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## Editor's Note:

In the spring 2003 issue of this publication, the editor's note was headlined "Beyond Cholesterol." In that issue, we reported and discussed the recently released (2003) American Heart Association/Centers for Disease Control and Prevention (AHA/CDC) scientific statement from the workshop on inflammatory markers and cardiovascular disease (CVD).

The concept of atherosclerosis as an inflammatory process was still relatively new at that time, and the body of evidence in support of the clinical use of inflammatory biomarkers was modest. The AHA/CDC statement made Level II recommendations on the use of high-sensitivity C-reactive protein (hs-CRP) for stratifying risk for cardiovascular disease. A Level II recommendation indicated that the weight of evidence was favorable, but more data were needed before general consensus could be reached.

Since 2003, considerable data have been published on the use of hs-CRP to improve assessment of cardiovascular risk for patients in primary prevention programs. A recent comprehensive review noted that at least 20 prospective studies of distinct cohorts demonstrated elevated hs-CRP levels, which were associated with future risk for coronary heart disease (CHD) even after adjustment for traditional risk factors, including the Framingham risk score and/or diabetes and obesity.

To refresh the reader's memory, tests for hs-CRP associated with vascular inflammation measure the same molecule as tests for CRP associated

with systemic or local inflammation. Vascular inflammation is associated with significantly lower levels of CRP than those seen in systemic inflammation. Assays for hs-CRP are more sensitive and reported in mg/L versus CRP that is reported in mg/dL. Therefore, it is important to order hs-CRP when testing for vascular inflammation associated with CVD. Quest Diagnostics uses the proprietary name of Cardio CRP™ (CCRP) for hs-CRP to differentiate between tests for vascular and systemic inflammation. In the following article titled "By JUPITER!" we will refer to hs-CRP as CCRP.

The above-noted studies published since the release of the 2003 AHA/CDC statement have provided a growing body of evidence that measurement of hs-CRP in a primary prevention setting adds predictive power to traditional risk scores for some intermediate risk individuals. Additionally, it has been noted that hs-CRP levels could assist in identifying individuals at increased risk who could benefit from lifestyle modification and pharmacologic preventive therapies such as the use of statin drugs.

The use of hs-CRP as a patient education and motivational tool, which is recommended in the AHA/CDC statement, also has been shown to be useful in practice. Although less robust, data support the use of hs-CRP results to guide treatment in the secondary prevention situation such as in the acute coronary syndrome.

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## Editor's Note

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One of the nagging questions about the use of hs-CRP has been—Does the presence of an elevated hs-CRP level in the absence of hyperlipidemia signal an increased CVD risk that should be treated with drugs to lower hs-CRP? That question has recently been answered by the results of the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial. The answer now is in and, according to most cardiologists, the answer appears to be a resounding yes!

Serologic testing for hepatitis B surface antigen (HBsAg) is the primary laboratory tool used to identify persons with chronic hepatitis B virus (HBV)

infection. In the past, HBsAg testing has been recommended previously by the CDC for pregnant women, infants born to HBsAg-positive mothers, household contacts and sex partners of HBV-infected individuals, persons born in countries with an HBsAg prevalence of  $\geq 8\%$ , persons who are the source of blood or body fluid exposures that might warrant postexposure prophylaxis (e.g., needlestick injury to a healthcare worker or sexual assault), and persons infected with the human immunodeficiency virus (HIV).

A recent report from the CDC updates and expands the previous guidelines for HBsAg testing and includes new recommendations for public health

evaluation and management for chronically infected individuals and their contacts. Routine testing for HBsAg now is recommended for additional groups. The recommendations now include populations with an HBsAg prevalence of  $\geq 2\%$ , persons born in areas with an HBsAg prevalence of  $\geq 2\%$ , men who have sex with men, and injection-drug users.

In this issue, we will review the progression of serologic events that occur in uncomplicated and chronic HBV infection, as well as discuss the interpretation of various serologic markers of HBV infection.

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## By JUPITER!

In 1998, the AHA convened Prevention Conference V to study strategies for identifying patients at high risk for CVD and in need of primary disease prevention. At that time, the conference concluded that inflammatory markers were not yet considered applicable for routine risk assessment.

In 2001, the National Cholesterol Education Program Adult Treatment Panel III Guidelines identified inflammatory markers as emerging factors, which could be used as an optional risk factor measurement to adjust estimates of absolute risk obtained using standard risk factors.

In March 2002, a workshop titled “CDC/AHA Workshop on Inflammatory Markers and Cardiovascular Disease: Applications to Clinical and Public Health Practice” was held. The purpose of the workshop was to determine which tests were most useful to assess cardiovascular risk; what results should be used to define high risk; and which patients should be tested. The workshop participants reviewed several inflammatory markers, including CCRP, serum amyloid A,

white blood cell count, fibrinogen, and ESR.

