Anti-HBc testing for blood donations in areas with intermediate hepatitis B endemicity

Celina Maria Turchi Martelli,\textsuperscript{1} Marilia Dalva Turchi,\textsuperscript{1} Francisco José Dutra Souto,\textsuperscript{2} Amadeo Sáez-Alquézar,\textsuperscript{3} Ana Lucia S.S. Andrade,\textsuperscript{1} and Fábio Zicker\textsuperscript{4}

Preventing hepatitis B virus and other transfusion-transmitted infectious diseases relies on stringent blood-donor qualifications and on serological screening for infectious disease markers among potential donors. Several studies have evaluated the reduced risk of transfusion-transmitted infections that comes from screening for hepatitis B core antibody (anti-HBc) in addition to testing for hepatitis B surface antigen (HBsAg), using the currently available serologic tests (1–7) or the newly developed molecular biology assays (8–10). However, most of these analyses were based on data from regions with low hepatitis B endemicity and/or from blood banks from developed countries, where repeat donors account for the majority of the blood supply. In South America, screening for hepatitis B surface antigen (HBsAg) is mandatory (11–13). Brazil, Venezuela, and Ecuador have also introduced anti-HBc testing in recent years (11, 14).

Evaluating the usefulness of anti-HBc screening is critical, particularly for Brazil and other countries that have intermediate and high hepatitis B endemicity. Reasons for this include: 1) a residual risk of transfusion hepatitis B is still present, despite the progressive improvement in the quality of the blood supply; 2) anti-HBc is the most prevalent marker among donors; and 3) anti-HBc seropositivity is the main cause of donor deferral (15, 16). Safe and affordable screening policies should be based on an analysis of the economic burden and possible blood supply shortages due to discarding anti-HBc-positive units. The epidemiologic context, donor characteristics, hepatitis B vaccine coverage, and availability and cost of serologic tests are key elements to be considered.

In order to discuss the pros and cons of anti-HBc screening in Brazil, we present an analysis of results from hepatitis B virus (HBV) and hepatitis C virus (HCV) serology in blood banks in that country. First, a brief description of the history and interpretation of the screening tests adopted to prevent posttransfusion hepatitis is presented. Second, hepatitis B screening data for all the regions of Brazil are reported. This overall analysis of anti-HBc screening among Brazilian blood donors can indicate the appropriateness of deferring blood units and also provide insights for research priorities to guide evidence-based policies on blood screening.
BACKGROUND

Preventing posttransfusion hepatitis relies on several assays sequentially introduced in the blood bank screening routine. Procedures to detect HBsAg have been available and used since the beginning of the 1960s. HBsAg is the earliest seromarker for HBV and indicates acute or chronic infection. Anti-HBc is a long-lasting marker detectable during all stages of HBV infection except the initial phase of viral exposure. This marker persists in acute infections even after HBsAg disappears, as well as in the chronic carrier stage. Anti-HBc is the only detectable seromarker in infected individuals with undetectable HBsAg during the window period, before the appearance of the antibody against the surface antigen (17). Anti-HBs is the antibody that appears in successfully vaccinated individuals. It indicates immunity, and it is not used for blood bank screening (11, 18).

Anti-HBc and alanine aminotransferase (ALT) tests were introduced in the late 1980s in the United States as indirect tests for non-A, non-B hepatitis (NANBH). Studies done in the late 1970s had shown a significantly increased risk of NANBH among recipients of anti-HBc-positive blood units (19–21). These two newer tests have been used in Brazil since 1993. In the early 1990s, several studies conducted among blood donors in Brazil supported the view that anti-HBc testing in parallel to HBsAg screening was likely to detect additional donors at risk of transmitting hepatitis B virus or hepatitis C virus (22–25). Using first-generation anti-HCV enzyme-linked immunosorbent assay (ELISA) tests, Gonçalves et al. (25) showed that both anti-HBc and anti-HCV screening are recommendable for preventing posttransfusion hepatitis B and C.

In the AIDS era and before the availability of HIV testing, anti-HBc was also considered a surrogate marker for HIV infection, given the similarity of risk factors between HBV and HIV (5, 7, 18). Specific assays for HCV became available in the early 1990s. The introduction of sensitive and specific assays for HIV and HCV raised many questions about the usefulness of continuing anti-HBc as a surrogate marker for both HIV and HCV.

In a recent review, Busch (7) pointed out that there was enough evidence to conclude that anti-HBc screening for the HIV-1 strain during its window period has become unwarranted due to the test’s low predictive value and its poor cost-effectiveness. There is also no justification to retain anti-HBc screening as an indirect marker of HCV, given the widespread use of commercially available highly sensitive and specific tests for the hepatitis C antibody (7). According to a consensus statement from the U.S. National Institutes of Health (18), anti-HBc screening should be continued because of its potential for reducing the risk of hepatitis B-infected blood units. The main sources of these infected units are HBV carriers with undetectable HBsAg in the window period (5, 18). Furthermore, some HBV variants may not be detected by certain HBsAg screening tests but could be detected by anti-HBc reactivity (26). Although outside the scope of this report, several studies support the discontinuance of ALT screening among voluntary blood donors as a surrogate marker to prevent posttransfusion hepatitis (5, 18, 27).

