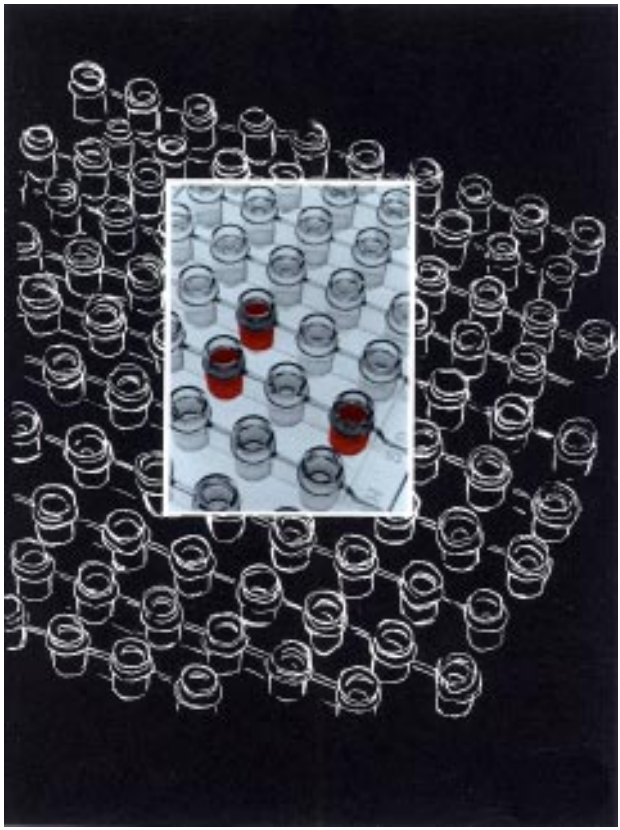
NIH Consensus Statement

Volume 13, Number 1
January 9–11, 1995



Infectious Disease Testing for Blood Transfusions

NATIONAL INSTITUTES OF HEALTH
Office of the Director

About The NIH Consensus Development Program

NIH Consensus Development Conferences are convened to evaluate available scientific information and resolve safety and efficacy issues related to a biomedical technology. The resultant NIH Consensus Statements are intended to advance understanding of the technology or issue in question and to be useful to health professionals and the public.

NIH Consensus Statements are prepared by a nonadvocate, non-Federal panel of experts, based on (1) presentations by investigators working in areas relevant to the consensus questions during a 2-day public session, (2) questions and statements from conference attendees during open discussion periods that are part of the public session, and (3) closed deliberations by the panel during the remainder of the second day and morning of the third. This statement is an independent report of the panel and is not a policy statement of the NIH or the Federal Government.

Free copies of this statement and bibliographies prepared by the National Library of Medicine are available from the NIH Consensus Program Information Service at 1-800-NIH-OMAR (644-6627) or from the Office of Medical Applications of Research, National Institutes of Health, Federal Building, Room 618, 7550 Wisconsin Avenue MSC9120, Bethesda, MD 20892-9120.

Reference Information

For making bibliographic reference to this Consensus Statement, it is recommended that the following format be used, with or without source abbreviations, but without authorship attribution:

Infectious Disease Testing for Blood Transfusions. NIH Consens Statement 1995 Jan 9–11; 13(1): 1–27.

NIH Consensus Statement
Volume 13, Number 1
January 9–11, 1995

Infectious Disease Testing for Blood Transfusions

This statement reflects the panel's assessment of medical knowledge available at the time the statement was written. Thus, it provides a "snapshot in time" of the state of knowledge on the conference topic. When reading the statement, keep in mind that new knowledge is inevitably accumulating through medical research.

NATIONAL INSTITUTES OF HEALTH
Office of the Director

Abstract

Objective. To provide physicians and other transfusion medicine professionals with a current consensus on infectious disease testing for blood transfusions.

Participants. A non-Federal, nonadvocate, 12-member consensus panel representing the fields of hematology, infectious disease, transfusion medicine, epidemiology, and biostatistics and a public representative. In addition, 23 experts in hematology, cardiology, transfusion medicine, infectious disease, and epidemiology presented data to the consensus panel and a conference audience of 450.

Evidence. The literature was searched through Medline and an extensive bibliography of references was provided to the panel and the conference audience. Experts prepared abstracts with relevant citations from the literature. Scientific evidence was given precedence over clinical anecdotal experience.

Consensus. The panel, answering predefined consensus questions, developed their conclusions based on the scientific evidence presented in open forum and the scientific literature.

Consensus Statement. The panel composed a draft statement that was read in its entirety and circulated to the experts and the audience for comment. Thereafter, the panel resolved conflicting recommendations and released a revised statement at the end of the conference. The panel finalized the revisions within a few weeks after the conference.

Conclusions. The serum alanine aminotransferase test should be discontinued as a surrogate marker for blood donors likely to transmit posttransfusion non-A, non-B hepatitis infection since specific hepatitis C anti-body testing has eliminated more than 85 percent of these cases. Anti-hepatitis B core antigen testing should continue as it may prevent some cases of posttransfusion hepatitis B; it also may act as a surrogate marker for HIV infection in donors and may prevent a small number of cases of transfusion-transmitted HIV infection. Syphilis testing should continue until adequate data can determine its effect on the rarity of transfusion-transmitted syphilis. Vigilant public health surveillance is critical in responding to emerging infectious disease threats to the blood supply.