The comparison of the various inflammatory markers favored CCRP as the analyte of choice because of sample stability, accuracy, precision availability, and existing proficiency testing among other reasons. The following recommendations were published in *Circulation* in 2003:

- Current evidence supports the use of CCRP as the analyte of choice to assess cardiovascular inflammation.
- CCRP should be measured in metabolically stable individuals without obvious inflammation or infections.
- To minimize intra-individual variation, results of two separate assays, two or more weeks apart, should be averaged to provide a more stable estimate of that individual's level.
- Results should be expressed in mg/L.
- The cut points of **low risk** ( $<1.0$  mg/L), **average risk** (1.0-3.0 mg/L),

and **high risk** ( $>3.0$  mg/L) correspond to approximate tertiles of CCRP in the adult population. The high-risk tertile has approximately a twofold increased relative risk compared to the low-risk tertile. Patients with results  $>10$  mg/L should be investigated for the possibility of systemic infection or inflammation.

- CCRP can be used to identify patients without known CVD who may be at higher absolute risk than estimated by major risk factors; i.e., a Framingham risk score of 10-20% over 10 years (intermediate risk score).
- At this time, CCRP is not recommended for general population screening nor should it be used as an alternative to evaluation of the major risk factors.
- CCRP measurement may be considered in order to motivate patients with moderate to high-risk levels to improve their lifestyle and comply with drug therapy.
- CCRP may be useful in estimating the prognosis in patients with stable coronary artery disease or acute coronary syndromes.

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## By JUPITER

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In the spring 2003 issue of this publication, which discussed the above recommendations, the reader was advised to “Stay tuned!” This is a continuation and update for the reader.

Tune in to the AHA Scientific Sessions held in November 2008. New results from three studies presented at the AHA 2008 Scientific Sessions and published in scientific journals provide strong evidence that CCRP is a useful marker for CVD. The most eagerly awaited and widely discussed JUPITER trial results promoted the most discussion, both in the medical community and the public media, with reports appearing in many newspapers, including the frequently read Health Sections of both the *New York Times* and the *Wall Street Journal*.

The *New England Journal of Medicine* published the results on its Web site ahead of print shortly after the findings were presented at the AHA Scientific Sessions. Prominent cardiologists issued comments such as “one of the most important clinical trials in the long history of statin studies” and “It is a true landmark in preventive cardiology . . .”

JUPITER is a large, multinational, long-term, double-blind, placebo controlled, randomized clinical trial that included 17,802 healthy men and women assigned to rosuvastatin 20 mg or the placebo. The study was designed to assess whether statin therapy should be given to apparently healthy individuals with normal LDL-cholesterol levels but elevated CCRP (CCRP >2.0 mg/L) values.

Among patients treated with rosuvastatin, LDL-cholesterol levels were reduced by half, decreasing from a median 108 mg/dL at baseline to 55 mg/dL at 12 months. CCRP levels declined 47%, from 4.2 mg/L at baseline to 2.2 mg/L at 12 months. Triglyceride levels fell 17% from baseline in the rosuvastatin group. These effects persisted over the course of the study.

The study, originally designed as a 4-year trial, was stopped after 1.9 years of follow-up, based on recommendations of the drug manufacturer and an independent data monitoring board. The decision to terminate was based on unequivocal evidence of a reduction in cardiovascular morbidity and mortality among patients treated with rosuvastatin compared with the placebo group. The study took into account the size and precision of the observed-treatment benefit, as well as effects on the rates of death and other secondary end points. The investigators continued the adverse-event reporting in a blinded manner for each participant until each patient’s closeout visit.

The study authors reported that treatment with rosuvastatin significantly reduced the primary composite end point by 44%, compared with the placebo. The primary end points were non-fatal myocardial infarction (MI), non-fatal stroke, hospitalization for unstable angina, an arterial revascularization procedure, or confirmed death from cardiovascular causes. There was a 55% reduction in non-fatal MI, a 48% reduction in the risk of non-fatal stroke, and a 47% reduction in the risk of hard cardiac events—a composite of MI, stroke, and death from cardiovascular events.

In terms of absolute advantage, the proportion of patients who had an MI, stroke, revascularization, or hospitalization for unstable angina or died from cardiovascular causes was 1.6% in the rosuvastatin group and 2.8% in the placebo arm—an absolute risk reduction of 1.2%. Likewise, the proportion of patients with hard cardiac events—MI, stroke, and cardiovascular death—was 0.9% in the treatment arm, compared with 1.8% in the placebo group—an absolute reduction of 0.9%.

Additionally, of the 6,801 women included in the JUPITER trial, rosuvastatin significantly reduced the composite end point by 46%.

