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Transfusion Medicine: An Overview and Update

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The discovery of AIDS in the 1980s and its rapid evolution as a major concern for physicians and their patients have led to many questions about the safety of the blood supply. The attention placed on AIDS has led to new discoveries and technologies to reduce the risk of other transfusion complications such as hepatitis, bacterial contamination, and transfusion-associated graft-vs-host disease. Concerns about blood safety have focused much attention on alternative blood transfusion strategies such as autologous blood, viral inactivation, and artificial blood substitutes. This review describes the transfusion medicine delivery system in the United States, with special emphasis on evolving developments and their implications for the discipline of chemical pathology.

Most of the blood collected for transfusion in the United States is collected at community blood centers; approximately one-half of these centers are maintained by the American Red Cross, whereas the others are run by other nonprofit community agencies. The remainder of blood collections are performed at hospitals. Plasma derivatives are provided by commercial vendors using paid plasma donors, whereas the Red Cross provides plasma components from volunteer donations.

Blood collections and usage declined in the mid-1980s *(1)*. The AIDS epidemic made efforts to convince clinicians to use clinically appropriate indications more effective, and autologous blood collections rose substantially. In 1997, ~12 millions volunteer collections occurred in the United States *(1)*. At the current time, collections and usage are rising, most likely as a result of more cancer and cardiovascular procedures being performed in our aging population.

Although current blood supplies usually are adequate to avoid unnecessary loss of life from unexpected hemorrhage, supply shortages are common at Christmas and during the summer months. In addition, group O blood, which can be used for any recipient, is often in short supply despite the fact that group O is the most common ABO type. Chemical efforts to enzymatically remove the sugars that define ABO specificity, converting group A or B blood to group O, are in commercial development and could be important to alleviate blood shortages and avoid the rare ABO hemolytic transfusion reactions that still occur *(2)*.

Whole blood units typically are converted into blood components at the blood center, with the production of a unit of red cells, a platelet concentrate, and a bag of fresh frozen plasma *(3)*. These individual blood components have unique storage requirements and different blood containers to maximize their storage potential and in vivo survival and function. Blood components can be further modified by the blood center to remove leukocytes, plasma, or volume to meet specific patient needs. Increasingly, blood centers and hospitals are collecting blood components by apheresis, a procedure by which greater quantities of a component can be provided to the recipient from a single donor. Technology is now available to collect two units of red cells from a single donor by apheresis *(4)*, an adult platelet dose to reduce infectious risks or handle alloimmunization problems, or large amounts of plasma to reduce donor exposure.

Blood components are provided by the blood center to the hospital transfusion service, where immune compatibility between the donor and recipient is assured. Although the hospital transfusion service still generally relies on manual methods dependent on the immune agglutination of test red cells, automated technology may soon replace some of these functions *(5)*. Other innovations include the development of centralized transfusion services to reduce costs and the development of computerized algorithms to speed compatibility testing and blood release for some patients *(6)*. Although the hospital transfusion service has been an area where direct contact with patient samples persisted despite automation in most of the clinical laboratory, the transfusion laboratory of the future may not appear very different from the chemistry laboratory.

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Transfusion Complications

AIDS

When the first case of transfusion-associated AIDS was reported late in 1982, there was rapid response in early 1983 by blood banks to educate blood donors that individuals at high risk for AIDS (gay or bisexual males, intravenous drug uses, hemophiliacs, and Haitian immigrants) must abstain from donating blood. Further reports in 1984 of 18 cases of transfusion-associated AIDS collected by the Centers for Disease Control confirmed the wisdom of this approach *(7)*. The etiologic agent for AIDS was identified later in 1984 *(8)*. The virus was originally called LAV by Montagnier and HTLV-3 by Gallo; later, the nomenclature for the retrovirus universally accepted as the cause of AIDS was changed to HIV.

These discoveries facilitated the development of a serologic assay for the HIV virus that was incorporated by blood banks as a part of routine donor screening in early 1985. Screening utilizes an ELISA method, which is sensitive but not adequately specific for definitive diagnosis, particularly in low-risk individuals such as blood donors. When ELISA testing is coupled with the more specific Western blot procedure for samples that are repeatedly reactive by the ELISA test, HIV testing is highly sensitive and specific. A similar algorithm is used for testing patient samples to diagnose the clinical entity of AIDS.

