Update on Blood Transfusions

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Since the recognition of non-A, non-B hepatitis (HCV) as a major complication of blood transfusions, other infectious agents, such as HTLV-I (human T-cell leukemia/lymphoma virus type I) and CMV (cytomegalovirus) have appeared with the most devastating infection being cause by the human immunodeficiency syndrome (AIDS). The infectivity of homologous blood has caused a shift in emphasis from perfecting crossmatch procedures and preventing transfusion reactions to issues ranging from prevention of transfusion - transmitted disease and transfusion-induced immunosuppression to questioning whether many homologous blood transfusions are really clinically indicated. Data of 1996 indicate that the infectious risks from homologous blood have markedly decreased (Table 1)[1]. This is largely because of extensive testing of all donated blood (Table 2).[2] Although not yet quantified in a precise manner, improved testing (i.e. molecular testing and viral inactivation),[3] by using a test that identifies the nucleic acids of the virus, the window period (Table 1) is markedly decreased and the incidence of HIV and hepatitis reduced to approximately 1/1,000,000. Before reviewing the status of synthetic blood products, the states of various concepts in transfusion medicine will be examined.

Table 1: Percentage Risk of Transfusion-transmitted Infection with a Unit of Screened Blood in the United States

		Risk	Window Period (days)
1.	HIV	1/493,000	22
2.	HTLV	1/641,000	51
3.	Cytomegalovirus	<1.0%	rapidly
4.	HCV	1/103,000	82
5.	HBV	1/63,000	59
6.	Aggregate infection risk	1/34,000*	——

HIV = human immunodeficiency virus type 1
HTLV = human T-cell lymphotropic virus
HCV = hepatitis C virus
HBV = hepatitis B virus
* 88% of which is HBV & HCV

Table 2: Infectious Disease Testing for Blood Transfusions H

1. Discontinue serum alanine aminotransferase testing
2. Hepatitis C antibody testing
3. Antibody to hepatitis B core antigen
4. HIV-1*
5. HIV-2
6. HTLV I/II**
7. Serologic test for syphilis

H from JAMA 1995; 274: 1374
* HIV = human immunodeficiency virus
** HTLV = human T-cell lymphotropic virus

I. Indications for Blood Transfusion

The indications for blood transfusions are increasingly being questioned. Blood transfusions usually are given to increase oxygen carrying capacity and intravascular volume. Yet, on a theoretical basis, increasing vascular volume should not be an indication for blood transfusions, per se, since intravascular volume can be augmented with administration of fluids that do not transmit infections (e.g., crystalloids or some colloids). Therefore, increasing oxygen carrying capacity is the only real indication for blood transfusions. On the practical side, when a patient is hemorrhaging, blood appropriately is given to both increase oxygen carrying capacity and intravascular volume.

The critical questions is how to define that hematocrit (or hemoglobin) (i.e., oxygen carrying capacity) at which whole blood or packed red blood cells should be given. Historically, a hematocrit less than 30% (or hemoglobin less than 10 g/dl) indicated a need for perioperative blood transfusions. However, the fear, in recent years, of transfusion induced diseases, especially acquired immunodeficiency syndrome (AIDS), has caused a re-examination of this indication. Clearly oxygen transport may be sustained with a hematocrit as low as 20%. This assumes a normal intravascular volume and normal cardiovascular compensatory responses (e.g., tachycardia). Recently, a National Institutes of Health Consensus Conference [4] concluded that otherwise healthy patients with a hematocrit greater than

30% rarely require perioperative blood transfusion whereas those patients with acute anemia (e.g., intraoperative blood loss) of less than 21% frequently require blood transfusions. The ultimate definition of that hematocrit or hemoglobin at which blood should be given will have to be a clinical judgment based on many factors such as cardiovascular status, age, anticipated additional blood loss, arterial oxygenation, mixed venous oxygen tension, cardiac output, and blood volume. To complicate this issue even more, indications for blood transfusions also probably depend on the source of the blood. For example, indications for autologous blood may be more liberal because it should not transmit diseases (e.g., hepatitis and AIDS) as compared to homologous blood.[5] However, autologous blood should not be viewed as completely safe because the possibility of clinical error and subsequent hemolytic transfusion reaction.