This finding was described by one cardiologist as “our most impressive data in women in the primary-prevention setting.”

A subgroup analysis showed no heterogeneity in any of the results, including an analysis based on age, race, or ethnic group, as well as baseline LDL-cholesterol and CCRP levels. The investigators reported that even patients considered being at very low risk—nonsmokers, not overweight, no metabolic syndrome, or had a Framingham risk score of  $\leq 10\%$ —benefited from the statin therapy.

Some physicians have urged caution going forward. An editorial accompanying the JUPITER study report in the *New England Journal of Medicine* agreed that the AHA/CDC and other guidelines relating to CCRP are likely to be revisited. There was some disagreement with the study authors regarding the number needed to treat in order to prevent hard cardiac events. Additional concern was expressed regarding the increase in glycosylated hemoglobin levels and diabetes mellitus incidence in the rosuvastatin arm. There was no disagreement, however, in the usefulness of measuring CCRP in asymptomatic individuals who have an intermediate level of risk and whose treatment might change based on their CCRP level.

*Editors Note: In the opinion of this editor, individuals with desirable LDL-cholesterol levels and at intermediate risk—now considered by many to be 5-20% using the Framingham risk score—can be better evaluated and managed for CVD risk by including CCRP values in the management decision.*

(*Circulation* 2003; **107**:499-511 — *NEJM* 2008; **359** (21):2195-2207, 2280-2282 — *Nat Clin Pract Cardiovasc Med* 2008; **5**:621-635 — [theheart.org](http://theheart.org) — [docguide.com](http://docguide.com) — [cardiosmart.org](http://cardiosmart.org))

# Chronic Hepatitis B Virus — Updated Recommendations from CDC

Chronic infection with hepatitis B virus (HBV) is a common cause of death associated with cirrhosis, liver failure, and hepatocellular cancer (HCC). Worldwide, approximately 350 million persons have chronic HBV infection, and an estimated 620,000 people die annually from HBV-related liver disease. In the United States, approximately 800,000 to 1.4 million persons were estimated to be living with chronic HBV infection in 2006. Additionally, chronic HBV infection is the underlying cause of an estimated 2,000-4,000 deaths annually in the United States.

Individuals with chronic HBV infection can remain asymptomatic for years and transmit the infection unintentionally to others, as well as increase their own risk for serious liver disease later in life. All persons with chronic HBV infection need medical management to monitor the onset and progression of liver disease and liver cancer. Safe and effective antiviral agents are now available to treat chronic HBV infection.

Serologic testing for hepatitis B surface antigen (HBsAg) is the primary laboratory tool used to identify persons with chronic HBV infection. In the past, HBsAg testing has been recommended for pregnant women,

infants born to HBsAg-positive mothers, household contacts and sex partners of HBV-infected individuals, persons born in countries with an HBsAg prevalence of  $\geq 8\%$ , persons who are the source of blood or body fluid exposures that might warrant postexposure prophylaxis (e.g., needlestick injury to a healthcare worker or sexual assault), and persons infected with HIV.

A recent report from the CDC updates and expands the previous CDC guidelines for HBsAg testing and includes new recommendations for public health evaluation and management for chronically infected individuals and their contacts. Routine testing for HBsAg now is recommended for additional groups, including populations with an HBsAg prevalence of  $\geq 2\%$ , persons born in areas with an HBsAg prevalence of  $\geq 2\%$ , men who have sex with men, and injection drug users. Areas with a prevalence of  $\geq 2\%$  include much of Eastern Europe, Asia, Africa, the Middle East, and the Pacific Islands.

In this issue, we will graphically review the progression of serologic events, which occur in uncomplicated and chronic HBV infection, as well as discuss the interpretation of various combinations of serologic markers in HBV infection. The reader is referred to the cited CDC reference for an in-depth discussion of the subject, including patient management.

I frequently am asked to assist in interpreting serologic markers for

suspected HBV infection. These markers are varied and complex. Antigens and antibodies associated with HBV infection include the following:

- HBsAg
- anti-HBs (antibody to HBsAg)
- anti-HBc (antibody to hepatitis B core antigen)
- HBeAg (hepatitis Be antigen)
- anti-HBe (antibody to HBeAg)

At least one serologic marker is present during HBV infection that either progresses to recovery or develops into a chronic, persisting illness. The following figures and charts from the CDC publication graphically illustrate the serologic findings in uncomplicated and chronic HBV infection. These charts are printed separately on page 5 for your convenience and future reference.

**Addendum:** The following NIH consensus statements were published in the *Annals of Internal Medicine* on January 6, 2009:

- “National Institutes of Health Consensus Development Conference Statement: Management of Hepatitis B”
- “Antiviral Therapy for Adults with Chronic Hepatitis B: A Systematic Review for a National Institutes of Health Consensus Development Conference”

Both documents are open access and available at <http://www.annals.org>.