Although these interventions clearly reduced the risk of AIDS from transfusion, it became apparent that some transfusion-related infections continued to occur *(9)*. Epidemiologic studies of seropositive donors revealed data that made it necessary to strengthen and redefine donor exclusion criteria. In September 1985, the Food and Drug Administration (FDA)[1] changed the wording of deferral criteria so that "any male who has had sex with another male since 1977, even one time", would be excluded. In November 1986, male and female prostitutes and their partners were included among those to be deferred. In December 1986, the confidential unit exclusion form became a required procedure at most blood centers *(10)*. This form provides an opportunity for high-risk persons who donate to indicate, in a confidential manner, that their blood should not be used for transfusion. Later modifications of donor screening procedures evolved so that donor room personnel directly confront each donor with questions about his or her high-risk activity for AIDS.

HIV-2 is a second retrovirus that can cause immune deficiency in patients *(11)*. Although it has not been identified as the cause of a case of transfusion AIDS as yet in the United States, the virus is sufficiently similar to HIV-1 to warrant its specific detection in blood donors and elimination from the blood supply. In 1992, an ELISA method that tests donor blood for both HIV-1 and HIV-2, the HIV-1/HIV-2 combination test, was introduced for blood donor screening. In addition, the new test shortened the window period of undetectable infectivity for HIV infection because the test is reactive with both IgM and IgG antibodies to HIV viruses. It currently is believed that the window period from infection of a potential blood donor to antibody detection is ~25 days.

Additional laboratory steps to reduce HIV infections were implemented by blood banks in 1995 with testing for HIV p24 antigen, which was proposed to shorten the seronegative window to ~20 days *(12)*; the detection rate of donors who are positive for p24 antigen but negative for antibody is several cases per year among ~12 million annual blood donations. In 1999, additional screening with nucleic acid testing (NAT) for HIV was implemented to potentially reduce the window by several additional days *(13)*; although the detection rate is expected to be very low, a donor has been identified by NAT who was negative by p24 and antibody screening.

There have been several studies that confirm that these interventions have been very successful in making transfusion-associated AIDS a rare event. A study was performed of multiply transfused cardiac surgery patients in Baltimore and Houston from 1985 to 1991 to provide a prospective evaluation of 11 535 cardiac surgery patients who were transfused with 120 290 units of tested blood; only two HIV-1 seroconversions occurred, corresponding to an HIV-1 infection rate of 0.0017% or a residual risk per unit of ~1 in 60 000 units *(14)*. This study was supported by another investigation of 61 000 units of blood tested for HIV-1 that were studied with HIV-1 viral culture and PCR; only 1 positive unit was identified *(15)*. Both of these studies overestimated the risk of posttransfusion AIDS because many patients die from their primary disease or natural causes in the latency period before clinical AIDS appears. The current risk of HIV infection from tested blood in the United States is 1 in 676 000 *(16)*. Current blood donor experience confirms a dramatic decrease in HIV-1 seropositive donors so that only 1 in 10 000 donors who present to blood centers is HIV infected; studies of this type lend objective support to the claim that the blood supply has never been safer.

HEPATITIS

Although AIDS has received most of the attention of patients, posttransfusion hepatitis (PTH) has been a more common problem and an underrecognized cause of morbidity in transfusion recipients. Early studies recognized two types of hepatitis viruses, type A, which is associated with infectious hepatitis, and type B, which is associated with serum hepatitis. In the early 1970s, the virus that causes hepatitis B was identified as the Australia antigen, and tests using sensitive radioimmunoassay systems were instituted *(17)*. These measures took place at about the same time that most hospitals switched to an all volunteer

[1] Nonstandard abbreviations: FDA, Food and Drug Administration; NAT, nucleic acid testing; PTH, posttransfusion hepatitis; ALT, alanine aminotransferase; HCV, hepatitis C; CJD, Creutzfeldt-Jakob disease; HDN, hemolytic disease of the newborn; and HBOC, hemoglobin-based oxygen carrier.

blood supply, a measure that was expected to lower the incidence of PTH as well. Despite these actions, cases of PTH still occurred. Because these cases had no serologic markers of infection with hepatitis A or B, the term non-A, non-B hepatitis was coined for this disease with a presumed viral etiology.

Studies of transfusion recipients clearly demonstrated that non-A, non-B hepatitis was a clinically, immunologically, and biologically independent disease. A vast number of virologic and immunologic assays were used until 1989 in an unsuccessful quest for the non-A, non-B agent. Despite the absence of a specific viral agent, however, several studies produced important information about non-A, non-B PTH.