Introduction

The United States has had an organized national blood collection system for 50 years. During this time, testing has been either mandated, recommended by regulatory authorities, or adopted voluntarily so as to make blood transfusions as safe as possible. Various strategies have been used during the past decade to exclude unsafe units from transfusion. These methods, which incorporate systems to ensure donor confidentiality, include refining and expanding the scope of the medical history, identifying behavior associated with high risk, and increased testing of donated blood. In the last 10 years alone, blood collection agencies have implemented five new tests applied to all donated blood: human immunodeficiency virus (HIV 1 and 2) antibodies, hepatitis B core antibody (anti-HBc); serum alanine aminotransferase (ALT), antibodies to human T-cell lymphotropic virus (HTLV I/II), and, most recently, antibodies to hepatitis C virus (HCV). At the time these tests were introduced, some were indirect tests, or "surrogates," whereas others were specific for a particular infection. These actions have been extremely effective, and today the nation's blood supply is safer than ever.

The continuing contribution of some of these tests to the safety of blood transfusions is uncertain. The epidemiology of a disease may change with time, as may immunization status and other factors, so that the optimum combination of donor screening tests is also likely to change. Now that more specific assays are available, the continuing need for certain surrogate assays has been questioned. Both ALT and anti-HBc were introduced as surrogates for an infection that is now subject to more specific testing. Both of these nonspecific tests have a low positive predictive value with frequent false positive results. This leads to disposal of blood from normal donors and to deferral of the donors from future donation. False positive values not only contribute to the present blood shortage but also result in emotional, psychological, and financial costs to the donor. Another test, the serological test for syphilis (STS), was introduced to protect against transfusion-transmitted syphilis; at the present time it is retained

primarily as a sign of risky behavior rather than as evidence for infection. STS, too, has a substantial false positive rate, leading to discarding blood and rejecting the donor with resultant distress. Moreover, the costs of these tests may make blood processing and blood transfusions needlessly more expensive.

To maintain the safety of blood transfusion, it is also important to be alert to the possible introduction of new infectious diseases that may be blood-borne and therefore a hazard of transfusion. Thus, whereas one aim is to eliminate tests that are no longer useful, it is equally important to introduce whatever new screening procedures may be necessary to maximize the safety of blood transfusions. An example of such a challenge is the possibility of Chagas disease in donors. Because of immigration from Mexico, South America, and Central America and reports of several cases of Chagas disease resulting from transfusions, testing of donors for *T. cruzi* infection is now being considered by many blood banks. No general plans are in place, however, to deal with the introduction of infectious agents that might threaten the safety of the blood supply.

The purpose of this consensus conference was twofold: (1) to evaluate the need for continued use of ALT, anti-HBc, and STS tests in volunteer blood donors and (2) to develop a proposal for determining mechanisms to cope with the introduction into the community of an infectious agent that might threaten the blood supply.

To address these issues, the National Heart, Lung, and Blood Institute, together with the Office of Medical Applications of Research of the National Institutes of Health, convened a Consensus Development Conference on Infectious Disease Testing for Blood Transfusions. The conference was cosponsored by the Transfusion Branch of the NIH Clinical Center and the National Institute of Allergy and Infectious Disease.

After 1 1/2 days of presentations and audience discussion, an independent, non-Federal consensus panel composed of specialists and generalists from medical and other related scientific disciplines considered the evidence and formulated

this consensus statement in response to the following four previously stated questions:

- To what extent does the alanine aminotransferase test contribute to transfusion safety? Should its use as in current practice continue or should its use be modified?
- To what extent do tests for hepatitis B core antibody and for syphilis contribute to transfusion safety? Should their use as in current practice continue or should their use be modified?
- To manage potential threats to transfusion safety from emerging infectious diseases, what are the appropriate ways to identify important diseases, to change blood donor screening practices, and to introduce new laboratory tests?
- What are the highest priorities for research to improve transfusion safety by reducing the transmission of infectious disease?

Background for the Role of ALT and Anti-HBc Testing

ALT and anti-HBc tests were introduced in 1986–87 in an effort to identify donors at risk of transmitting posttransfusion non-A, non-B (PT-NANB) hepatitis. Two major studies in the late 1970's indicated that the rate of non-A, non-B hepatitis in transfusion recipients was higher in those receiving units from donors with high ALT levels than in those receiving units from donors with low ALT levels. In the Transfusion Transmitted Virus Study (TTVS) 45 percent of recipients of blood from donors with ALT in a high range (60–284 IU/L) developed PT-NANB hepatitis, whereas only 5 percent of recipients of blood from donors with ALT in a low range (1–14 IU/L) developed PT-NANB hepatitis. Intermediate rates of PT-NANB hepatitis were observed in recipients of units from donors with intermediate levels of ALT. In addition, recipients of units of blood from anti-HBc positive donors experienced a two- to threefold greater risk of PT-NANB hepatitis compared with recipients of units from donors without anti-HBc. A similar correlation between posttransfusion hepatitis and

elevated ALT and the presence of anti-HBc in donors was observed at the National Institutes of Health. These two studies suggested that anti-HBc testing of donors, in concert with ALT testing, might eliminate 30–50 percent of PT-NANB hepatitis. Based on these studies, testing of volunteer donors for ALT and anti-HBc was begun by blood banks to reduce PT-NANB hepatitis. Several years later, HCV was identified, an anti-HCV test was developed, and HCV was shown to be responsible for most, if not all (>90 percent) cases of PT-NANB hepatitis. The more sensitive second-generation test for anti-HCV combined with improved donor selection has effectively eliminated 85–90 percent of posttransfusion hepatitis due to HCV. It is likely that newer tests for anti-HCV will improve this level of protection against posttransfusion hepatitis C. The issue at present is whether these two surrogate tests (ALT and anti-HBc) continue to contribute to transfusion safety.