In the July, 1989 FDA Drug Bulletin, stringent guidelines were given for red blood cell administration. That Bulletin states that "adequate oxygen-carrying capacity can be met by a hemoglobin of 7 g/dl or even less when the intravascular volume is adequate for perfusion." There are medical conditions that could justify giving blood to achieve a higher hemoglobin (e.g., coronary artery disease). Nevertheless, the general concern of many individuals in regulatory positions that blood is often given inappropriately will inevitably lead to more scrutiny of our transfusion practice. For example, many hospital transfusions committees are conducting audits in which patients who have postoperative hematocrits higher than a certain percentage (e.g., 33-34%) and have received blood will have the original indications for blood transfusion re-evaluated. This audit is done to determine if blood was given inappropriately. When a possible inappropriate transfusion is identified, both the clinician and the transfusions committee will further evaluate the appropriateness of the transfusion. This increased scrutiny dictates that anesthesiologists clearly state in the hospital record the reasons for giving a blood transfusion.

More recently, usually in intensive care patients, several groups have attempted to define the point at which blood transfusions should be given by measures of tissue oxygenation and hemodynamics (e.g., increase in oxygen consumption in response to added oxygen content). No specific measure could consistently predict when a patient would benefit from a blood transfusion.

Yet, there is suggestive evidence that the quality (e.g., age) and increased oxygen capacity (e.g., hemoglobin higher than 10 g/dl) may benefit very sick patients.[6] In fact one study found that when blood stored for more than 15 days was given, evidence of splanchnic ischemia occurred. More recently, this concept was confirmed by Purdy et al [7] who found that patients who received 17-day-old blood (range 5-35 days) versus 25-day-old blood (range 9-36 days) had a higher survival rate. The influence of age of blood infused will be discussed later in this presentation.

Perhaps the development of more sensitive indicators of tissue oxygenation (e.g., intramucosal pH) will provide indicators for transfusion.[6,7] Using outcome data in an orthopedic surgery population, variations in hemoglobin levels were unrelated to duration of hospitalization.[10] Yet, trained athlete and postoperative cardiac patients improve physical capabilities when hemoglobin levels were increased.[8] Conversely, Weiskopf et al [9] found, in healthy patients, that decreases in hemoglobin concentration to 5.0 g/dl did not produce any evidence of inadequate oxygenation. However, these patients were not subjected to the stresses of recovering from surgery and anesthesia. However, Weiskopf et al [9] found that these patients who have a more than expected heart rate or cannot increase their cardiac output should receive a transfusion to a higher hemoglobin level than 10 g/dl. Unfortunately, precise conclusions cannot be derived from these helpful, but suggestive data.

The American Society of Anesthesiologists (ASA) has developed Practice Guidelines for Blood Component Therapy .[11] Their recommendations for blood transfusions are:

Recommendations: RBC

The task force concludes that:

1. Transfusion is rarely indicated when the hemoglobin concentration is greater than 10 g/dL and is almost always indicated when it is less than 6 g/dL and is almost always indicated when it is less than 6 g/dL, especially when the anemia is acute.
2. The determination of whether intermediate hemoglobin concentrations (6-10 g/dL) justify or require RBC transfusion should be based on the patient's risk for complications of inadequate oxygenation.
3. The use of a single hemoglobin "trigger" for all patients and other approaches that fail to consider all important physiologic and surgical factors affecting oxygenation are not recommended.
4. When appropriate, preoperative autologous blood donation, intraoperative and postoperative blood recovery, acute normovolemic hemodilution, and measures to decrease blood loss (deliberate hypotension and pharmacologic agents) may be beneficial.
5. The indications for transfusion of autologous RBCs may be more liberal than for allogeneic RBCs because of the lower (but still significant) risks associated with the former.

