

*Medical Progress***TRANSFUSION MEDICINE****Second of Two Parts****BLOOD CONSERVATION**

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**PREOPERATIVE AUTOLOGOUS DONATION**

Preoperative autologous donation was rarely used before the recognition that HIV could be transmitted by blood transfusion. Fifteen years ago, fewer than 5 percent of eligible patients who were scheduled for elective surgery chose autologous blood donation.<sup>121</sup> When public awareness of the possibility of transfusion-transmitted HIV became widespread, however, there was concern that too few patients were choosing autologous blood donation as an option. Several states, including California, passed legislation requiring that whenever it was "reasonably" likely that transfusion would be needed, a patient should be informed of all of the options regarding and alternatives to allogeneic blood transfusion. Subsequently, the use of preoperative autologous donation increased substantially, with 50 to 75 percent of patients choosing this option before certain types of elective surgical procedures<sup>122</sup>; in 1992, 1 of every 12 blood units collected in the United States was the result of autologous donation (Table 2).

Up to half the autologous blood that is collected is discarded.<sup>123</sup> Reasons for the overcollection of autologous blood include local legislation, physicians' fear of legal liability, a perception that there are few or no adverse consequences to preoperative autologous donation, and an attempt to address patients' fear of contracting transfusion-transmitted diseases.

Moreover, preoperative autologous donation is used to cover the need for a range (up to 90 percent) of patients who might need blood, which results in the routine collection of more blood than is needed for the average patient. Since the use of surplus autologous units in patients other than the donor is not recommended,<sup>124</sup> preoperative autologous donation is inherently wasteful.<sup>125</sup> Increasing pressures to decrease the costs of medical care, along with the lack of reimbursement for preoperative autologous donation from Medicare and some private insurers, have also focused attention on the overcollection of autologous blood.<sup>126</sup>

The decreased likelihood of the transmission of viruses by the transfusion of allogeneic blood<sup>10</sup> has caused the practice of autologous blood donation to be reevaluated.<sup>127,128</sup> Both autologous blood donation and transfusion are associated with risks. In one study,<sup>129</sup> 1 in 16,783 autologous donations was associated with an adverse reaction severe enough to require hospitalization; this risk is 12 times as high as the risk associated with voluntary donations by healthy persons. Ischemic events have also been reported in association with but not necessarily as a result of autologous blood transfusion.<sup>130,131</sup> The transfusion of autologous blood has many of the same complications as transfusion of allogeneic units, including the risk of bacterial contamination, hemolysis (ABO incompatibility due to administrative errors), and volume overload.<sup>127</sup> Since 1992, the percentages of autologous blood collected and transfused have declined (Tables 1 and 2). Some advantages and disadvantages of autologous blood donation are summarized in Table 4.

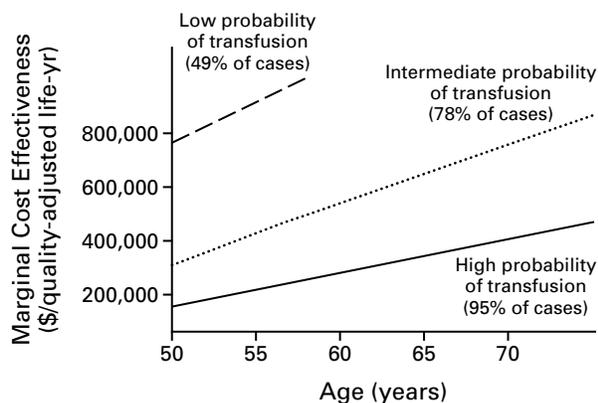
Cost-effectiveness models also serve to illustrate the potential risks of autologous blood donation; even a very remote risk of death in patients with ischemic heart disease may entirely negate the benefits of having autologous blood available before coronary-artery bypass grafting.<sup>132</sup> Key factors include the estimated postoperative life span of the patient and the likelihood of transfusion (Fig. 2).<sup>133,134</sup> In a study of autologous blood donation before coronary-artery bypass grafting,<sup>132</sup> the preoperative donation of two units was estimated to have a cost of \$500,000 per quality-adjusted life-year. In comparison, most commonly accepted medical and surgical interventions have a cost of less than \$50,000 per quality-adjusted life-year. The risk of exposure to a hepatitis virus or to HIV has declined by at least an order of magnitude since the calculation of this estimate, and the current cost effectiveness would be significantly worse.