To What Extent Does the Alanine Aminotransferase Test Contribute to Transfusion Safety; Should Its Use as in Current Practice Continue or Should Its Use Be Modified?

The panel reviewed the background data of changes in the risk of hepatitis following blood transfusion resulting from implementation of increasingly sophisticated tests for HCV infection. Also reviewed were data regarding the interpretation of an elevated ALT level in otherwise healthy blood donors.

The potential utility of ALT testing is as follows:

- To reduce the risk of posttransfusion hepatitis C not prevented by screening of donors for antibody to HCV;
- To reduce the risk of posttransfusion hepatitis caused by other known hepatotropic viruses, such as hepatitis A and hepatitis B;
- To reduce the risk of putative infectious agent(s) associated with posttransfusion non-A, non-B, non-C hepatitis.

Now that sensitive tests for HCV infection in donors are available, the value of ALT must be questioned. In addition, the current policy of ALT testing results in the elimination of many acceptable donors and causes additional cost.

Setting criteria for discarding units of donated blood because of ALT elevations has been problematic because modest elevations of serum ALT are common in healthy blood donors. Elevations may reflect acute or chronic liver disease of infectious or noninfectious etiologies. However, frequent alcohol consumption, obesity, or other factors not related to transfusion-transmitted diseases may cause ALT to rise to levels that lead to unnecessary exclusion of donors.

Furthermore, studies in the United States and Europe have confirmed that values of ALT in normal males are considerably higher than those in normal females so that a single cutoff value for ALT rejects a higher proportion of men than women.

Because several different methodologies are available to measure ALT activity, some variation in ALT results will occur even if the same sample is tested in different laboratories. Thus, the interpretation of an ALT level is affected by the assay and by the laboratory in which the determination is made. The lack of standardized interpretation of test results and cutoff values for these results contributes to inconsistent rules regarding the inclusion and exclusion of donors. ALT is a continuous variable, but the decision to discard a unit of blood is a binary one. Thus, healthy donors with borderline elevations of ALT may be deferred or permanently excluded from donating blood.

Prior to the introduction of anti-HCV testing, surrogate markers including ALT may have reduced the overall posttransfusion hepatitis rate by 30–40 percent on a per unit basis. Improved donor recruitment and selection also contributed to this reduction. However, the preponderance of the available data indicates that, in the presence of anti-HCV testing, retention of ALT testing of blood donors has little additional value. Several observational studies failed to demonstrate an additional benefit of ALT testing in the prevention of posttransfusion hepatitis C. This conclusion was further supported by a prospective randomized study. With specific anti-HCV testing, the risk of posttransfusion hepatitis was equivalent in groups receiving blood screened with or without surrogate markers, pointing to the redundancy of ALT testing.

ALT elevation has been proposed as a surrogate marker of HCV infection in the “window period” prior to anti-HCV seroconversion, because ALT rises approximately 4 weeks prior to production of anti-HCV. Implementation of newer,

unlicensed anti-HCV tests (HCV 3.0) is expected to reduce this 4-week window period. In spite of the theoretical window period, there are no data from clinical studies indicating that ALT screening would improve the margin of safety of blood transfusion.

Even with anti-HCV testing of blood donors, a small but measurable risk of posttransfusion hepatitis remains (<0.8 percent in both U.S. and Canadian studies). Possible explanations for this residual posttransfusion hepatitis include infection with new agents or known viruses presenting in an atypical fashion. Examples of the latter might include serotypic variants of HCV not currently detected by standard assays, HBV variants with mutations in the envelope protein that are not identified by standard HBsAg testing, and window period infections with HBV not detected by standard assays. In addition, some cases of apparent posttransfusion hepatitis may have a noninfectious etiology. Although the potential benefit of ALT for early detection of unknown hepatotropic viruses is intriguing, current data suggest that such testing will rarely, if ever, be helpful. The potential benefit of ALT for the detection of posttransfusion hepatitis A infection is also likely to be limited since the brief period of viremia largely precedes the rise in ALT.

The direct cost of the ALT test is low. On the other hand, ALT testing incurs very high indirect costs as measured by lost resources, both of discarded units (approximately 200,000 annually) and of donors temporarily deferred or permanently excluded (approximately 150,000 annually). Moreover, evaluation of donors with abnormal ALT represents an additional fiscal burden to the health care system. A substantial, but underappreciated, consequence of ALT testing is the direct psychological and financial impact on the deferred donor. A donor with borderline elevated ALT may be denied health and life insurance and may suffer from unwarranted anxiety and stress.

Recommendation

ALT testing of volunteer blood donors should be discontinued. Persons previously deferred for an isolated elevation in ALT only may now be reevaluated for donor eligibility.

To What Extent Do Tests for Hepatitis B Core Antibody and for Syphilis Contribute to Transfusion Safety? Should Their Use as in Current Practice Continue or Should Their Use Be Modified?

Anti-HBc

Studies indicate that anti-HBc testing does not identify additional donors capable of transmitting HCV infection when such donors are also screened by the current, sensitive anti-HCV tests. However, anti-HBc screening of donors provides two additional benefits that may warrant its retention as a test used to screen blood donors.