These guidelines emphasize the need for assessment of patient risk for complications associated with inadequate oxygenation, a concept which has been emphasized more recently.[11a] Furthermore, some organizations are emphasizing using vital signs and blood loss as indicators:

American College of Surgeons Classes of Acute Hemorrhage

Factors	I	II	III	IV
Blood loss, *ml*	up to 750	750-1500	1500-2000	2000 or more
Blood loss, *%BV*	up to 15	15-30	30-40	40 or more
Pulse, *BPM*	>100	>100	>120	140 or higher
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure (mm Hg)	Normal/increased	Decreased	Decreased	Decreased
Capillary refill test	Normal	Positive	Positive	Positive
Respiration *per min*	14-20	20-30	30-40	>35
Urine output, *ml/hr*	30 or more	20-30	5-10	Negligible
CNS (mental status)	Slightly anxious	Mildly anxious	Anxious confused	Confused lethargic
Fluid replacement (3:1 rule)	Crystalloid	Crystalloid	Crystalloid + blood	Crystalloid +blood

Less complicated guidelines would be helpful. For example, with the help of Habibi et al (12), the following guidelines are recommended with the rule of thumb that administration of one unit of packed red cells will increase hematocrit by 3-5%. Indications are:

- Blood loss > 20% of blood volume when more than 1000 ml.
- Hemoglobin < 8 g/dL
- Hemoglobin < 10 g/dL with major disease (e.g., emphysema, ischemic heart disease)
- Hemoglobin < 10 g/dL with autologous blood
- Hemoglobin < 12 g/dL and ventilator dependent

Despite the intellectual appeal of these approaches, the ability to separate inadequate intravascular volume versus oxygen carrying capacity as the cause is very difficult. Therefore, this author would like to emphasize the need for a hemoglobin or hematocrit determination with this assessment. Also, in contrast to many blood bank recommendations, the Task Force recommended being more liberal with autologous versus allogeneic blood which makes sense based on their relative risk-benefit ratios.

II. Autologous Versus Allogeneic Blood

Surprisingly, there is increasing opinion that autologous blood is no safer than allogeneic blood (i.e., primarily based on infectious risks). Therefore, autologous blood programs may be eliminated.[13] An example of such a study is hysterectomy patients. Kanter et al [14] found that 25 out of 140 patients who donated blood received blood transfusions whereas one out of 123 patients who did not donate autologous blood was transfused. Therefore, they concluded that elimination of preoperative autologous blood donation does not increase risk of allogeneic blood transfusion. They further argue that autologous blood does have risks. One out of 16,000 autologous blood donations result in a reaction severe enough to require hospitalization.[15] In fact, some complications associated with autologous blood transfusion are listed below:

1. Anemia
2. Preoperative myocardial ischemia from anemia
3. Wrong unit (1:100,000)
4. More frequent blood transfusions

However, the relative value of autologous blood is based on the assumption that the risks of allogeneic blood has been properly assessed. The advocates for the elimination of autologous blood transfusion have not included immunosuppression (see discussion later) or outbreaks of other infections in allogeneic blood. For example, from 1986 to 1991, there were 182 transfusion-associated fatalities reported to the FDA, 29 (16%) of which were caused by bacterial contamination.[16] Since then, 10 cases of Yersinia enterocolitica have been reported. There are all with allogeneic blood although two patients also received autologous blood. This author concludes that allogeneic blood has sufficient risk to deem the consideration of eliminating the autologous program premature. Furthermore, the testing and screening of blood donors is by no means perfect.[17] Afterall, ask yourself the question, if given a choice would you want your own blood or allogeneic blood?

III. Coagulation

As is well known to anesthesiologists, a bleeding tendency often occurs in massively transfused patients. However, it is increasingly clear that dilution of coagulation factors represents only part of the total picture. This coagulopathy is caused by a combination of factors the most important of which are the volume of blood given and the duration of hypotension or hypoperfusion.[18-21] Patients who are well perfused and not hypotensive for a long period of time (e.g., > 1 hour) can tolerate many units of blood without developing a coagulopathy. In fact, many patients who have received more than 100 units of blood have survived with minor alterations in coagulation.[20,21] Clearly, the patient who is hypotensive and has received many units of blood

probably has a coagulopathy from both disseminated intravascular coagulation and dilution of coagulation factors from stored bank blood.