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**TABLE 4. ADVANTAGES AND DISADVANTAGES OF AUTOLOGOUS BLOOD DONATION.**

ADVANTAGES	DISADVANTAGES
Prevents transfusion-transmitted disease	Does not eliminate the risk of bacterial contamination or volume overload
Avoids red-cell alloimmunization	Does not eliminate the risk of administrative error, resulting in ABO incompatibility
Supplements the blood supply	Costs more than allogeneic blood donation
Provides compatible blood for patients with alloantibodies	Results in discarding of blood that is not transfused
Prevents some adverse transfusion reactions	Causes perioperative anemia and increases the likelihood of transfusion



**Figure 2.** The Effect of the Likelihood of Transfusion and the Patient's Age on the Cost Effectiveness of Autologous Blood Donation before Coronary-Artery Bypass Grafting.

If two units of blood were collected preoperatively, younger patients, in whom projected postoperative survival is longer, and patients who are undergoing surgery in centers with a higher likelihood of perioperative transfusion derive more benefit from autologous blood donation. Adapted from Birkmeyer et al.<sup>132</sup> with the permission of the publisher.

Estimates of the cost effectiveness of autologous blood donation are predicted according to known risks of transfusion. Should a new risk emerge, the estimates may become inaccurate. Similarly, should allogeneic transfusion be ultimately proved to be a cause of postoperative infection or recurrent cancer, the relative risks of allogeneic blood transfusion could change substantially.<sup>134</sup> The use of leukoreduced allogeneic blood products might diminish these potential risks, albeit at a substantial increase in cost.

**Erythropoiesis**

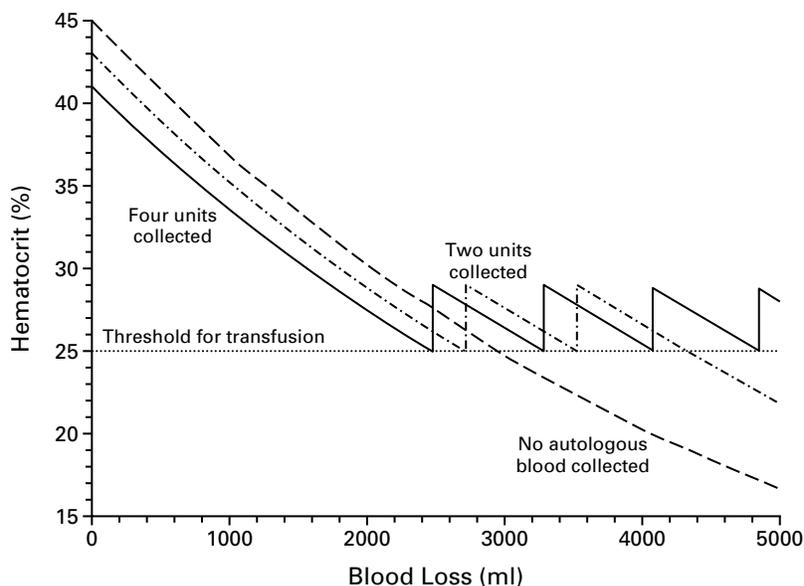
Autologous blood donation may actually be harmful to patients. Figure 3 illustrates the effects of preoperative blood donation and the collection of two

or four units of autologous blood on the preoperative hematocrit (before blood loss) and the final hematocrit on discharge from the hospital in a 70-kg patient with a blood volume of 5000 ml. In this model<sup>128</sup> it is assumed that compensatory erythropoiesis results in the replacement of two thirds of the red cells donated.<sup>135</sup> In the absence of autologous blood donation, the patient could sustain estimated losses of 2939 ml of blood before requiring a blood transfusion with the use of a hematocrit of 25 percent as a threshold for transfusion; however, with the preoperative collection of two or four units of blood a transfusion would be required after estimated blood losses of 2712 or 2473 ml, respectively. A study that analyzed blood transfusion in patients undergoing elective hysterectomy confirmed the accuracy of this model.<sup>136</sup> In essence, preoperative autologous donation appears to increase the risk of postoperative anemia, as well as the likelihood of transfusion and its attendant risks (Table 3).