First, it is likely that anti-HBc testing contributes to the safety of blood transfusion by helping to reduce the risk of hepatitis B virus (HBV) infectious units entering the donor pool. Such units may come from two sources: (1) individuals chronically infected with HBV in whom HBsAg is not detectable and (2) donors with acute hepatitis B who are in the window period following disappearance of HBsAg and prior to the appearance of anti-HBs. Whereas relatively few HBV infectious units are likely to be excluded solely on the basis of anti-HBc testing, current use of anti-HBc screening probably contributes to the low rates of transfusion-transmitted hepatitis B in the United States. In addition, anti-HCV positivity may act as a surrogate marker for HBV infectious donors who are HBsAg negative.

A second rationale for retention of anti-HBc testing relates to its activity as a surrogate marker for HIV infection. Its ability to serve as a surrogate marker for HIV is due to the overlapping epidemiology of HIV and HBV with common parenteral and sexual transmission risk factors. Given the availability of sensitive serologic markers for HIV infection, the value of anti-HBc as a surrogate marker of HIV infection is restricted to recently infected donors who are in the window period of HIV infection prior to the detectability of HIV antibodies. Although window period donors are extremely

rare (presently approximately 1:210,000–1:1,140,000), the severe consequence of transfusion-transmitted HIV infection supports the retention of the anti-HBc test for this purpose. Anti-HBc testing may currently be eliminating as many as one-third of HIV window period units. However, the value of anti-HBc testing as a surrogate for HIV is likely to decline with expanding HBV immunization and changing HIV epidemiology.

Despite these potential benefits of anti-HBc screening, the present test for anti-HBc has many false positive results leading to the unnecessary deferral of tens of thousands of donors. This results in the loss of a large number of units of blood that are otherwise suitable for transfusion. In addition, donors are provided with confusing test results and are subjected to needless anxiety and medical expense, brought about by the mistaken thinking that they may have a contagious disease.

Anti-HBs testing is helpful in confirming the specificity of anti-HBc testing: anti-HBc positivity in donors who also test positive for anti-HBs usually indicates prior HBV infection. Present data suggest that such donors are not likely to be infectious. On the other hand, a small proportion of donors who are anti-HBc positive in the absence of anti-HBs are HBV DNA positive and likely to be infectious. An argument may be made that donors positive for both anti-HBs and anti-HBc have a low probability of transmitting HBV and thus could be returned to the donor pool, but such a strategy would eliminate the potential value of anti-HBc screening in preventing HIV transmission. It would also complicate donor management. Thus the panel concluded that anti-HBs testing should not be a part of donor screening, although it will be useful in the medical evaluation of donors found to be anti-HBc positive.

The value of the anti-HBc test in improving the safety of the blood supply is tempered by the impact of high false positive rates. Its positive predictive value for past or present infection with the hepatitis B virus must be improved.

Recommendation

Although there is no reason to retain the anti-HBc test to prevent posttransfusion hepatitis C, it is recommended that the anti-HBc test be retained for donor screening for the following purposes:

- Prevention of posttransfusion hepatitis B.
- Prevention of some cases of transfusion-transmitted HIV from donors who test negative for anti-HIV because they are in the window phase of the infection.

Syphilis

Syphilis is one of the oldest recognized infectious risks of blood transfusion, and serologic tests for syphilis have been routinely carried out on blood donors for more than 50 years. In recent years, transfusion-transmitted syphilis has become exceptionally rare, with very few cases reported in the literature. In 1985, an FDA advisory panel proposed eliminating the requirement for serologic testing for syphilis. This proposal was not acted upon because of the possible value of the test as a surrogate marker of HIV. Given this, is it reasonable to continue donor screening for syphilis?

Several factors probably contribute to the absence of reported cases of transfusion-transmitted syphilis. These include improved donor selection processes, the uniform application of serologic tests for syphilis to all donors, and a general shift from transfusion of fresh blood to transfusion of refrigerated blood components. The relative role of these three factors in excluding syphilis as an infectious hazard of blood transfusion is difficult to ascertain because of a paucity of data that specifically address these issues. In addition, uncertainty exists concerning the extent to which current surveillance practices would detect occasional cases of transfusion-transmitted syphilis. Antibiotics received by many hospitalized, transfused patients may partially treat transfusion-transmitted syphilis, obscuring the diagnosis but not necessarily preventing long-term complications of the infection.

The general use of refrigerated blood for transfusion is often cited as an important factor in reducing the risk of transfusion-

transmitted syphilis, as *Treponema pallidum* loses its viability within a few days in whole blood stored at 4˚C. However, available data indicate that a small proportion of viable organisms may survive up to 96 hours under such storage conditions, and many units of blood are refrigerated for shorter time periods prior to transfusion. In addition, platelet concentrates are stored at room temperature and no data are available concerning the survival of *T. pallidum* under these conditions.

Thus, current blood storage conditions would not appear to provide an adequate margin of safety against transfusion-transmitted syphilis, should the donor screening test be eliminated. Further information concerning *T. pallidum* survival under blood and platelet storage conditions, and the application of molecular techniques to assess the presence of *T. pallidum* DNA in serologically positive units, would allow better assessment of this question.