Dilutional thrombocytopenia is a cause of hemorrhagic diathesis in a patient who has received multiple units of blood. Although major emphasis has been placed on monitoring the platelet count, several authors have questioned the role of dilutional thrombocytopenia on the coagulopathy of a massively transfused patients. They correctly point out that the platelet count rarely decreases as low as what would be predicted from dilution alone. This is probably because platelets are released into the circulation from the spleen, bone marrow and because of the presence of nonfunctional platelets. Furthermore, Reed et al [21] found no benefit to prophylactic platelet administration during massive transfusions. Platelets should not be given to treat laboratory evidence of thrombocytopenia unless a clinical coagulopathy also is present.

Despite evidence to the contrary, fresh frozen plasma continued to be commonly given for treatment of transfusion induced coagulopathies. The overall increased use of fresh frozen plasma in the 1970s led the National Institutes of Health (NIH) to conduct a consensus conference on this issue in 1985.[22] This conference concluded that there was little or no scientific evidence for the administration of fresh frozen plasma as part of the therapy for a coagulopathy induced by multiple blood transfusions. Despite this NIH statement, component blood therapy, especially fresh frozen plasma, continues to be given. If the clinician insists on seriously considering giving fresh frozen plasma, continues to be given. If the clinician insists on seriously considering giving fresh frozen plasma, this author believes the following criteria should be established:

1. Generalized bleeding which cannot be controlled with surgical sutures or cautery.
2. A partial thromboplastin times at least 1.5 times normal.
3. A platelet count greater than 70,000/mm^3 (to insure that thrombocytopenia is not the cause of the blooding).

A recent (July 1989) FDA Drug Bulletin [22] has concluded that fresh frozen plasma should not be given:

1. For volume expansion, as a nutritional supplement
2. Prophylactically with massive blood transfusion
3. Prophylactically following cardiopulmonary bypass.

More recently, the ASA task force[11] recommends the administration of FFP with the following guidelines:

1. For urgent reversal of warfarin therapy.
2. For correction of known coagulation factor deficiencies for specific concentrates are unavailable.
3. For correction of microvascular bleeding in the presence of elevated (>1.5 times normal) PT or PIT.
4. For correction of microvascular bleeding secondary to coagulation factor deficiency in patients transfused with more than one blood volume and when PT and PIT cannot be obtained in a timely fashion.
5. FFP should be given in doses calculated to achieve a minimum of 30% of plasma factor concentration (usually achieved with administration of 10-15 mL/kg of FFP), except for urgent reversal of warfarin anticoagulation, for which 5-8 ml/kg of FFP usually will suffice. Four to five platelet concentrates, on unit of single donor aphersis platelets, or one unit of whole blood provide a quantity of coagulation factors similar to that contained in one unit of FFP (except for decreased, but still hemostatic, concentrations of factors V and VIII in whole blood).
6. FFP is contraindicated for augmentation of plasma volume or albumin concentration.

The above conclusions are based on the assumption that whole blood had been given. Most studies have examined the influence of massive transfusion of whole blood on coagulation because many trauma centers use whole blood. Yet, packed red blood cells are often given because whole blood may not be available. With much less plasma, dilution of certain coagulation values may be more profound with the use of packed red blood cells rather than whole blood. Murray et al.[23] specifically examined the question of using packed red blood cells for major blood loss. In general, the direction of coagulation changes were similar to those seen with whole blood with one major exception. With use of packed red blood cells, fibrinogen levels decreased significantly in contrast to use of whole blood when fibrinogen levels remain unchanged unless DIC is present. Although all the coagulation factors decreased, the decrease was not as much as expected from dilution. They felt that Factors, such as VIII, were probably stored in endothelial cells and released from the endothelium during surgical stress. When packed red blood cells are used to replace major blood loss, the clinician may be tempted to give fresh frozen plasma prophylactically. However, Murray et al.[23] specifically recommended not following this policy, but stated that fresh frozen plasma was only needed when the prothrombin time and partial thromboplastin time were at least 1.5 times normal and fibrinogen levels less than 75 mg/dL. These recommendations are similar to those stated above regarding the use of fresh frozen plasma with whole blood. More recent studies by Murray et. al.[24] indicate that when intravascular volume loss is replaced by packed red blood cells and crystalloid, prothrombin and partial thrombo-plastin times frequently exceed 1.5 time normal before thrombocytopenia results. Thus, in contrast to concepts previously described above, fresh frozen plasma would be given sooner than predicted. This finding places greater emphasis on laboratory analysis as the basis for fresh frozen plasma therapy.[25]