BRAZILIAN BLOOD BANK DATA

Results from serologic screening done during 1996 in the Brazilian public blood bank system, known as “Hemorede,” are presented below. The information is from the database of the Blood Bank Foundation. Based in São Paulo, that organization is a WHO collaborating center that provides expertise on blood bank serology quality control. The participating Hemorede blood bank centers are mainly located in large cities throughout Brazil. Together, these centers collect about 1.6 million units of blood per year (15). It is estimated that the public blood banks collect about two-thirds of all the donations nationwide. Although there is little information about the characteristics of the donor population as a whole, several regional studies have reported that the majority of donations are from first-time, unpaid male donors (16, 22, 28).

Table 1 presents the positivity of HBsAg, anti-HBc, and anti-HCV seromarkers for Brazil. Countrywide, 8.3% of the tests were positive for anti-HBc. This seropositivity was higher than for any of the other screening tests, which showed: HBsAg = 1.0%; Trypanosoma cruzi antibody = 1.8%; syphilis = 1.1%; HCV infection = 1.2%; HIV infection = 0.5%; abnormal ALT levels = 1.9%; and human T-cell leukemia virus = 0.8%. Serological screening for HBsAg, anti-HBc, and anti-HCV were mainly performed by ELISA tests. The data clearly show that anti-HBc positivity alone contributes the highest proportion of rejected blood units.

The southeast is the most populated region of Brazil and accounts for 75% of all the country’s blood pool supply. The central western, the northeastern, and the southeastern regions are categorized as low HBV endemic areas. In contrast, the northern and southern regions have intermediate endemicity, with some pockets of high endemicity (16, 29).
Anti-HBc prevalence ranged from 5.8% in the southeastern states up to some 16.0% in the northern and southern parts of the country (Table 1). This variation could be explained by differences in test sensitivity and/or performance among the blood banks. When more specific anti-HBc screening tests were performed at a large blood bank in São Paulo, there was a decrease in rejected blood units between 1994 and 1997, from 8.1% to 4.8%. Even if a more specific anti-HBc test were universally adopted, rejection due to anti-HBc reactivity would still persist as the major cause of blood donor deferral. In comparison, Venezuela and Ecuador reported anti-HBc seropositivities of 3.4% and 4.3%, respectively, among potential donors in 1996 (14, 30).

The interpretation of the Brazilian data merits some caution. The basic assumption is that the tests performed are roughly representative of the donor population. The current Hemorede donor profile does not distinguish between first-time and repeat donors, so the comparison of different settings has its limitations. Repeat donors are more likely to be seronegative due to earlier screening. In addition, the hepatitis tests used in the various regions are based on the same immunoassay principle but may vary in sensitivity and specificity and thus yield different seropositivity results (31). The inclusion of donor demographic and prior-donation characteristics is essential for generating useful epidemiologic information.

**CONCLUSIONS**

In several countries, the anti-HBc screening approach has been evaluated using molecular biology markers. The assumption is that if HBV DNA is detected among donors who are positive only for anti-HBc, this serologic test is useful in identifying infectious blood during the HBV window period. However, these studies have provided no clear conclusions, with wide-ranging results depending on the techniques used and a region's endemicity (7). Along the same line, two recent studies conducted in the state of São Paulo found, with anti-HBc as the only positive marker, HBV DNA positivity varying from 0.8% among blood donors to 23.4% among individuals attending outpatient clinics. Both São Paulo studies supported the continued use of anti-HBc screening for additional prevention of post-transfusion HBV (32, 33). However, in the reported studies, approximately 80% of the anti-HBc-positive donors were also anti-HBs-reactive, indicative of a full recovery from a natural HBV infection, according to previous reports (25). In this sense the majority of such persons would be noninfectious and therefore suitable as donors. It has been proposed that blood units with high titers for anti-HBs would be considered noninfectious and consequently returned to the donor pool (4). On the other hand, a serial approach of adding anti-HBs tests sequentially to all anti-HBc-seropositive samples would increase operational costs and might not be the best approach to building the donor pool, even if useful for individual counseling (18).

Large-scale blood bank screening for HCV, HBV, and HIV by polymerase chain reaction (PCR) among a selected donor population in Germany was considered a suitable procedure to reduce transfusion-transmitted viral infections (10). However, this notion of applying more sophisticated tests needs to be validated in the context of intermediate HBV endemicity and among first-time donors.

In Brazil, there is not enough evidence to discontinue anti-HBc screening. Screening procedures should be introduced based on scientific evidence. Assessing the cost-effectiveness of a molecular biology marker in comparison to the current anti-HBc test routine should be considered a high priority in order to improve blood safety screening procedures.