An alternative rationale often cited as a reason for retaining serologic testing of donors for syphilis is the potential ability of such tests to serve as surrogate markers of other transfusion-transmissible infections, especially HIV. However, cross-sectional studies and examination of prior donations from donors undergoing HIV seroconversion indicate that serologic tests for syphilis have very little value as surrogate markers for HIV infection in recently infected persons who have not yet developed detectable antibodies to HIV. Syphilis testing is likely to identify less than one such donor annually within the United States. This low efficacy of syphilis testing as a surrogate marker of HIV is not sufficient by itself to warrant its application to all blood donors. Low positive predictive values for HBV, HCV, or HTLV infections similarly do not support retention of syphilis testing as a surrogate for these infections.

Recommendation

Because the contribution of serologic tests for syphilis in preventing transfusion-transmitted syphilis is not understood, the panel concludes that testing of donors for syphilis should continue.

To Manage Potential Threats to Transfusion Safety From Emerging Infectious Diseases, What Are the Appropriate Ways to Identify Important Diseases, to Change Blood Donor Screening Practices, and to Introduce New Laboratory Tests?

Assurance of transfusion safety relies upon effective public health surveillance for emerging infectious diseases. Appropriate management of newer disease threats requires effective surveillance in combination with the rational use of screening measures to eliminate or minimize the risk of transfusion-associated disease transmission.

Decisions regarding the appropriate response to a new infectious disease involve many considerations. The answers to the following three questions will direct a logical approach to a control strategy.

Is the disease potentially transmissible through blood products?

Not every existing or emerging infectious disease is potentially transmissible through transfusion. On the other hand, diseases with a long and relatively asymptomatic period during which microorganisms are present in the blood are of particular concern to transfusion safety.

Potential threats to transfusion safety from emerging infectious diseases can be identified in a number of ways. Case reports of infection following transfusion or infections appearing in patients who have received blood from multiple donors should prompt epidemiologic investigation. Even in the absence of such reports, if the disease has a significant period during which the causative microorganism is present in the bloodstream, it may be important to institute surveillance systems to detect transfusion-acquired infections. The potential survival of the organism in an infectious form during blood processing and storage should also be investigated.

Is the disease an important public health problem?

The effort expended and resources committed to the disease threat will be determined by the severity, incidence, prevalence, and potential for secondary spread of the infection. HIV infection, when it first appeared, affected only a small number of patients, yet the dire consequences of infection triggered a focused effort to exclude HIV from the blood supply. CMV infection is an example at the other end of the spectrum. CMV antibody is present in approximately 50 percent of donors, representing active infection in some, which can in turn be transmitted to recipients. CMV antibody-positive donors are retained since infection in immunocompetent adult recipients is usually mild, and exclusion of CMV positive donors would drastically reduce the nation's blood supply. Only in immunocompromised patients is CMV potentially fatal, and in these patients blood components lacking CMV infection are preferentially transfused.

The incidence and prevalence of the infection in the donor population are also critical determinants. The approach to a widespread infection will require strategies different from those required for a rare or regionally concentrated infection. An example of the latter is *T. cruzi* infection, a proven transfusion threat currently limited to blood from donors who were born in or resided for prolonged periods in Mexico, Central America, or South America. Thus, regionality, habits, travel history, country of birth, medical history, and perhaps other indices of donor behavior are important considerations in the potential of any infectious agent to emerge as a threat to the blood supply. Another consideration in evaluating the public health importance of an emerging infection is the potential of that infection for secondary spread.

What are the appropriate responses to the threat?

Identification of an emerging transfusion-transmitted infectious disease and assessment of its magnitude will determine the balanced response required to ensure the continuing safety of blood components while maintaining an adequate supply. Management of an emerging threat to the blood supply involves refinement of donor recruitment and selection

practices, donor testing, and blood processing. Recipient surveillance may also be important. The appropriate strategy is based on careful assessment of the risk:benefit ratio, cost-effectiveness, and availability of procedures to remove that threat from the donor pool. Each intervention must be tailored to the epidemiology and microbiology of the infection.

The intervention strategy that may have the greatest potential efficacy is refinement of the donor history. Data from the early 1980's demonstrate that a substantial reduction in the incidence of posttransfusion hepatitis B, hepatitis C, and HIV transmission occurred following redesign of donor recruitment and selection practices as well as improved transfusion practice. The efficacy of this approach is further corroborated by recent studies on Chagas disease, which show that careful design and validation of historical questions can separate high-risk from low-risk donors. Further studies on the development and validation of this instrument should be encouraged.

The next step in screening for potential transfusion-transmitted infection is implementation of new laboratory tests of donor blood. Ideally such tests should be very sensitive, in order to lead to the rejection of all dangerous donors, and also very specific, in order to achieve a strong positive predictive value and minimize unnecessary deferral of otherwise acceptable donors. In the absence of reliable assays specific for the infection in question, it may be necessary to institute surrogate testing as was done for posttransfusion hepatitis. Implementation of revised donor questionnaires and introduction of laboratory testing must be accompanied by evaluation of outcomes demonstrating that the interventions favorably influence component safety and supply. Ineffective or inefficient interventions should be discontinued if their impact is negative or neutral.

Implementation of a response to an emerging infectious disease threat to the blood supply requires a wide range of activities. Once a strategy is adopted, personnel must be trained, equipment and supplies obtained, procedures and policies prepared and validated, and appropriate documentation prepared. In view of the fact that any change per se may

induce a higher error rate for some time, close supervision is critical at this phase. Numerous other effects result from changes in donor screening strategy. For example, the donor will now be required to answer additional or different questions, or may receive notification of the result of unfamiliar tests. Planning must include these considerations.