A major study was conducted among 1513 transfusion recipients and control patients from 1974 to 1979 in four United States cities *(18)*. These patients were followed after transfusions with serologic and biochemical markers to determine the incidence of PTH; patients with non-A, non-B PTH were identified by fluctuating concentrations of alanine aminotransferase (ALT), the only means of identifying this disease because ~50% of patients do not develop overt jaundice or acute clinical illness. Approximately 10% of patients developed non-A, non-B PTH. The study also demonstrated that 40% of the cases of non-A, non-B PTH could have been prevented by screening blood donors with the ALT test. This test was not immediately adopted because it remained unclear whether non-A, non-B PTH produced major pathology or was merely a "transaminitis". When cohorts of patients with non-A, non-B PTH were followed for longer periods of time, results of liver biopsies clearly demonstrated that 50% of patients developed serious clinical problems such as chronic active hepatitis, cirrhosis, and hepatocellular carcinoma *(19)*.

On the basis of the evolving picture of non-A, non-B PTH, ALT screening was implemented in 1988 because a specific screening test remained elusive. When further studies demonstrated that the antibody to hepatitis B core antigen (anti-HBc) also identified a separate population of blood donors more likely to transmit disease, both of these assays were introduced as surrogate tests for non-A, non-B PTH. Together with the more rigid screening of donor histories for high-risk activities associated with AIDS and HIV screening, these surrogate tests probably reduced the rate of non-A, non-B PTH by 50% *(20)*.

In 1989, molecular techniques were used to derive clones from the genome of the agent associated with non-A, non-B PTH *(21)*. The proteins derived from these clones were used to develop an ELISA assay to detect antibodies to the virus now known as hepatitis C (HCV). In May 1990, this assay was placed into routine use in blood donor screening. Several modifications of the test have been implemented with improved test kits, leading to current estimates that the risk of HCV is on the order of 1 in 103 000 donations *(16)*. The efficacy of HCV serologic screening has led to the discontinuation of ALT screening by most blood centers; because ALT screening removed ~2% of all blood donations and lacked specificity for hepatitis infectivity, HCV serologic screening has helped to increase blood supplies without compromising blood safety. The recent use of NAT for HCV will decrease PTH further because the seronegative window for development of antibody to HCV is known to be on the order of 70 days and NAT positivity may develop within 30 days *(22)*.

These developments have made cases of PTH rare events. The remaining cases may be attributable to other hepatitis viruses; although several candidate viruses have been identified *(23)*, most of these candidates have been discredited as responsible for persisting cases of PTH.

OTHER INFECTIONS FROM TRANSFUSIONS

Although any infection carried by an asymptomatic blood donor can be transmitted to a blood recipient, the likelihood of another infection in the United States is less than 1 in 1 000 000 *(24)*. The possible agents include malaria, bacterial infection from a skin contaminant or a donor with asymptomatic bacteremia, or other parasites such as Chagas disease. Despite the widespread publicity given to Lyme disease, transfusion-associated Lyme disease has not occurred. Considerable public attention has also been placed on the risk of transmission of Creutzfeldt-Jakob disease (CJD), including the new variant CJD described in Great Britain *(25)*. Although there is no evidence that either of these entities have ever been passed to a blood recipient, the FDA recently banned blood donors who have lived in Great Britain for longer than 6 months from blood donations in the future.

DONOR PROCEDURES

The protection of blood recipients from infectious agents derives from four key principles: (*a*) Essentially all blood in the United States comes from volunteer donors who have nothing to gain from giving blood except the satisfaction of helping a needy patient; a confidential unit exclusion mechanism is available to allow donors who face social pressure to donate to go through the motions of giving blood but assure that a patient does not receive that unit. (*b*) Each donor is carefully screened by an extensive health history to determine whether it is safe for that donor to give blood and whether it is safe for a recipient to receive that blood; the history questions are very strictly interpreted so that many noninfectious donors are eliminated to assure the highest recipient safety. (*c*) Donors undergo physical examinations of their temperature, pulse, blood pressure, and have both arms examined for signs of intravenous drug abuse. (*d*) A series of laboratory tests are applied to each unit of blood to eliminate potentially infectious units; the current battery of seven screening tests includes the RPR test for syphilis, three tests for hepatitis (HBsAg, anti-HBc, anti-HCV), a test for the unusual retrovirus HTLV-1, and two tests for HIV (HIV-1/HIV-2 antibody, p24 antigen). On the basis of

these procedures and tests, the patient can be reassured that the blood supply has never been safer.