The degree of anemia induced by autologous blood donation varies, even though iron supplementation is routinely prescribed for patients who donate blood. This variability may be explained in part by the heterogeneity of patient populations and by differences in the timing of blood donations in relation to the date of surgery. Some studies have reported that the average decrease in the hemoglobin level was 1.0 g per deciliter per unit of autologous blood obtained (i.e., there was no compensatory erythropoiesis) before hysterectomy,<sup>136</sup> radical prostatectomy,<sup>137</sup> or colectomy.<sup>75,76</sup> However, in a recent study, Kasper et al. estimated that compensatory erythropoiesis resulted in the replacement of 60 percent of the blood lost by weekly donations of three units of autologous blood over a period of three weeks.<sup>135</sup> This rate of erythropoiesis was noted in other studies only when an aggressive strategy of phlebotomy (six units obtained over a period of three weeks) was used,<sup>138</sup> or when intravenous iron therapy was given in addition to oral iron supplementation.<sup>139</sup> The variability of compensatory erythropoiesis is dependent on initial iron status<sup>140</sup> but not on the age or sex of the patient.<sup>141</sup> Given that normal persons take many weeks to regenerate the blood lost in donation and that a lower hemoglobin level at admission is associated with an increased likelihood of transfusion, it would seem prudent to maximize the time between the last donation and the date of surgery.

**Use in Managed Care**

Guidelines have been published on the types of patients for whom autologous donation is most appropriate.<sup>142,143</sup> Most commonly, the number of units of autologous blood obtained preoperatively is based on the number of units that would be crossmatched before surgery if allogeneic blood were being used.<sup>144</sup> This approach was designed to allow the collection



**Figure 3.** Hematocrit in the Absence of Autologous Blood Donation and after the Preoperative Collection of Two or Four Units of Blood from a 70-kg Patient with a Blood Volume of 5000 ml and Postoperative Hematocrit, after Surgical Blood Losses of 500 to 5000 ml.

The hematocrit decreases by 1 percent (i.e., compensatory erythropoiesis results in the replacement of two thirds of the red cells removed) after each donation. The initial hematocrit was 45 percent, and a hematocrit of 25 percent was the perioperative threshold for transfusion. As can be seen, moderate or even substantial blood loss (up to 2473 ml) in a patient who donated up to four units of whole blood preoperatively would result in a lower hematocrit at discharge from the hospital than if the patient had not given blood preoperatively. If the degree of regeneration of red cells between donations is less than the estimate, the differences would be even greater. Data were based on a model suggested by Cohen and Brecher.<sup>128</sup>

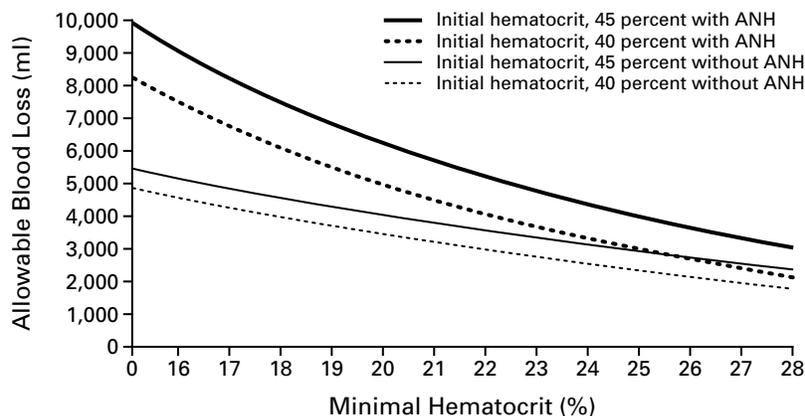
of enough autologous blood so that fewer than 10 percent of patients who were undergoing surgery would receive allogeneic blood transfusions. Not all countries adhere to this recommendation. A recent British consensus conference on autologous transfusion stated that autologous blood donation should be considered only if the likelihood of transfusion exceeds 50 percent.<sup>145</sup> However, even for procedures such as joint replacement or radical prostatectomy, as much as 50 percent of autologous blood goes unused.<sup>123</sup> When autologous blood is collected for procedures that seldom require transfusion, such as hysterectomy, vaginal delivery, and transurethral resection of the prostate, up to 90 percent of the units collected before these procedures go unused.<sup>146,147</sup> In one study in a managed-care setting, the risks of autologous donation and the likelihood of transfusion were made clear to gynecologists and their patients who were scheduled to undergo hysterectomy. This approach resulted in the collection of fewer units of autologous blood, higher hematocrit levels, and fewer autologous transfusions (saving the hospital an estimated \$16,000 in one year) without an increase in the rate of allogeneic transfusion.<sup>148</sup>