The infectivity of fresh frozen plasma will be decreased. Currently, three options are being considered by most blood banks:

A. Solvent-Detergent! Plasma from multiple donors is pooled and subjected to a lipid-destroying mixture of a solvent (tri-n-butyl phosphate) and a detergent (Triton X-100) to inactivate lipid enveloped infectious agents, including HIV, HTLV, HCV, HBV. It is currently (1998) available through the Red Cross. It has several disadvantages, including pooling which can lead to contamination of non-enveloped agents. Recalls can occur after any fraction of a lot has been released. It could be much more expensive.

B. Single-donor plasma, donor retested! A donation is made and FFP is prepared. The unit (the "first" donation) is kept if all history and infectious disease markers are negative. That unit is not released for use until the same donor donates a "second" unit >3 months after the "first" donation and again passes all donor intake and serologic testing. At that time, the "first" unit is released. The "second" unit is not released until the person returns >3 months later for a "third" donation and again passes all the testing. At that time, the "second" unit can be released for us. This approach has obvious advantages, but would be administratively complex.

C. Frequent-Donor Plasma! An inverse relationship exists between the number of donations a person has given and the chance they will become sero-positive. The relationship is independent of the time over which the donations were given. One appears to reach a maximum reduction of the incidence of sero-positivity at $\geq$ 4 donations. Predictions are that a reduction in sero-positivity (and therefore transmission) to 1/3 - 1/2 the current figures.

The above options were presented at the University of California San Francisco Transfusion Committee meeting and indicate that clinicians will have many options of safer plasma for patients.

IV. Immunosuppression

Homologous blood transfusion exerts a nonspecific immunosuppressive action on the recipient. This effect is therapeutic for kidney transplant recipients. However, many authors have presented data to indicate that blood transfusions increase susceptibility to infection[26] and enhance progression of malignant tumors.[27] Although many factors may be involved with seriously ill patients (e.g., patients who receive blood transfusions probably have more extensive and invasive disease), evidence is convincing that there is a relationship between perioperative transfusion and tumor recurrence or survival in patients with many types of cancer as reviewed by Schriemer et al.[28]

The mechanism of this effect on cancer is unknown, but has been related to increased synthesis of prostaglandin E,[29] decreased interleukin 2 generation,[31] and fibrinogen degradation products in fresh frozen plasma.[31] This later finding has led to some concern about giving fresh frozen plasma to immunosuppressed patients. Blumbert et al.[32] found that patients transfused with packed red blood cells had better survival than those patients receiving whole blood. As a result, Schriemer et al.[28] recommended that packed red blood cells should be given instead of whole blood when transfusions are indicated in patients with cancer. As with all aspects of transfusion medicine, careful evaluation of the indications for blood transfusions and emphasis on autologous blood transfusions is especially helpful in these patients.

More recently, Landers et. al.[33] have reviewed the mechanisms of transfusion-induced immunomodulation (Table 3) and the down-regulated immune functions following allogeneic or homologous blood transfusion (Table 4).