An additional level of safety has been obtained in laboratory centralization. Taking the lead from other clinical laboratories where centralized facilities allow greater reliance on carefully trained technologists, automated equipment, and strict adherence to FDA regulations, most donor testing is now performed in larger centralized facilities throughout the country.

Immunologic Complications of Transfusions

As the infectious complications of blood transfusions recede from clinical importance, the immunologic consequences of receiving blood from donors takes on greater importance. Patients can become sensitized to antigens on transfused red cells as well as other accompanying blood cells (platelets, white blood cells); women can also become sensitized and form antibodies to these blood group antigens from exposure to blood cells carried by their children during pregnancies. Because sensitization to red cell antigens can induce hemolytic disease of the newborn (HDN) in their children, avoidance of blood bank transfusions is particularly important for women who may choose to bear children.

Sensitization to red cell antigens through previous pregnancies or transfusions can lead to clinical problems for the patient and her offspring. Because the antibodies formed in response to red cell transfusions or pregnancies tend to fade or disappear, a previously sensitized patient is a likely candidate for a delayed hemolytic transfusion reaction with subsequent transfusions *(26)*. The more serious immediate hemolytic transfusion reactions are usually attributable to ABO-incompatible blood issued to a patient who has been misidentified on the ward or from whom the correct blood sample was not obtained. Although most cases of delayed hemolytic transfusion reaction do not cause clinical symptoms, they can cause fever, anemia, jaundice, renal failure, and death in rare cases. All transfusion candidates are screened for red cell antibodies to prevent this complication. In addition, patients who have previously formed red cell antibodies should be notified that they should warn their doctors of possible problems with transfusions; some blood banks issue antibody cards to these patients, but all blood banks should retain records of patients with previous evidence of red cell antibodies.

The other complication of red cell alloantibody formation is HDN in offspring. Whereas Rh incompatibility was formerly the most common cause, the widespread availability of antepartum and postpartum Rh immune globulin now prevents most cases of HDN attributable to anti-Rh(D). Management protocols are available for obstetric patients to detect and prevent Rh sensitization *(27)*. Other Rh antigens and blood groups of the Kell, Duffy, and Kidd system can cause HDN and require similar management protocols for their detection.

Sensitization to platelet antigens can cause the failure of transfused platelets. Patients who have made platelet antibodies from transfusions or pregnancies can transfer these antibodies to their offspring during pregnancies, causing the problem of neonatal alloimmune thrombocytopenia *(28)*. The most common setting is a mother who is negative for the platelet antigen Pl^{A1}. Because 2% of patients lack Pl^{A1}, the problem is not rare, and profound thrombocytopenia and bleeding in the newborn can occur. The problem can be managed by transfusions of washed maternal platelets, and intrapartum platelet transfusions can be administered for subsequent pregnancies.

Sensitization to white cell antigens can cause febrile nonhemolytic transfusion reactions *(29)*. Although these reactions cause no permanent sequelae, they can be difficult to separate from more serious transfusion reactions involving hemolysis. Subsequent reactions can be prevented by using leukocyte-depleted blood components. Allergic transfusion reactions are common but usually present as mild hives and are preventable with pretransfusion antihistamines; more serious cases can be prevented by washing red cells to remove plasma.

Transfusion Alternatives

The only positive benefit of the AIDS epidemic and its associated publicity has been the increased utilization of alternatives to blood transfusion. In 1988, the National Institutes of Health held a consensus conference on "Perioperative Red Cell Transfusion" *(30)*. The conference suggested that there was no evidence to support the widespread practice of using a hemoglobin concentration of $<$100 g/L (10 g/dL) as a transfusion indicator; 70 g/L (7 g/dL) was suggested as a more reasonable alternative. On the basis of this recommendation, most authorities advise physicians to forego transfusions unless the patient has symptomatic anemia or the hemoglobin concentration is below 70 g/L. The conference also presented reaffirming data that mild to moderate anemia does not contribute to perioperative morbidity or delayed wound healing.

On the basis of increased perception of the infectious risks of transfusions, reduction of homologous blood transfusions was recommended and the increased utilization of alternatives to transfusion, such as autologous blood, was advocated.