Attempts to stratify patients according to the risk

of transfusion on the basis of the base-line level of hemoglobin and the type of procedure planned have shown some promise. Using a system of points, Larocque et al. found that 80 percent of patients who were scheduled to undergo orthopedic procedures were at low risk for transfusion, so that autologous blood donation was not recommended.<sup>149,150</sup> Algorithms that take into account the estimated blood loss and preoperative hematocrit also have the potential to identify patients at low and high risk for transfusion.<sup>151</sup> One problem with these approaches is that blood losses are difficult to predict, and specific surgical procedures, even those performed by the same surgeon, can be accompanied by a wide range of blood loss.

#### ACUTE NORMOVOLLEMIC HEMODILUTION

Acute normovolemic hemodilution entails the removal of whole blood from a patient immediately before surgery and simultaneous replacement with an acellular fluid, such as crystalloid and colloid, to maintain normovolemia. Blood is collected in standard blood bags containing anticoagulant, remains in the operating room, and is reinfused after any major loss of blood has ceased, or sooner if indicated. Re-



**Figure 4.** Maximal Allowable Blood Loss in a Patient with a Blood Volume of 5000 ml and an Initial Hematocrit of 45 Percent or 40 Percent in the Presence and Absence of Acute Normovolemic Hemodilution (ANH).

The maximal allowable blood loss in a patient treated with acute normovolemic hemodilution can be calculated with use of the following equation: maximal blood loss = estimated blood volume  $\times$  (initial hematocrit  $\div$  target hematocrit  $- 1$ ). The maximal allowable blood loss in a patient not treated with acute normovolemic hemodilution can be calculated with use of the following equation: maximal blood loss = estimated blood loss  $\times 1n$  (target hematocrit  $\div$  initial hematocrit). The target hematocrit is the threshold for transfusion. Data were modified from Goodnough et al.<sup>158</sup>

cent guidelines state that acute normovolemic hemodilution should be considered when the potential surgical blood loss is likely to exceed 20 percent of the blood volume in patients who have a preoperative hemoglobin level of more than 10.0 g per deciliter and who do not have severe myocardial disease, such as moderate-to-severe left ventricular impairment, unstable angina, severe aortic stenosis, or critical left main coronary artery disease.<sup>152</sup>

#### Efficacy

The value of hemodilution comes from the fact that the losses in red-cell volume are reduced during perioperative blood loss because of the attendant lowering of hematocrit levels preoperatively.<sup>153</sup> Moderate hemodilution to maintain a preoperative hematocrit of 28 percent results in the preservation of 100 to 200 ml of red cells (the equivalent of one half to one unit of blood).<sup>154-156</sup> Mathematical modeling has suggested that severe hemodilution in which the preoperative hematocrit is less than 20 percent, accompanied by substantial blood losses, would be required before the red-cell volume saved by hemodilution becomes clinically important.<sup>157</sup>

Nevertheless, the clinical effect of acute normovolemic hemodilution is shown in Figure 4.<sup>158</sup> Without hemodilution, an adult with an initial hematocrit of 45 percent could sustain surgical blood losses of up to 3939 ml without the need for transfusion yet have a hematocrit of at least 25 percent postoperatively. The use of hemodilution in this patient would still allow a surgical blood loss of up to 3036 ml,

yet the hematocrit would remain at least 28 percent. The aim of hemodilution is to protect patients who might have unpredictable or substantial blood losses,<sup>159</sup> yet maintain perioperative hematocrit values that minimize the risks related to ischemia.<sup>130</sup>

A prospective study of patients who underwent acute normovolemic hemodilution before radical prostatectomy found that 21 percent of patients received allogeneic blood<sup>156</sup>; this rate is similar to the rate in patients who undergo autologous blood donation before radical prostatectomy<sup>160,161</sup> and in patients who undergo autologous blood donation before elective orthopedic surgery.<sup>162,163</sup> A retrospective European case-control analysis<sup>164</sup> of hemodilution in more than 800 patients who underwent total joint arthroplasty concluded that acute normovolemic hemodilution reduced the need for allogeneic blood transfusions. The results of selected randomized, prospective studies comparing hemodilution with autologous blood donation are summarized in Table 5. Although the numbers of patients are small, there is no evidence that there is a meaningful difference in outcomes between autologous blood donation and acute normovolemic hemodilution for patients who undergo radical prostatectomy or total joint arthroplasty.