(*MMWR* 2008; **57**(No. RR-8):1-20 — *Ann Intern Med* 2009;**150**(2):104-110, 111-124)

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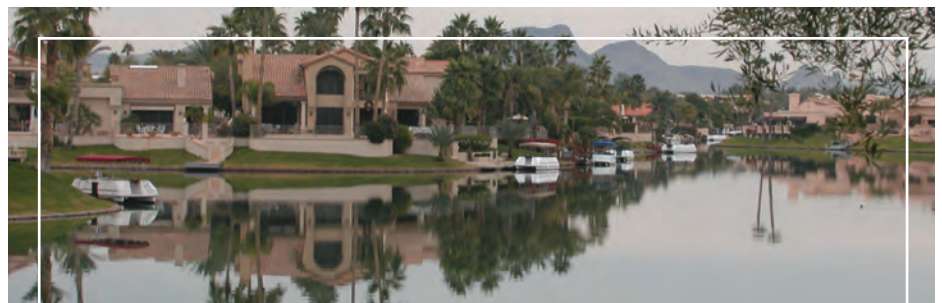
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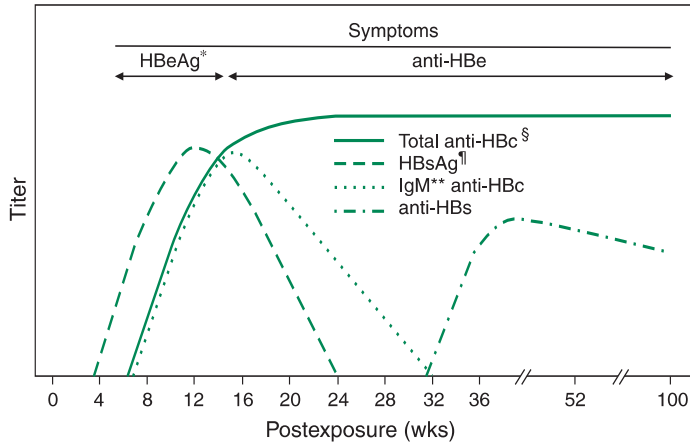
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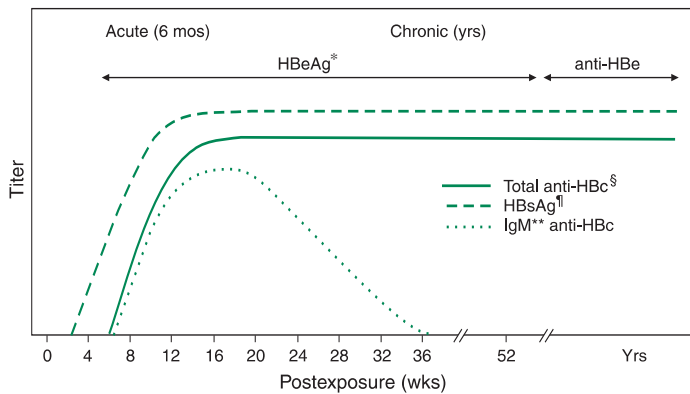
# Serologic Markers For HBV Infection

## Serologic Course of Acute HBV Infection with Recovery



\* Hepatitis Be antigen.  
 † Antibody to HBeAg.  
 § Antibody to hepatitis B core antigen.  
 ¶ Hepatitis B surface antigen.  
 \*\* Immunoglobulin M.  
 †† Antibody to HBsAg.

## Serologic Course of Acute HBV Infection with Progression to Chronic HBV Infection



\* Hepatitis Be antigen.  
 † Antibody to HBeAg.  
 § Antibody to hepatitis B core antigen.  
 ¶ Hepatitis B surface antigen.  
 \*\* Immunoglobulin M.

## Interpretation of Serologic Test Results for HBV Infection

Serologic marker				Interpretation
HBsAg*	Total anti-HBc†	IgM§ anti-HBc	Anti-HBs¶	
—**	—	—	—	Never infected and no evidence of immunization
+††	+	—	—	Chronic infection
+	+	+	—	Acute infection
—	+	—	+	Recovered from past infection and immune
—	—	—	+	Immune (immunization or natural)

\* Hepatitis B surface antigen.  
 † Antibody to hepatitis B core antigen.  
 § Immunoglobulin M.  
 ¶ Antibody to HBsAg.  
 \*\* Negative test result.  
 †† Positive test result. To ensure that an HBsAg-positive test result is not a false positive, samples with repeatedly reactive HBsAg results should be tested with a licensed neutralizing confirmatory test.