Despite reassuring data from studies such as the Retrovirus Epidemiology Donor Study *(16)*, which have been featured in the medical and public media, pressure to seek alternatives to transfusions has increased. This theme was given strong governmental support by the NIH Consensus Conference in 1988, which helped stimulate our current medical practices of reducing the transfusion trigger to levels based on physiologic principles, minimizing donor blood exposure, and encouraging alternatives to blood transfusions (Table 1).

Table 1. Transfusion alternatives.

Perioperative autologous blood donation
Perioperative hemodilution
Blood salvage
Pharmacologic therapies
Apheresis to reduce donor exposure
Viral inactivation
Blood substitutes

AUTOLOGOUS OPTIONS

Although transfusion experts have championed the use of autologous blood, the AIDS epidemic led to widespread enthusiasm among patients and their physicians for this practice. Predeposit autologous donations have become the standard of care for many elective surgery procedures *(31)*. At Johns Hopkins, ~10% of the red cells transfused are autologous, despite many patient populations who are not eligible for autologous transfusion programs (organ transplant recipients, trauma victims, neonates and small children, patients with hematologic malignancies). Perioperative hemodilution, a procedure whereby autologous blood is collected in the operating room, is performed more commonly, although definitive proof of its efficacy to reduce volunteer blood transfusions is lacking *(32)*. The use of intraoperative autologous transfusion has also grown with common usage in cardiovascular, orthopedic, and neurosurgical cases despite persistent efficacy questions *(33)*.

PHARMACOLOGIC AGENTS

In addition to autologous options, other transfusion alternatives have been pursued. Physicians are now encouraged to use drugs without biohazardous risks in favor of blood components. Patients with von Willebrand disease are given DDAVP rather than cryoprecipitate to improve hemostasis *(34)*, aprotinin and other fibrinolytic inhibitors have been used in high blood loss surgeries *(35)*, and hematopoietic growth factors such as erythropoietin are advocated for dialysis patients or for patients undergoing elective surgery *(36)*.

REDUCING DONOR EXPOSURE

Another growing transfusion trend is the attempt to minimize donor exposure. The use of apheresis platelets limits the trivial risks of viral transmission, but its major advantage over whole blood-derived platelet concentrates is to reduce the risk of bacterial contamination *(37)*. Our experience at Johns Hopkins has demonstrated the reduction of cases of septic reactions to platelets by conversion to apheresis platelets; over a 12-year period, the rate of septic reactions has dropped to 1 in 15 000 transfusions from 1 in 5000 transfusions with the conversion of our inventory from 50% apheresis platelets to a 100% apheresis platelet supply *(38)*. Because of the growing desire to limit donor exposure, neonatologists have reconsidered their former rigid demands for fresh red cells in favor of using a single donor product for its entire life span *(39)*.

VIRAL INACTIVATION

Because donor testing and screening will never be perfect, viral inactivation has been pursued and is becoming available. Leukodepletion can limit the transmission of cell-borne viruses such as cytomegalovirus. Data have been obtained in bone marrow transplant recipients that show that removing white cells from transfused blood components is equivalent to providing blood components from donors who are seronegative to cytomegalovirus *(40)*. To accomplish this degree of viral safety, it is necessary to decrease the concentration of contaminating white cells below 5×10^6; this reduction represents a 1000-fold reduction, which is best accomplished by new filters that can be applied in blood centers to provide prestorage leukocyte-depleted blood products. Because the removal of white cells to this concentration also reduces the risks of alloimmunization to HLA factors and reduces the rate of other immunologic transfusion reactions in blood recipients, the implementation of universal leukodepletion is proceeding in transfusion medicine practice *(41)*. These measures may reduce the risks of other infections such as CJD as well, leading to widespread leukodepletion around the world in an attempt to reduce the unlikely spread of CJD by transfusion.

Lipid-enveloped viruses can be eradicated from plasma fractions or fresh-frozen plasma by the use of solvent-detergent treatment *(42)*. This chemical process has been applied for many years for fractionation products such as factor VIII, but it recently became available for fresh-frozen plasma. The chemical process is applied to batches of 1500 volunteer plasma products. The process eliminates any risk of lipid-envelop virus infections but does not inactivate other viruses such as hepatitis A or parvovirus B19; some clinicians are concerned that the pooled product may transmit viruses that are yet undiscovered more rapidly because the product is pooled, and these concerns as well as the high costs for the product have slowed widespread acceptance. Other improvements to the product are in progress, such as screening for parvovirus infectivity by PCR testing and the removal of ABO system antibodies, which would eliminate ABO-typed plasma inventories *(43)*.