Acute normovolemic hemodilution has several advantages over autologous blood donation. First, the units procured by hemodilution require no testing, so that the costs are substantially lower than those of autologous blood donation.<sup>170</sup> Second, since the units of blood are not removed from the operating

**TABLE 5.** RESULTS OF SELECTED PROSPECTIVE, RANDOMIZED TRIALS COMPARING ACUTE NORMOVOLEMIC HEMODILUTION WITH AUTOLOGOUS BLOOD DONATION.\*

TYPE OF SURGERY AND STUDY	ACUTE NORMOVOLEMIC HEMODILUTION	AUTOLOGOUS BLOOD DONATION	No AUTOLOGOUS BLOOD DONATION†	ACUTE NORMOVOLEMIC HEMODILUTION	AUTOLOGOUS BLOOD DONATION	No AUTOLOGOUS BLOOD DONATION†
	no. enrolled			no. receiving allogeneic blood transfusions		
<b>Prostatectomy</b>						
Ness et al. <sup>165</sup>	30	30	—	0	1	—
Monk et al. <sup>166</sup>	26	26	—	5	4	—
<b>Orthopedic surgery</b>						
Lorentz et al. <sup>167</sup>	16	16	15	1	2	8
Goodnough et al. <sup>168</sup>	15	17	—	7	4	—
White et al. <sup>169</sup>	25	23	—	3	3	—

\*There were no significant differences in the need for allogeneic blood transfusions between the groups assigned to acute normovolemic hemodilution and the groups assigned to autologous blood donation.

†This group served as the control group.

room, the possibility of an administrative error that could lead to an ABO-incompatible blood transfusion is theoretically eliminated, as is the risk of bacterial contamination. Third, blood obtained by hemodilution does not require an additional investment of time by the patient since it is done at the time of surgery, nor does it prolong the duration of surgery or anesthesia.<sup>168,170</sup>

**INTRAOPERATIVE RECOVERY OF BLOOD**

Intraoperative recovery of blood involves the collection and reinfusion of autologous red cells lost by a patient during surgery. Cell-washing devices can provide the equivalent of 10 units of banked blood per hour to a patient with massive bleeding. The survival of the red cells that are recovered appears to be similar to that of transfused allogeneic red cells.<sup>171</sup> Relative contraindications include the potential for the aspiration of malignant cells, the presence of infection, and the presence of other contaminants such as amniotic or ascitic fluid in the operative field. Because washing does not completely remove bacteria from the recovered blood, intraoperative recovery should not be used if the operative field has gross bacterial contamination.<sup>152</sup>

As with other strategies of autologous blood procurement, the safety and cost effectiveness of intraoperative recovery of autologous blood should be carefully scrutinized. Four deaths related to the intraoperative recovery of blood were reported to the New York Department of Health from 1990 through 1995, for an estimated prevalence of 1 in 35,000 procedures.<sup>55</sup> A controlled study of patients who were undergoing cardiothoracic surgery demonstrated that this approach had no benefit when transfusion requirements and clinical outcome were evaluated.<sup>172</sup> A prospective, randomized trial of patients

who were undergoing repair of abdominal aortic aneurysms also found that intraoperative recovery of blood did not result in the need for fewer blood transfusions. In the absence of cell washing, the equivalent of one unit of blood can be obtained relatively inexpensively; with the use of automated cell-washing devices, it is generally agreed that the equivalent of at least two units of blood needs to be recovered in order for the method to be cost effective.<sup>173-175</sup> Even in the case of a patient with substantial blood losses during vascular surgery, intraoperative recovery of blood may be of value not because it reduces the requirements for blood transfusion, but because it provides blood that is less costly to obtain and immediately available in the event of rapid blood loss.

**POSTOPERATIVE RECOVERY OF BLOOD**

Postoperative recovery of blood involves the collection of blood from surgical drains followed by reinfusion, with or without processing. The blood recovered is dilute, is partially hemolyzed and defibrinated, and may contain high concentrations of cytokines. For these reasons, programs set an upper limit on the volume of unprocessed blood (1400 ml at one of the hospitals in which we work) that can be reinfused.

