VCA, is also diagnostic of currently active mono.

However, if EBNA antibody is present, EBV is NOT the likely cause of the current problem. I use an EBNA mnemonic, "EB Not Active." Occasionally an anti-EBNA–positive patient is entering recovery even if they don't feel well quite yet. We can assure them that they will feel better soon.

If EBV serology indicates recovery from a past EBV infection (positive for both IgG to VCA and anti-EBNA) or it is completely negative, a different cause for current symptoms could be sought by testing for cytomegalovirus, adenovirus, or *Toxoplasma gondii*.

EBV-mono patients should expect to have symptoms for at least 4-6 weeks before recovery. Reactivation may occur, but is nearly always asymptomatic or involves short-lived nonspecific symptoms. Chronic mono is so rare as to not be considered in primary care.

► **Pitfall 4.** Avoid having the patient stay too long on bed rest. Patients infected with EBV should be on bed rest only for the highly febrile stage, usually less than a week. We no longer recommend that they stay home from school or away from routine activities while riding out mononucleosis. Once the fever goes away, encourage patients to return to as much activity as their energy level will allow. The important exception is to refrain from contact sports as long as the spleen is palpable (and perhaps a little longer) to minimize chance of splenic rupture. I tell athletes to hang up the current sports season.

Patients kept in bed too long have more difficulty readjusting to normal life routines. Some may even experience clinical depression. It's important to consider how a patient with mono is coping psychologically when fatigue remains the main complaint.

► **Pitfall 5.** Active treatment is not usually helpful. Unfortunately, antivirals such as acyclovir don't work. Current consensus is not to give patients corticosteroids during acute mononucleosis. Steroids were postulated to speed recovery, and subjective mood improvement is possible due to the "steroid high" effect. However, in controlled trials they do not improve recovery other than reducing pain in first 12 hours (Cochrane Database Syst. Rev. 2006;3: CD004 402).

Further, steroids kill off defensive T cells that hold EBV-driven expansion of potentially malignant B cells in check. Such an imbalance could lead to later lymphoma. Although I don't think this is a huge risk, transient symptom relief does not seem worth the risk to me and I don't believe it's something we should do routinely. However, there are a few exceptions: The risk/benefit ratio changes in favor of corticosteroids if tonsillar swelling compromises the airway, or if there are other life-threatening EBV complications such as severe thrombocytopenia, neutropenia, or encephalitis.

But for uncomplicated EBV-mono, our best tools are ibuprofen, supportive care, and the tincture of time. ■

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Excess Antibiotics Beefing Up Bacteria in Soil, Study Says

BY SHERRY BOSCHERT
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STANFORD, CALIF. — Bacteria are no longer just resistant, but have learned how to live on antibiotics as their only food source, according to the first study to analyze bacterial resistance in soil samples.

Dr. Alan Greene, a pediatrician with a special interest in the environment, found this study in Science while reviewing journals for articles that affected the practice of pediatrics. This article revealed that antibiotics excreted from humans and livestock are plentiful in soil (Science 2008;320:100-3).

"We're treating not just our patients but the environment, and it's beginning to have an impact," Dr. Greene said at a pediatric update sponsored by Stanford University.

Reducing U.S. beef consumption by 10% or replacing 10% of conventional livestock with organic beef sources would eliminate 2.5 million pounds of antibiotics from the environment and soil, more than twice the amount of antibiotics prescribed by U.S. physicians each year, said Dr. Greene of the university.

'We're treating not just our patients but the environment, and it's beginning to have an impact.'

DR. GREENE

About 40% of health care dollars spent on drugs in pediatrics buy antibiotics, which has got to change, Dr. Greene said. He reported having no financial relationships relevant to his presentation.

A subsequent issue of Science devoted entirely to drug resistance recommended drastically reducing the prescribing of antibiotics, and saving them for when they are really needed (2008;321:313-423). Rather than completing a 7- to 10-day course of antibiotics, it may be better to treat for a day or two until the patient is feeling better, then stop the drug and rely on the immune system, some of the authors suggested.

"I'm not ready to say that we should do that," but antibiotic prophylaxis is being deemphasized for some pediatric medical problems, Dr. Greene said. Recent guidelines recommend limiting antibiotic prophylaxis for infective endocarditis to select patients, and say prophylaxis will not prevent pyelonephritis and renal scars in children with vesicoureteral reflux. ■