Table 3: Mechanisms of Transfusion-Induced Immunomodulation*

- Overload of R-E system with iron salts causing most of the changes
- Prostaglandin E_2 production by monocytes is increased which down-regulates macrophage class II antigen expression, inhibits interleukin-2 production
- Inhibition of interleukin-2 by T_H lymphocytes will decrease B-cell stimulation and antibody production
- Clonal Depletion Theory - remove or incapacitate cells that would reject graft
- Decrease suppresser T-lymphocyte production
- Anti-idiotypic production - T-cell receptors or antibodies generated against blood transfusion form new antigens that compete for binding locations on initial antibodies

* From Landers et.al. Anesth Analg 1996;82:187

Table 4: Down-Regulated Immune Functions Following Allogeneic Blood Transfusions*

- Reduced response in mixed lymphocyte culture
- Decreased cytokine production
- Decreased response to mitogens (substance that stimulates mitosis and lymphocyte transformation) or soluble antigens *in vivo* or *in vitro*
- Increased suppresser-cell number or function
- Decreased natural killer-cell activity
- Decreased monocyte function
- Decreased cell-mediated cytotoxicity against certain

target cells
- ! Enhanced production of soluble mediators and anti-idiotypic antibodies suppressive or mixed lymphocyte response

* From Landers et.al. Anesth Analg 1996;82:187 (33)

V. Component Therapy

A. Platelets

As indicated earlier, these is an increasing concern that homologous blood products may be given inappropriately. As with red blood cells and fresh frozen plasma, the July 1989 FDA Drug Bulletin has tried to provide specific guidelines and has stated that platelets should not be given:

1. To patients with immune thrombocytopenia purpura (unless there is life-threatening bleeding).
2. Prophylactically with massive blood transfusion.
3. Prophylactically following cardiopulmonary bypass.

The FDA does state that in a patient undergoing surgery or other invasive procedure is unlikely to benefit from prophylactic platelet transfusion if the platelet count is at least 50,000/mm_3 and thrombocytopenia is the sole abnormality.

More recently the ASA task force [11] recommends that:

1. Prophylactic platelet transfusion is ineffective and rarely indicated when thrombocytopenia is due to increased platelet destruction (e.g., idiopathic thrombocytopenic purpura).
2. Prophylactic platelet transfusion is rarely indicated in surgical patients with thrombocytopenia due to decreased platelet production when the platelet count is greater than 100 x 10^9/L and is usually indicated when the count is below 50 x 10^9/L. The determination of whether patients with intermediate platelet counts (50-100 x 10^9/L) require therapy should be based on the risk of bleeding.
3. Surgical and obstetric patients with microvascular bleeding usually require platelet transfusion if the platelet count is less than 50 x 10^9/L and rarely require therapy if it is greater than 100 x 10^9/L. With intermediate platelet counts (50-100 x 10^9/L), the determination should be based on the patient's risk for more significant bleeding.
4. Vaginal deliveries or operative procedures ordinarily associated with insignificant blood loss may be undertaken in patients with platelet counts less than 50 x 10^9/L.
5. Platelet transfusion may be indicated despite an apparently adequate platelet count if there is known platelet dysfunction and microvascular bleeding.

Platelet transfusions at higher platelet counts may be required for patients with systemic bleeding and for patients at higher risk of bleeding due to additional coagulation defects, sepsis, or platelet dysfunction related to medication or disease. Clearly, the intent is to make clinicians more precise in establishing the indications for platelet transfusions. Because of the increasing concern about bacterial contamination, it is now strongly recommended that any patient who becomes febrile after receiving platelet concentrates should be considered septic until proven otherwise. [3]

B. Cryoprecipitate

Cryoprecipitate contains Factor VIII:C (the procoagulant activity), Factor VIII:vWF (von Willebrand factor), fibrinogen, Factor XIII, and fibronectin, which is a glycoprotein that may play a role in reticuloendothelial clearance of foreign particles and bacteria from the blood.

With low fibrinogen levels being more common with packed red blood cells, the ASA task force (11) recommends considering the administration of cryoprecipitate for:

1. Prophylaxis in nonbleeding perioperative or peripartum patients with congenital fibrinogen deficiencies or von Willebrand's disease unresponsive to DDAVP (whenever possible, these decisions should be made in consultation with the patient's hematologist).
2. Bleeding patients with von Willebrand's disease.
3. Correction of microvascular bleeding in massively transfused patients with fibrinogen concentrations less than 80-100 mg/dL (or when fibrinogen concentrations cannot be measured in a timely fashion).

