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

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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.

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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).

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

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

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

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.

SINOPSIS

Detección de anticuerpos anti-HBc en sangre donada en lugares donde la hepatitis B tiene endemicidad 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 detectora de antígenos de superficie (HbsAg). No obstante, la mayoría de estos estudios se basaron en datos procedentes de zonas con baja endemicidad 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 contras del 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 detectora de anticuerpos anti-HBc aplicada comúnmente, a fin de mejorar las medidas de tamizaje que garantizan la inocuidad de la sangre.

REFERENCES

1. Dodd RY, Popovsky MA, Members of the Scientific Coordinating Committee. Antibodies to hepatitis B core antigen and the infectivity of the blood supply. Transfusion 1991;31(5):443–449.
2. Schifman RB, Rivers SL, Sampliner RE, Krammes JE. Significance of isolated hepatitis C core antibody in blood donors. Arch Intern Med 1993;153(19):2261–2266.
3. Chung HT, Lee JSK, Lok ASF. Prevention of posttransfusion hepatitis B and C by screening for antibody to hepatitis C virus and antibody to HbcAg. Hepatology 1993;18(5):1045–1049.
4. Mosley JW, Stevens CE, Aach RD, Hollinger FB, Mimms LT, Solomon LR, et al. Donor screening for antibody to hepatitis B core antigen and hepatitis B virus infection in transfusion recipients. Transfusion 1995;35(1):5–12.
5. Schreiber GB, Busch MP, Kleinman SH, Korelitz JJ. The risk of transfusion-transmitted viral infections. N Engl J Med 1996;334(26):1685–1690.
6. Molijn MHJ, van der Linden JM, Ko LK, Gorgels J, Hop W, van Rhenen DJ. Risk factors and anti-HBc reactivity among first time blood donors. Vox Sang 1997; 72(4):207–210.
7. Busch MP. Prevention of transmission of hepatitis B, hepatitis C and Human Immunodeficiency Virus infections through blood transfusion by anti-HBc testing. Vox Sang 1998;74(Suppl. 2):147–154.
8. Iizuka H, Ohmura K, Ishijima A, Satoh K, Tanaka T, Tsuda F, et al. Correlation between anti-HBc titers and HBV DNA in blood units without detectable HBsAg. Vox Sang 1992;63:107–111.
9. Douglas DD, Taswell HF, Rakela J, Rabe D. Absence of hepatitis B virus DNA detected by polymerase chain reaction in blood donors who are hepatitis B surface antigen negative and antibody to hepatitis B core antigen core positive from a United States population with a low prevalence of hepatitis B serologic markers. Transfusion 1993;33(3):212–216.
10. Roth WK, Weber M, Seifried E. Feasibility and efficacy of routine PCR screening of blood donations for hepatitis C virus, hepatitis B virus, and HIV-1 in a blood-bank setting. Lancet 1999;353 (9150):359–363.
11. Ministério da Saúde do Brasil. Normas técnicas em hemoterapia. Portaria nº 1376 de 19 de novembro de 1993; 1993.
12. Schmuñis G, Zicker F, Pinheiro F, Brandling-Bennett D. Risk of transfusion-transmitted infectious disease in Central and South America. Emerg Infec Dis 1988;4(1):5–11.
13. Organización Panamericana de la Salud. Situación de los bancos de sangre en la Región de las Américas, 1994–1995. Boletín Epidemiológico 1997;18(1):11–12.
14. Organización Panamericana de la Salud. Situación de los bancos de sangre en América Latina, 1996: marcadores serológicos para enfermedades transmisibles en donantes de sangre. Bol Epidemiol 1998;19(3):11–12.
15. Ministério da Saúde. Estrutura e produção da hemorrede pública [Internet site]. Available from: http://datasus.fns.gov.br/internet/Cosah5.htm
16. Souto FJD. Distribuição da Hepatitis B no Brasil: atualização do mapa epidemiológico e proposições para seu controle. Gastroenterologia e Endoscopia Digestiva. Forthcoming 1999.
17. Lee WM. Hepatitis B virus infection. N Engl J Med 1997;337(24):1733–1745.
18. Infectious disease testing for blood transfusions. NIH Consensus Statement Jan. 9–11 1995;13(1):1–27.
19. Stevens CE, Aach RD, Hollinger FB, Mosley JW, Szmuness W, Kahn R, et al. Hepatitis B virus antibody in blood donors and the occurrence of non-A, non-B hepatitis in transfusion recipients. An analysis of the transfusion-transmitted viruses study. Ann Intern Med 1984; 101(6):733–738.
20. Koziol DE, Holland PV, Alling DW, Melpolder JC, Solomon RE, Purcell RH, et al. Antibody to hepatitis B core antigen as a paradoxical marker for non-A, non-B hepatitis agents in donated blood. Ann Intern Med 1986;104(4):488–495.
21. Sugg U, Schenzle D, Hess G. Antibodies to hepatitis B core antigen in blood donors screened for alanine aminotransferase level and hepatitis non-A, non-B in recipients. Transfusion 1988;28(4):386–388.
22. Wendel S, Luzzi JR, Russo C, Fontão RCL, Ghaname J. Pesquisa de anti-HBc em doadores de sangue em São Paulo: deverá esse teste ser adotado pelo Brasil? Rev Paul Med 1991;109(2):77–83.
23. Leite NC, Nogueira CM, Coelho HSM, Perez R, Martins SJ, Soares JAS, et al. Prevalência do anticorpo contra hepatite C (Anti VHC) em doadores de sangue no Rio de Janeiro, Brasil. Sua relação com ALT e Anti-HBc+. Arq Gastroenterol 1992;29(1):5–11.
24. Andrade Jr. DR, Andrade DR. Hepatite não-A, não-B pós-transfusional: o caminho para o risco zero. Arq Gastroenterol 1992;29(1):1–4.
25. Gonçalves Júnior FL, Pedro RJ, Silva LJ, Boccato RSBS, Gonçalves NSL. Hepatitis pós-transfusionais na cidade de Campinas, SP, Brasil. II. Presença dos anticorpos anti-HBc e anti-HCV em candidatos a doadores de sangue e ocorrência de hepatites pós-transfusionais pelo vírus C nos receptores de sangue ou derivados. Rev Inst Med Trop São Paulo 1993;35(1):63–71.
26. Jongerius JM, Wester M, Cuypers HTM, van Oostendorp WR, Lelie PN, van der Poel CL, et al. New hepatitis B virus mutant form in a blood donor that is undetectable in several hepatitis B surface antigen screening assays. Transfusion 1998;38(1):56–59.
27. Busch MP, Korelitz JJ, Kleinman SH, Lee SR, AuBuchon JP, Schreiber GB. Declining value of alanine aminotransferase in screening of blood donors to prevent posttransfusion hepatitis B and C virus infection. The Retrovirus Epidemiology Donor Study. Transfusion 1995;35(11):903–910.