---

**TABLE 1. Hepatitis B and C screening among blood donors in Brazil, 1996**

<table>
<thead>
<tr>
<th>Region</th>
<th>HbsAg Positive/Total (%)</th>
<th>Anti-HBc Positive/Total (%)</th>
<th>Anti-HCV Positive/Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>North</td>
<td>843/77 218 (1.1)</td>
<td>11 436/71 328 (16.0)</td>
<td>1 058/75 969 (1.4)</td>
</tr>
<tr>
<td>Northeast</td>
<td>1 760/16 1233 (1.1)</td>
<td>13 458/152 880 (8.8)</td>
<td>1 878/159 702 (1.2)</td>
</tr>
<tr>
<td>Central west</td>
<td>508/60 982 (0.8)</td>
<td>6 646/62 207 (10.7)</td>
<td>581/62 320 (0.9)</td>
</tr>
<tr>
<td>Southeast</td>
<td>5 702/657 845 (0.9)</td>
<td>38 189/659 469 (5.8)</td>
<td>8 924/666 849 (1.3)</td>
</tr>
<tr>
<td>South</td>
<td>2 028/120 997 (1.7)</td>
<td>19 356/124 208 (15.6)</td>
<td>1 178/123 231 (1.0)</td>
</tr>
<tr>
<td>Brazil, total</td>
<td>10 841/1 078 275 (1.0)</td>
<td>89 085/1 070 100 (8.3)</td>
<td>13 622/1 088 071 (1.2)</td>
</tr>
</tbody>
</table>

*Source: Fundação Pró-Sangue, São Paulo, Brazil, 1996.*
SINOPSIS

Detección de anticuerpos anti-HBc en sangre donada en lugares donde la hepatitis B tiene endemidad intermedia

En otros estudios se ha evaluado el menor riesgo de infecciones transmitidas por transfusión sanguínea que acarrea el tamizaje de anticuerpos contra los antígenos nucleares de la hepatitis B (anti-HBc), sumado a la prueba detección de antígenos de superficie (HbsAg). No obstante, la mayoría de estos estudios se basaron en datos procedentes de zonas con baja endemidad por hepatitis B o de bancos de sangre de países desarrollados, donde la mayoría de la sangre proviene de personas que han donado previamente. A fin de examinar los pros y los contra el tamizaje de anticuerpos anti-HBc en el Brasil, los autores describen los antecedentes y la interpretación de las pruebas de tamizaje para prevenir la hepatitis postransfusión. También presentan los datos sobre el tamizaje de la hepatitis B en todas las regiones del Brasil. No hay pruebas suficientes para suspender el tamizaje de los anticuerpos anti-HBc en el país. Debe darse alta prioridad a comparar el costo-efectividad de un marcador basado en la biología molecular con el de la actual prueba deteectora de anticuerpos anti-HBc aplicada comúnmente, a fin de mejorar las medidas de tamizaje que garantizan la inocuidad de la sangre.

REFERENCES


Reunión en ocasión del 50.º aniversario del Instituto de Nutrición de Centro América y Panamá

Fechas: 6 a 8 de septiembre de 1999
Lugar: Guatemala, Guatemala
Tema: El INCAP Colaborando con Centro América hacia la Seguridad Alimentaria y Nutricional en el Siglo XXI

El presente año cumple su quincuagésimo aniversario el Instituto de Nutrición de Centro América y Panamá (INCAP), centro especializado de la OPS reconocido en el mundo entero por su extraordinaria labor en beneficio de la salud alimentaria y nutricional de los pueblos mesoamericanos. La ocasión ha sido resaltada durante todo 1999 mediante actividades científicas destinadas a promover, en los ámbitos regional, nacional y local, la participación interdisciplinaria y multisectorial en la Iniciativa sobre Salud Alimentaria y Nutricional que se ha desarrollado en Centroamérica durante el último decenio. Estas actividades, llevadas a cabo en la Sede de la Organización Panamericana de la Salud y en los Estados Miembros de la OPS, culminarán con una reunión científica denominada oficialmente “El INCAP Colaborando con Centro América hacia la Seguridad Alimentaria y Nutricional en el Siglo XXI”. Los temas centrales abarcarán, entre otros, los últimos conocimientos sobre requerimientos nutricionales; el tratamiento y la prevención de la desnutrición en la mujer y en los niños; la prevención y el control de las carencias de micronutrientes; la seguridad de los alimentos en el ámbito local; las medidas de preparación para situaciones de desastre y los factores ambientales que influyen en la seguridad alimentaria y nutricional. Habrá conferencias magistrales, simposios y exposiciones de carteles, así como cursillos sobre el monitoreo y la evaluación de la seguridad nutricional y alimentaria; la formulación de proyectos según el marco lógico; métodos de evaluación cualitativa; prevención de enfermedades carenciales; cultivos hidropónicos, y muchos temas más. Los cursillos, que se celebrarán del 30 de agosto al 3 de septiembre, estarán dirigidos a investigadores, académicos, profesionales, técnicos y estudiantes en materia de alimentación y nutrición.

Información:
Hernán L. Delgado, Director
Instituto de Nutrición de Centro América y Panamá
Carretera Roosevelt, zona 11
Apartado postal 1188
01901 Guatemala, Guatemala, C.A.
Tel.: PBX (502) 472-3762 ó 471-5655
Fax: (502) 473-6529
Página web: http://www.incap.org.gt