With the coagulopathies being more complicated with packed red blood cells, perhaps whole blood should be given when massive transfusion occurs.

Commercial concentrates of Factor VIII have been the standard therapy for hemophiliacs. Despite heat inactivation of Factor VIII concentrates, infectivity is reduced, but still present. Recently recombinant DNA techniques have been used to develop Factor VIII which is free of disease transmission.[34]

VI. Complications

Taking into account the above considerations, the incidence of adverse reactions are:

Adverse Reactions to Transfusion*

Type of reaction	*Incidence*
Febrile reactions	1% of PRBC transfusions
Allergic (urticarial) reactions	20% of PLT transfusions
Acute hemolytic transfusion reactions	1/1000 transfusions
Delayed hemolytic transfusion reactions	~ 1/33,000 U PRBCs
Graft *vs* host disease (GVHD)	~ 1/2,500 U PRBCs
Transfusion related acute lung	1/10,000 U PRBCs

injury (TRALI)

PRBC = packed red blood cells
BLT = platelet

* From Principles of Anesthetic Techniques and Anesthetic Emergencies

The increasing or ultimately required use of leukodepleted blood should decrease the chances of immunosuppression and the incidence of many transfusion reactions[3].

VII. Synthetic Blood

Because of many problems, including those listed above, with allogeneic, many companies are attempting to make synthetic hemoglobin. Most of these products are far enough along that they have been given to human volunteers and patients with modest success. These were summarized by Dietz et.al. in the February 1996 issue of *Anesthesia & Analgesia*.[35] Basically these products are:

1. Stroma-free hemoglobin solutions containing some modifications of the hemoglobin molecule.
2. Genetically-engineered hemoglobin (e.g., having E. coli produce human red cells).
3. Liposome-encapsulated hemoglobin solutions, containing hemoglobin with a synthetic membrane.
4. Perfluorocarbons, organic solutions with high oxygen solubility.

To prevent many of the complications, such as renal damage, endotoxin release, etc., various approaches have been used, such as cross-linking, polymerization, and conjugators have been used either with chemistry or genetic engineering as summarized below. With stroma-free hemoglobin, out-dated human cells strip the oxygen-carrying substance out of the cell coating and then chemically modifies it by one or more of the approaches above. By removing the cell lining, allergic reactions are prevented. The result of these efforts may result in us being able to give oxygen carrying substances with no more complications than currently exists for crystalloids (Table 5).

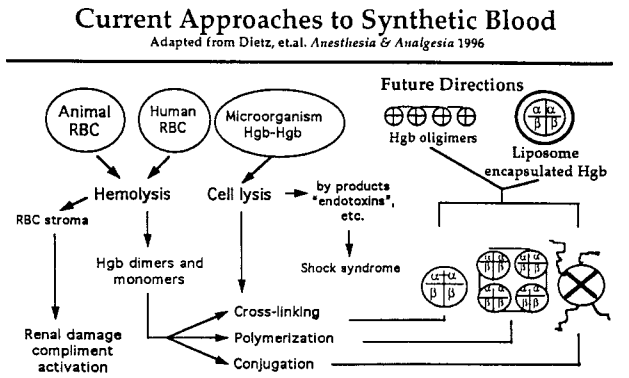
Table 5: RBC Substitutes

Activity (biological effect)	Efficacy (benefit to patient)
! O2 transport	! Decreased us of blood products
! Life support during severe anemia	! Decreased transfusion related morbidity & mortality
! Volume resuscitation	! use in logistically difficult environments

Originally, these products were viewed as blood substitutes. However, comparing safety is easy, but efficacy to that of bank blood is difficult. FDA criteria of efficacy are difficult to establish (36). Now more emphasis is on their ability to transport oxygen which will be discussed.[37]

Various Phase II and III studies [38] have been and are being conducted. So far, most products cause slight hypertension and increases in amylase and lipase concentrations the significance of which has yet to be determined.

Figure
("Current Approaches to Synthetic Blood" slide from Blood Lecture 1995 slides)



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