28. Martelli CMT, Andrade ALSS, Cardoso DDP, Silva AS, Zicker F. Considerações metodológicas na interpretação do rastreamento sorológico da hepatite B em doadores de sangue. Rev Saude Publica 1991;25(1):11–16.
29. Strauss E. Marcadores de hepatites virais em doadores de sangue: o dilema da escassez versus possibilidade de contaminação. Gastroenterologia e Endoscopia Digestiva 1995;14(2):72–76.
30. Leon G, Hernandez T, Garcia L, Maio A, Quiroz A, Gamboa M. Serum hepatitis B markers in blood donors in Venezuela. What do they mean?. Sangre (Barc) 1998 Oct;43(5):385–391.
31. Souto FJD, Fontes CJF, Oliveira JM, Gaspar AMC, Lyra LGC. Comparison of two enzyme immunoassays for the detection of antibody to hepatitis B virus core antigen. Mem Inst Oswaldo Cruz 1997;92(1):89–90.
32. Sucupira MCA. Prevalência do DNA do HBV em amostras de doadores de sangue com AgHBs negativo e anti-HBc positivo [master's thesis]. São Paulo: Instituto de Ciências Biomédicas da Universidade de São Paulo; 1997.
33. Cruz CFN. Estudo de doadores de sangue com a presença do anticorpo anti-HBc sérico como marcador isolado de infecção pelo vírus da hepatite B [PhD dissertation]. São Paulo: Universidade Federal de São Paulo, Escola Paulista de Medicina; 1997.

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 científico-técnicas 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 la metodología del 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.

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