Recommendations

In the absence of any formal mechanism by which transfusion medicine evaluates the threat of a potential transfusion transmitted infection, it is recommended that:

- The blood transfusion community arrange for periodic communication with the Centers for Disease Control and Prevention to proactively review emerging infectious disease threats to the United States and its borders.
- The appropriate responses once a potential threat to transfusion safety is identified include:

  (a) evaluation of transmissibility by transfusion

  (b) assessment of public health significance

  (c) definition of responses appropriate to the potential transfusion safety risk.

What Are the Highest Priorities for Research to Improve Transfusion Safety by Reducing the Transmission of Infectious Disease?

The panel believes that the following issues represent important needs in improving transfusion safety. Recognizing that research is already under way in most of these areas, the panel wishes to provide a comprehensive list of research issues, not in any priority.

- *T. pallidum* in relation to transfusion
- Definition of the incidence and causes of bacterial contamination of blood
- Better methods for eliminating or inactivating infectious agents in blood components
- Improved direct tests for infectious agents
- Definition of the biology and natural history of non-A, non-B, non-C, posttransfusion hepatitis
- Prevalence of residual hepatitis B and hepatitis C post-transfusion hepatitis; large-scale, prospective donor repositories and recipient surveillance
- Implications of transfusion-transmitted diseases in neonates
- Evaluation of the risk of nonenveloped viruses in patients receiving plasma derivatives
- Epidemiology of Chagas disease in the United States
- Design of questionnaires to elicit evidence of risk in donors
- Impact of deferral on donors
- Improved understanding of donor motivation and recruitment practices
- Development of artificial blood components

Conclusions

- Since the determination of ALT has not been shown to be a useful surrogate marker in the present setting, the panel recommends that it be discontinued.
- Anti-HBc testing does have the potential to prevent some cases of posttransfusion 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. However, it has a high false positive rate, which results in the deferral of many acceptable donors. The panel therefore recommends that the test be continued but that its specificity be improved. Since disease prevalence in populations is in constant flux, the accuracy of direct and indirect tests for disease also changes. The panel therefore also recommends periodic critical reevaluation of the utility of these tests.
- The test for syphilis has been used for many years, and data are inadequate to ascertain whether it accounts for the rarity of transfusion-transmitted syphilis. The panel therefore recommends that use of the test continue. It also recommends that research be done to determine if seropositivity is predictive of spirochetemia and to better define the extent to which the organism remains viable and infective in blood components.
- Public health surveillance, and collaboration between public health and transfusion medicine specialists, is critical in responding to emerging infectious disease threats to the blood supply.
- An organized multidisciplinary approach to these threats must be formulated (including Federal and State public health agencies, the medical community in general, and the transfusion medicine community).

Consensus Development Panel

Jane F. Desforges, M.D.
Panel and Conference Chairperson
Distinguished Professor of Medicine–Emerita
Division of Hematology/Oncology
Department of Medicine
New England Medical Center
Boston, Massachusetts

Freydoon Athari, M.D.
Medical Director
Blood Bank and Donor Services
Department of Pathology
Fairfax Hospital
Falls Church, Virginia

E. Shannon Cooper, M.D., J.D.
Laboratory Director
Ochsner Transplant Center
New Orleans, Louisiana

Cage S. Johnson, M.D.
Professor of Medicine
Division of Hematology
Department of Medicine
University of Southern California School of Medicine
Los Angeles, California

Stanley M. Lemon, M.D.
Professor and Associate Chairman for Research
Department of Medicine
University of North Carolina
Chapel Hill, North Carolina

Karen L. Lindsay, M.D.
Associate Professor of Clinical Medicine
Division of Gastrointestinal and Liver Diseases
Department of Medicine
University of Southern California
Los Angeles, California

Jeffrey McCullough, M.D.
Professor and Associate Chief
Clinical Affairs
Department of Laboratory Medicine and Pathology
Director
Division of Laboratory Medicine and Section of Transfusion Medicine
University of Minnesota Hospital
Minneapolis, Minnesota

Kenneth McIntosh, M.D.
Professor of Pediatrics
Harvard Medical School
Chief
Division of Infectious Diseases
Children's Hospital
Boston, Massachusetts

Robert K. Ross, M.D.
Director
Department of Health Services
San Diego, California

Carolyn F. Whitsett, M.D.
Associate Professor
Department of Pathology and Laboratory Medicine
Emory University School of Medicine
Atlanta, Georgia

Janet Wittes, Ph.D.
President
Statistics Collaborative, Inc.
Washington, District of Columbia

Teresa L. Wright, M.D.
Associate Professor of Medicine
University of California, San Francisco
San Francisco, California

Speakers

Harvey J. Alter, M.D.
"Alanine Aminotransferase and HBcAb as Surrogate Tests for Hepatitis C Transmissibility"
Chief
Infectious Diseases Section
Department of Transfusion Medicine
Warren Grant Magnuson Clinical Center
National Institutes of Health
Bethesda, Maryland

Miriam J. Alter, Ph.D.
"Residual Risk of Transfusion-Associated Hepatitis"
"ALT and Hepatitis C"
Chief
Epidemiology Section
Hepatitis Branch
Division of Viral and Rickettsial Diseases
National Center for Infectious Diseases
Centers for Disease Control and Prevention
Atlanta, Georgia