The evolution of cardiac surgery has been accompanied by considerable experience in the use of postoperative reinfusion of blood. Nevertheless, the practice of postoperative recovery and reinfusion of autologous blood varies among institutions.<sup>103,104</sup> Prospective and controlled trials have reached disparate conclusions about the efficacy of postoperative recovery of blood from patients after cardiac surgery: at least three such studies demonstrated a lack of efficacy,<sup>176-178</sup> whereas at least two have reported a benefit.<sup>179,180</sup> The disparity in results may

be explained in part by the variability in transfusion practices among institutions.

The safety and the benefit of the use of unwashed blood obtained from surgical drains after orthopedic surgery remain in question.<sup>181,182</sup> One large group that initially found this approach to be beneficial<sup>183</sup> subsequently reported that this costly practice is of no clinical benefit.<sup>184</sup> Because the blood-cell volume of the fluid collected is low (hematocrit, 20 percent), the volume of red cells reinfused is often small.<sup>185</sup> Selective use of the method in situations in which large postoperative blood losses are anticipated, such as in bilateral joint-replacement surgery, would improve the efficacy of the procedure, but such blood losses are difficult to predict.<sup>159</sup>

### EMERGING DEVELOPMENTS IN TRANSFUSION MEDICINE

#### Inactivation of Microbes in Platelet Units

The inactivation of viruses in a unit of platelets while retaining the viability and hemostatic properties of these blood cells has proved to be a formidable challenge. Inactivation of virus in units of platelets by means of exposure to psoralen derivatives followed by exposure to ultraviolet A has been intensely investigated and can greatly reduce the levels of HIV and hepatitis viruses.<sup>186</sup> In order to limit the damage to platelets caused by irradiation, however, the process must be conducted in the absence of oxygen or in the presence of agents that remove damaging reactive intermediate compounds.<sup>187</sup> In many systems, the proportion of plasma in the medium in which the platelets are suspended must be limited (to less than 15 percent) to prevent viruses from escaping inactivation.<sup>188</sup>

These treatments also appear to inactivate any contaminating bacteria<sup>186</sup> and to reduce or eliminate immunomodulation due to lymphocytes.<sup>189</sup> The po-

tential toxicity of a viral-inactivation process that adds photoreactive dyes or other potentially carcinogenic or teratogenic compounds will require careful assessment.<sup>190</sup> Since the current risks of blood transfusion are low, a small risk of an untoward effect of the inactivating agents could represent a larger health threat than the one that is being targeted.

#### Use of Plasma with Reduced Viral Infectivity

Efforts to inactivate viruses in plasma have proceeded more rapidly, and one technique is now licensed for use in the United States. Treatment of plasma with a solvent-detergent process provides a means to inactivate all viruses with lipid envelopes, including HIV and hepatitis B and C viruses.<sup>191</sup> The process, accomplished on a commercial scale by pooling plasma from 2500 donors, yields units of standard size (200 ml) that are refrozen for distribution. The cost of a 200-ml unit of pooled plasma treated with the solvent-detergent process is two to five times as high as the cost of a 250-ml unit of untreated plasma from a single donor. The contents of the plasma appear to be unchanged except that procoagulant activity is reduced by about 15 percent and that levels of large multimers of von Willebrand factor and some other factors, including protein S, are decreased by over 50 percent.

The pooling of plasma from so many donors as part of the solvent-detergent process has aroused concern about the possible transmission of nonenveloped viruses that are not inactivated by the process (Table 6). The manufacturer and distributor have attempted to allay fears about the transmission of hepatitis A virus by documenting the presence of antibodies against this virus in their product. The transmission of parvovirus B19 is a potential problem for some transfusion recipients, such as patients with sickle cell disease or thalassemia, but it has not

**TABLE 6.** ADVANTAGES AND DISADVANTAGES OF THE USE OF POOLED PLASMA TREATED WITH A SOLVENT AND DETERGENT RATHER THAN THE USE OF PLASMA FROM A SINGLE DONOR.\*

