

Issue Summary
Blood Products Advisory Committee
October 21, 2004
Holiday Inn Gaithersburg, Gaithersburg, MD

Topic I: FDA's Current Thinking on Reentry of Donors Deferred for Repeated Detection of Antibody to Hepatitis B Core Antigen

Issue

FDA seeks the advice of the Committee on a proposed algorithm that would permit reentry of donors previously deferred for testing repeatedly reactive (RR) on more than one occasion for antibodies to hepatitis B core antigen (anti-HBc).

Background

FDA recommends screening of Whole Blood and components for transfusion for anti-HBc. In a memorandum to blood establishments, dated September 10, 1991¹, the FDA recommended the following:

- ? ? Donations intended for transfusion should be tested for anti-HBc, and only negative units should be used for transfusion (with the exception of autologous donations under specific conditions).
- ? ? Donors should be deferred indefinitely from further donations whenever they test repeatedly reactive for anti-HBc on more than one occasion, regardless of the time interval between the two repeatedly reactive tests.

A donor re-entry protocol for anti-HBc was not recommended at that time because there was no supplemental (additional, more specific) test available. Although donor screening for anti-HBc has contributed to blood safety (see discussion in the appendix), a large proportion of donors with anti-HBc reactivity, but who otherwise fulfill all other donor suitability criteria, have been deferred on the basis of potentially false positive anti-HBc test results.^{2, 3} It remains the case that there is no algorithm recommended by FDA for reentry to the donor pool of donors of blood intended for use in transfusion who have been deferred for testing RR on more than one occasion for anti-HBc. It is estimated that as many as 21,500 potentially eligible donors have been deferred annually in the late 1980s and 1990s because of false positive anti-HBc results and that over 200,000 donors could potentially be reentered in the donor pool.³

FDA is considering the suitability of a testing algorithm to permit reentry of these indefinitely deferred donors based on a determination that the historical tests for anti-HBc were falsely positive and that there is no evidence of infection with HBV. Specifically, it is our current thinking that a testing algorithm to re-enter anti-HBc RR donors, can be based on the use of the following FDA-licensed assays: hepatitis B surface antigen (HBsAg) assays, anti-HBc assays, hepatitis B virus (HBV) nucleic acid tests (NAT).

Discussion

As mentioned above, donors, who are repeatedly reactive on more than one occasion for anti-HBc, are indefinitely deferred. Although it may seem unlikely that two anti-HBc tests would be false positives, we believe that such situations have occurred with some frequency, because of the relative nonspecificity of these tests, particularly in the past. While we believe that specificity of some anti-HBc donor screening tests has improved recently, otherwise suitable donors have been, and still are being, deferred.

In December 1998, both FDA and AABB presented reentry algorithms for anti-HBc RR donors to BPAC. Under both of these algorithms, the donor would have been reentered on subsequent negative tests for HBsAg, anti-HBc and antibody to hepatitis B surface antigen (anti-HBs). The Committee did not agree with the proposed algorithms, because of data presented by American Red Cross showing that some samples that were HBsAg negative and were RR in one type of anti-HBc test, but negative in another type of anti-HBc test, were HBV DNA positive using an experimental HBV NAT.

Recently HBV NAT assays for detection of HBV DNA have been developed for screening blood donations using a minipool (MP) sample format. These assays can also be used to test single samples, thus increasing test sensitivity. The availability of potentially very sensitive, FDA-licensed, HBV NAT assays, particularly when single samples are tested, would provide an additional, powerful, method of determining whether a donor, who has been deferred because of anti-HBc reactivity, is truly infected by HBV. Also, as mentioned above, some anti-HBc screening assays seem to have better specificity than tests available in the past. For these reasons, FDA is again considering a reentry algorithm for anti-HBc.

The algorithm that FDA is considering is as follows:

A donor, who has been indefinitely deferred because of having tested repeatedly reactive for anti-HBc on more than one occasion, may be reentered if:

- a) after a minimum of 8 weeks subsequent to the last repeatedly reactive anti-HBc test, a new sample is collected from the donor, and this sample tests negative for HBsAg, anti-HBc and HBV DNA by NAT (sensitivity of 95% detection at ≤ 10 copies/mL) in FDA-licensed assays,

and;

- b) when the donor presents at a blood center to donate, subsequent to the negative tests for HBsAg, anti-HBc and HBV NAT, all suitability criteria for donors of Whole Blood and components are fulfilled.

FDA is not proposing additional testing for anti-HBs as part of donor reentry because extensive hepatitis B vaccination programs have been in place for a number of years, resulting in many individuals having anti-HBs from vaccination. As a result, anti-HBs now has questionable value as a marker of hepatitis B infection.