Psoralen and ultraviolet treatment are entering clinical trials to eradicate viruses and bacteria from platelets and plasma *(44)*. This technology may be particularly important for platelet transfusions in view of the persistent problem of bacterial contamination, which is enhanced by the storage of platelets at room temperature. The storage temperature permits growth of bacteria, which can be introduced at the time of phlebotomy through skin contaminants or donations from donors with asymptomatic bacteremia. Psoralen treatment has the additional advantage of inactivating the leukocytes that contaminate most cellular blood components. These leukocytes can cause transfusion-associated graft-vs-host disease, a lethal complication of transfusion; although patients who are immunosuppressed and considered at risk currently receive

γ-irradiated blood components, irradiation can be expensive and some patients may be at unsuspected risk *(45)*.

BLOOD SUBSTITUTES

Some believe that absolute transfusion safety will not be realized until blood substitutes can be infused. Current blood substitutes are oxygen carriers with a short intravascular life span and in only limited ways substitute for all of blood's functions. Their toxicities are becoming better understood, and formulations of hemoglobin-based oxygen carriers (HBOCs) *(46)* and perfluorocarbons are undergoing clinical trials in trauma and elective surgery with minimal adverse effects *(47)*.

HBOCs can be produced from outdated human blood, animal blood, or by recombinant technology. Most of the products under development are chemically modified by several steps to reduce their potential toxicity. The hemoglobin tetramer is cross-linked or polymerized to increase its intravascular survival and minimize the renal toxicity that occurs when the tetramer dissociates into dimers. Polymerization also permits infusion of a solution with a greater concentration of hemoglobin with oncotic properties similar to blood. It appears that vasoconstriction, one of the major toxicities of HBOCs, can be reduced by polymerization or coupling to a large macromolecule such as polyethylene glycol; vasoconstriction is lessened when the extravasation of the HBOC is reduced so that nitric oxide is not bound in the endothelial cell. In addition, some HBOCs are chemically modified to enhance oxygen delivery with chemicals such as pyridoxal phosphate.

HBOCs have several potential advantages: the shelf life would be much longer than the 42-day period for which red cells can be stored; room temperature storage would be permitted; the solutions would not have blood group antigens; and HBOCs can be treated to achieve viral inactivation. On the other hand, they have a very short intravascular survival of only 12–24 h compared with the 50-day half-life of the red cell, and their infusion can interfere with several laboratory tests in the chemistry laboratory *(48)*.

Perfluorcarbon emulsions, in which large quantities of oxygen can be dissolved, have advantages in ease of production and absence of viral risks. However, their potential clinical use is limited by the toxicity of some of the emulsifying agents in the preparations, activation of the complement system, the thrombocytopenia that may occur from uptake of the perfluorocarbon in the reticuloendothelial system, and the fact that current perfluorocarbon formulations would deliver enough oxygen only in patients breathing very high oxygen concentrations *(49)*.

Although red cell substitutes have not been approved by the FDA, several HBOCs are in phase III clinical trials. The two clinical applications that seem most likely to be approved are for patients with acute trauma, where several blood volumes of HBOCs have been infused without complications, and in acute normovolemic hemodilution protocols, where the HBOC permits aggressive lowering of the patient's red cells for re-infusion after surgery. Other potential applications include infusions for several clinical problems in sickle cell anemia or in other patients with vascular obstruction that could be perfused by an HBOC.

Platelet substitutes may provide rapid hemostasis without the benefits of long-term platelet survival *(49)*. Several approaches are under study, including the use of lyophilized platelets or microparticles coupled to hemostatically active proteins. These approaches may be able to circumvent the problems of alloimmunization that currently limit platelet transfusion practices.

Conclusions

This review has attempted to provide information on the current risks of blood transfusion in the United States and how the use of alternatives to transfusion can mitigate some of those concerns now and in the future. In addition, chemical processes and practices in clinical chemistry laboratories are providing these transfusion improvements in many areas. Although many enhancements in transfusion medicine have improved the safety of blood transfusions for patient care, the basic premises of transfusion practice at the current time are (*a*) avoiding blood transfusions unless specific indications are met; (*b*) using transfusion alternatives if medically and economically prudent; and (*c*) using homologous blood components with the recognition that the safety profile recently has undergone major improvements.

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