ADVANTAGES	DISADVANTAGES
Kills viruses with lipid envelopes Human immunodeficiency virus Hepatitis B virus Hepatitis C virus	Is ineffective against nonenveloped viruses Hepatitis A virus Parvovirus B19 T.T. virus
Eliminates the risk of transfusion-related acute lung injury because it dilutes the amount of donor antibody against specific HLA antigens	May not prevent transfusion-related acute lung injury mediated by biologically active lipids
May contain neutralizing antibodies against hepatitis A virus and parvovirus B19	May not contain neutralizing antibodies against unknown viruses May be overused, with few constraints, as is the case with albumin

\*Pooled plasma is obtained from at least 2500 donors.

been reported among European recipients of plasma treated with the solvent-detergent process. However, if an HIV-like nonenveloped virus were to evolve, it could be present at an undetectably low frequency in donors (e.g., 1 in 100 million) and yet present a threat in a pooled product.<sup>192</sup>

The recent identification of a potential pathogen, T.T. virus,<sup>193</sup> illustrates the validity of the concern about pooled blood products. This nonenveloped virus is present in 1 to 7.5 percent of blood donors in the United States and is transmissible by blood.<sup>194</sup> Although it is not known to cause disease, the virus has been described in a preliminary report as present in 15 percent of patients with cryptogenic cirrhosis and in 27 percent of patients with idiopathic fulminant hepatic failure.<sup>194</sup>

Other alternatives for increasing the safety of plasma through the selection of donors and various collection techniques have been proposed. Because plasma can be stored frozen for a year, units can be held in quarantine until the donor returns and is retested after a period that is longer than the window period of known viruses. The results of this test, if negative, would provide reassurance that the stored plasma unit did not contain certain infectious agents. This approach was approved in September 1998 by the Food and Drug Administration for units in which the donor is retested over a minimal period of 112 days. The costs and availability of plasma tested in this fashion are currently unknown.

#### Use of Red-Cell Substitutes

In recent years, there has been increasing interest in the development of red-cell substitutes.<sup>195</sup> Efforts have included the development of cell-free hemoglobin solutions that approximate the oxygen-carrying and oxygen-delivery capacity of cellular hemoglobin and the development of perfluorocarbon emulsions (as synthetic oxygen carriers). The hemoglobin solutions are polymerized or cross-linked (or both) to maximize the length of time in which they are in circulation and to minimize nephrotoxicity. The potential advantages of such products include a prolonged shelf life, the fact that they can be stored at room temperature, universal biocompatibility (since ABO-blood-group testing is not necessary), and the fact that such products are subjected to viral-inactivation procedures.<sup>196</sup> The disadvantages of such products include potential interference with the results of laboratory tests,<sup>197</sup> their relatively short time in circulation (24 to 48 hours), and the fact that perfluorocarbons require a forced inspiratory oxygen concentration of 100 percent to be effective.

The two principal uses of red-cell substitutes currently under clinical investigation are for patients with acute trauma and patients who are undergoing surgery, with or without acute normovolemic hemodilution. The rationale for the use of red-cell

substitutes with hemodilution is twofold: the cellular hemoglobin collected during hemodilution would be used to replace the hemoglobin solution or other synthetic oxygen carrier as it is eliminated, and the use of a red-cell substitute would permit more aggressive hemodilution with lower targeted cellular hemoglobin levels than would otherwise be tolerated. However, patients with preexisting anemia can be expected to derive only limited benefit from this approach, since there is less autologous cellular hemoglobin to begin with.<sup>198</sup> Moreover, studies of some hemoglobin solutions that have been administered to anesthetized surgical patients in clinically relevant doses have demonstrated that the ability of hemoglobin-based oxygen carriers to increase oxygen delivery is limited by their vasoactivity.<sup>199</sup> This vasoactivity is thought to be a direct effect of the free hemoglobin, since free hemoglobin has a different affinity for or proximity to nitric oxide than cellular hemoglobin.<sup>200</sup>

Several of these products are in various stages of clinical development. They would most likely be used in military and trauma settings; their role in other arenas will most likely be determined by issues related to blood inventory and costs, rather than the safety of the blood supply.

#### CONCLUSIONS

Increased attention to the costs of health care delivery has caused the relative benefits and costs of blood conservation to be scrutinized. The prospective identification of surgical candidates who will need transfusion and therefore will truly benefit from blood conservation must be based on patient-specific factors, such as the base-line hematocrit and the anticipated blood loss during surgery. The challenge for physicians will be to educate their patients that the decision to conserve blood should no longer be based on the safety of the blood supply, but on evidence that blood conservation is safe and of value for individual patients.

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