Morris A. Blajchman, M.D., F.R.C.P.(C.)
"A Multicenter Randomized Trial to Evaluate the Impact of the Non-A, Non-B Surrogate Tests (ALT and Anti-HBc) Before and After Anti-HCV Testing"
Professor
Division of Hematology
Departments of Pathology and Medicine
McMaster University
Medical Director
Canadian Red Cross Society
Hamilton, Ontario
Canada

Michael P. Busch, M.D., Ph.D.
"Incidence of Infectious Disease Markers in Blood Donors: Implications for Residual Risk of Viral Transmission by Transfusion"
"Relationship Between Antibody to Hepatitis B Core Antigen (anti-HBc) and Retrovirus Infections Among Volunteer Blood Donors"
Associate Professor of Laboratory Medicine
University of California, San Francisco
Vice President
Research and Scientific Services
Irwin Memorial Blood Centers
San Francisco, California

Ritchard G. Cable, M.D.
"Value of Testing for Syphilis in Blood Donors"
Associate Professor of Medicine and Laboratory Medicine
Division of Hematology/Oncology
Department of Medicine
University of Connecticut School of Medicine
Medical Director
American Red Cross Blood Services, Connecticut Region
Farmington, Connecticut

Roger Y. Dodd, Ph.D.
"Preventing Transfusion-Transmitted Chagas Disease: The American Red Cross Approach"
Head
Transmissible Diseases Department
Holland Laboratory
American Red Cross
Rockville, Maryland

Jay S. Epstein, M.D.
"Food and Drug Administration Approach to Testing"
Acting Director
Office of Blood Research and Review
Center for Biologics Evaluation and Research
Food and Drug Administration
Rockville, Maryland

S. Victor Feinman, M.D., B.Sc. (Med.), F.R.C.P.(C.)
"Posttransfusion Transaminitis Seronegative for Hepatitis A, B, and C: Is There Yet Another Posttransfusion Viral Hepatitis?"
Professor of Medicine
Hepatology and Gastroenterology
University of Toronto
Director
Liver Study Unit
Department of Medicine
Mt. Sinai Hospital
Toronto, Ontario
Canada

Raymond Gambino, M.D.
"Overview of Testing Blood for Markers of Infectious Disease"
Executive Vice President and Chief Medical Officer–Emeritus
MetPath, Inc.
Teterboro, New Jersey

Ronald O. Gilcher, M.D., F.A.C.P.
"Using Alanine Aminotransferase Testing More Effectively"
President and Chief Executive Officer
Sylvan N. Goldman Center
Oklahoma Blood Institute
Oklahoma City, Oklahoma

Guillermo A. Herrera, M.D.
"Syphilis as a Surrogate Marker for HIV, Hepatitis B Virus, and Hepatitis C Virus"
Epidemic Intelligence Service Officer
Medical Epidemiologist
HIV Seroepidemiology Branch
Division of HIV/AIDS
National Center for Infectious Diseases
Centers for Disease Control and Prevention
Atlanta, Georgia

Paul V. Holland, M.D.
"The Effect of Indirect Markers of Infectious Diseases on Blood Transfusion Safety: Overview"
Clinical Professor of Medicine
Division of Hematology/Oncology
University of California at Davis Medical Center
Medical Director/Chief Executive Officer
Sacramento Medical Foundation Blood Center
Sacramento, California

F. Blaine Hollinger, M.D.
"PCR-Based Analysis of Sera From Patients With Negative Tests for HCV Antibodies and Abnormal ALT, Hepatitis B Core Antibody, or Both"
Professor of Medicine, Virology, and Epidemiology
Baylor College of Medicine
Houston, Texas

Harold S. Kaplan, M.D.
"Human Error: More Tests at What Risk?"
Professor and Director
Transfusion Medicine
Department of Pathology
University of Texas Southwestern Medical Center at Dallas
Dallas, Texas

Eve M. Lackritz, M.D.
"Residual Risk of Transfusion-Associated HIV Transmission"
Medical Epidemiologist
HIV Seroepidemiology Branch
Division of HIV/AIDS
National Center for Infectious Diseases
Centers for Disease Control and Prevention
Atlanta, Georgia

James W. Mosley, M.D.
"Indirect Tests for Transfusion-Transmitted Diseases"
"Recipient Outcomes Associated With Donors Screened by ALT and Anti-HBc Assays: The Transfusion-Transmitted Viruses Study"
Professor of Medicine
Division of Infectious Diseases
Department of Medicine
University of Southern California School of Medicine
Los Angeles, California

Kenrad E. Nelson, M.D.
"Incident Hepatitis C Virus (HCV) and Hepatitis B Virus (HBV) Infections in Transfused Cardiac Surgery Patients: Infection Rates During Different Methods of Donor Screening"
Professor and Director
Infectious Diseases Program
Department of Epidemiology
School of Hygiene and Public Health
Johns Hopkins University
Baltimore, Maryland

Lyle R. Petersen, M.D., M.P.H.
"Comparing Surrogate Lifestyle Tests and HIV p24 Antigen Testing With Regard to Transfusion Safety"
Chief
HIV Seroepidemiology Branch
Division of HIV/AIDS
National Center for Infectious Diseases
Centers for Disease Control and Prevention
Atlanta, Georgia

Mark A. Popovsky, M.D.
"Alanine Aminotransferase Test to Predict Hepatitis C Virus Seroconversion"
Medical Director
American Red Cross Blood Services, Northeast Region
Dedham, Massachusetts