Questions for the Committee

1. Do the available scientific data support FDA's proposed criteria for reentry of donors previously deferred on the basis of a repeatedly reactive screening test for anti-HBc on more than one occasion?
2. Please discuss any alternative approaches that FDA should consider.

References

1. FDA Recommendations Concerning Testing for Antibody to Hepatitis B Core Antigen (Anti-HBc), September 10, 1991.
2. Tegtmeier G, Henderson S, McNamara A, Kuhns M. Contribution of anti-HBc screening to blood safety at a regional blood center in the United States. *Transfusion* 1997; 37S; 11S (Abstr. S439)
3. Kleinman SH, Kuhns MC, Todd DS, Glynn SA, McNamara A, DiMarco A, Busch MP for REDS. Frequency of HBV DNA detection in US blood donors testing positive for the presence of anti-HBc: implications for transfusion transmission and donor screening. *Transfusion* 2003; 43:696-704.
4. Allain J-P. Occult hepatitis B virus infection: implications in transfusion. *Vox Sang* 2004; 86:83-91.
5. Busch MP. Should HBV DNA NAT replace HBsAg and/or anti-HBc screening of blood donors? *Transfusion Clinique et Biologique* 2004; 11:26 – 32.
6. Roth WK, Weber M, Petersen D, Drosten C, Buhr S, Sireis W, Weichert W, Hedges D, Seifried E. NAT for HBV and anti-HBc testing increase blood safety. *Transfusion* 2002; 42:869-875.
7. Hoofnagle JH. Posttransfusion hepatitis B (Editorial). *Transfusion* 1990; 30:384 – 386.
8. FDA Recommendations for the Quarantine and Disposition of Units from Prior Collections from Donors with Repeatedly Reactive Screening Tests for Hepatitis B Virus (HBV), Hepatitis C Virus (HCV) and Human T-Lymphotropic Virus Type I (HTLV-I) (January 19, 1996).

APPENDIX

History and Current Scientific Rationale for Donor Screening to Detect Antibodies to HBc

In the mid-1980s, blood establishments in the United States voluntarily introduced anti-HBc screening of Whole Blood and components intended for transfusion as a surrogate test for non-A, non-B hepatitis, now known to be almost exclusively hepatitis C. These tests were initially approved under Premarket Approval Application (PMA) procedures. However, in March 1991 following FDA's Blood Product Advisory Committee (BPAC) recommendations total (IgG and IgM) anti-HBc assays were licensed as biologics products. In May 1990 specific tests to detect antibody to the hepatitis C virus were licensed, and as a result the utility of continued donor testing for anti-HBc came into question.

The implementation of anti-HBc testing of blood donors was followed by a small reduction in the number of cases of transfusion-associated hepatitis B. At that time, in the 1980s, it was unclear, whether this reduction was due to anti-HBc testing *per se*, or because of the introduction of specific testing and donor questions to evaluate donors who might be infected with HIV, and hence HBV in some cases. However, recent studies have shown that a few anti-HBc-only reactive, units contain low levels of HBV DNA.^{3,4,5,6} These recent observations are consistent with the earlier observations that transfusion of such blood was associated with some transmission of hepatitis B.⁷

On January 18, 1991, in a public meeting, BPAC discussed a proposed FDA memorandum to formally recommend anti-HBc testing of donors that had already been implemented voluntarily by blood establishments, as mentioned above. The Committee concluded that continued testing of Whole Blood and components for anti-HBc would contribute to the safety of the blood supply by reducing the incidence of transfusion-associated hepatitis B virus (HBV) infection.

In January 1995, at a National Institutes of Health Consensus Development Conference, at which infectious disease testing for blood transfusions was discussed, the panel recommended that testing blood donors for anti-HBc "should continue as it may prevent some cases of post-transfusion hepatitis B; it may also act as a surrogate marker for HIV infection in donors and may prevent a small number of cases of transfusion-transmitted HIV infection." Although the panel recommended that anti-HBc testing of blood be retained as an additional safeguard against HIV transmission, this recommendation would not apply to the situation being discussed here, because the current discussion is focused on the problem of anti-HBc false positive results.

On January 19, 1996, in another memorandum, FDA recommended that prior collections of viral marker test-negative Whole Blood and blood components from a donor who later tests anti-HBc repeatedly reactive on more than one occasion be withdrawn.⁸

The FDA does not currently recommend that Source Plasma donors be tested for anti-HBc. If anti-HBc reactive units were excluded from pools used for the manufacture of plasma derivatives, titers of anti-HBs in those pools would be expected to diminish, as both these antibodies usually occur together. The presence of anti-HBs is believed to contribute to the safety of certain plasma products such as the immunoglobulins (September 10, 1991, Memorandum). Plasma units that are untested, nonreactive, or repeatedly reactive for anti-HBc are currently acceptable for the manufacture of plasma derivatives (September 10, 1991, Memorandum) .