Leonard B. Seeff, M.D.
"Long-Term Hepatitis Morbidity and Mortality"
Chief of Gastroenterology/Hepatology
Veterans Affairs Medical Center
Professor of Medicine
Georgetown University School of Medicine
Washington, District of Columbia

Ira A. Shulman, M.D.
"Preventing Transfusion-Transmitted Chagas Disease: The Los Angeles County/University of Southern California Experience"
Professor of Pathology
Director of Transfusion Medicine
Department of Pathology and Laboratory Medicine
University of Southern California
Chief
Division of Transfusion Medicine, Immunology, and Infectious Disease Diagnostics
Los Angeles County and University of Southern California Medical Center
Los Angeles, California

Cladd Stevens, M.D.
"HIV and Hepatitis: Compared and Contrasted"
Head
Laboratory of Epidemiology
The New York Blood Center
New York, New York

Gary E. Tegtmeier, Ph.D.
"Antibodies to Hepatitis B Core Antigen As a Surrogate Test for Hepatitis C or a Specific Test for Occult Hepatitis B Infection in Blood Donors"
Director of Research
Community Blood Center of Greater Kansas City
Kansas City, Missouri

Planning Committee

Paul R. McCurdy, M.D.
Chairperson
Chief
Bone Marrow Transplantation Branch
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

Luiz H. Barbosa, D.V.M.
Deputy Chief
Transfusion Medicine Branch
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

Robin M. Biswas, M.D.
Chief
Laboratory of Hepatitis
Division of Transfusion Transmitted Diseases
Office of Blood Research and Review
Center for Biologics Evaluation and Research
Food and Drug Administration
Rockville, Maryland

Jane F. Desforges, M.D.
Panel and Conference Chairperson
Distinguished Professor of Medicine–Emerita
Division of Hematology/Oncology
Department of Medicine
New England Medical Center
Boston, Massachusetts

Roger Y. Dodd, Ph.D.
Head
Transmissible Diseases Department
Holland Laboratory
American Red Cross
Rockville, Maryland

Jerry M. Elliott
Program Analyst
Office of Medical Applications of Research
National Institutes of Health
Bethesda, Maryland

John H. Ferguson, M.D.
Director
Office of Medical Applications of Research
National Institutes of Health
Bethesda, Maryland

William H. Hall
Director of Communications
Office of Medical Applications of Research
National Institutes of Health
Bethesda, Maryland

Indira K. Hewlett, Ph.D.
Laboratory Chief
Division of Transfusion Transmitted Diseases
Center for Biologics Evaluation and Research
Food and Drug Administration
Rockville, Maryland

Paul V. Holland, M.D.
Clinical Professor of Medicine
Division of Hematology/Oncology
University of California at Davis Medical Center
Medical Director/Chief Executive Officer
Sacramento Medical Foundation Blood Center
Sacramento, California

Leslye D. Johnson, Ph.D.
Chief
Enteric Diseases Branch
Division of Microbiology and Infectious Diseases
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, Maryland

Harvey G. Klein, M.D.
Chief
Department of Transfusion Medicine
Warrent Grant Magnuson Clinical Center
National Institutes of Health
Bethesda, Maryland

George J. Nemo, Ph.D.
Chief
Transfusion Medicine Branch
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

Elaine M. Sloand, M.D.
Special Assistant to the Director
AIDS Coordinator
Office of the Director
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

Ellen K. Sommer
Public Affairs Specialist
Communications and Public Information Branch
Office of Prevention, Education, and Control
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

Conference Sponsors

Office of Medical Applications of Research, NIH
John H. Ferguson, M.D.
Director

National Heart, Lung, and Blood Institute
Claude J. M. Lenfant, M.D.
Director

Conference Cosponsors

Department of Transfusion Medicine
Warren Grant Magnuson Clinical Center, NIH
Harvey G. Klein, M.D.
Chief

National Institute of Allergy and Infectious Diseases
Anthony S. Fauci, M.D.
Director

Statement Availability

Preparation and distribution of this statement is the responsibility of the Office of Medical Applications of Research of the National Institutes of Health. Free copies of this statement and bibliographies prepared by the National Library of Medicine are available from the Office of Medical Applications of Research, National Institutes of Health, or the NIH Consensus Program Information Service by 24-hour voice mail. In addition, free copies of all other available NIH Consensus Statements and NIH Technology Assessment Statements may be obtained from the following resources:

NIH Consensus Program Information Service
P.O. Box 2577
Kensington, MD 20891
Telephone 1-800-NIH-OMAR (644-6627)
Fax (301) 816-2494

NIH Office of Medical Applications of Research
Federal Building, Room 618
7550 Wisconsin Avenue MSC 9120
Bethesda, MD 20892-9120

Full-text versions of statements are also available online through an electronic bulletin board system and through the Internet:

NIH Information Center BBS
1-800-NIH-BBS1 (644-2271)

Internet
Gopher
gopher://gopher.nih.gov/Health and Clinical Information

World Wide Web
http://text.nlm.nih.gov

ftp
ftp://public.nlm.nih.gov/hstat/nihcdcs

U.S. DEPARTMENT OF HEALTH
AND HUMAN SERVICES
Public Health Service
National Institutes of Health
Office of Medical Applications of Research
Federal Building, Room 618
7550 Wisconsin Avenue MSC 9120
Bethesda, MD 20892-9120

Official Business
Penalty for private use $300

BULK RATE
Postage & Fees
PAID
DHHS/NIH
Permit No. G763