The ability to administer blood products is a critically important therapeutic modality in the care of patients with acute and chronic problems. When carried out with a thorough, up-to-date understanding of indications, risks, and benefits, blood transfusion is exceedingly safe and effective. Physicians encounter a large spectrum of medical and surgical conditions requiring transfusion therapy, including acute blood loss, catastrophic illness in the critical care setting, diseases associated with chronic anemia, and a variety of congenital and acquired bleeding disorders. The modern-day care of the critically ill requires a thorough knowledge of the pathophysiology of blood loss and anemia, as well as an understanding of normal hemostatic mechanisms and the sometimes complex disorders of coagulation encountered in these populations.

In this chapter, the basic concepts of acute blood loss are discussed, and the indications for and use of blood components, potential risks of blood products, and alternatives to blood transfusion are reviewed. Because blood products are a limited resource with potential serious adverse side effects, knowledge of appropriate indications, potential risks, and available alternatives should allow clinicians to exercise judgment in using this important resource. Based on the accumulating evidence, special emphasis will be placed on minimizing transfusion in the critical care setting.

### HISTORY OF BLOOD TRANSFUSION

The ability to transfuse blood safely and successfully is a relatively recent medical advance. Early historical references to the use of bloodletting and phlebotomy were common, and were applied to many diseases and disorders. It is possible that salutary effects were realized in some situations, such as congestive heart failure, but the vast majority of these applications were based on medical ignorance and likely resulted in harm to unsuspecting patients.

In February 1666 in Oxford, England, Richard Lower demonstrated what is thought to be the first known successful transfusion on an animal. The technical details were published in the Philosophical Transactions of the Royal Society within a year of the experiment. Another Englishman, Francis Porter, may have preceded him with transfusions to animals, and possibly to humans, some years prior (1,2). Jean-Baptiste Denis is credited with the first transfusion to a human in 1667 performed in France. Denis gave 3 pints of sheep blood to a patient without ill effects. A subsequent attempt to give blood to the same man “to mollify his fiery nature” led to the patient’s death shortly after the transfusion. A lawsuit resulted, and Denis went to trial but was ultimately exonerated. The Paris medical faculty then forbade blood transfusion, which led to bans on transfusion throughout Europe that lasted until modern times. An 1825 medical journal credited Dr. Philip Syng Physick of Philadelphia with blood transfusion to a patient, possibly the first record of successful transfusion of human blood (3). In 1828 in England, Blundell administered a small amount of human blood to a patient with postpartum hemorrhage, apparently small aliquots from himself, the husband, and another man (4). The patient reportedly felt better, but it is likely that the small-volume transfusion had little impact on her outcome. In fact, the patient was fortunate not to have suffered a serious transfusion reaction.

The routine, safe administration of blood products required several important scientific advances. The discovery of the A, B, and O blood types by Karl Landsteiner in 1900 and the AB blood type by Alfred Decastello and Adriano Sturli in 1902 began the era of modern blood transfusion. The first blood bank was established in 1932 in a Leningrad hospital. The first blood bank in the United States was established by Bernard Fantus in 1937 at Cook County Hospital in Chicago. By the 1940s, techniques of cross-matching, anticoagulation, and storage of blood, and the establishment of blood banks made routine blood transfusion a reality. The introduction of plastic storage containers in 1950 and the introduction of refrigerated centrifugation instruments in 1953 made component therapy possible (5).

### BLOOD PRODUCT COLLECTION AND ADMINISTRATION

Approximately 14 million units of red blood cells (RBCs) (packed RBCs and whole blood), 9.875 million units of platelets, and 4 million units of plasma are transfused annually in the United States (6,7). This represents an 11.8% increase since 1999 and a 56% increase since 1980 (8). The use of other components, especially platelets, has also increased. Because only about 5% of eligible donors ever donate blood, future increases may exacerbate shortages, especially as the U.S. population ages. Transfusion rates in the United States for 2001 have been estimated at 48.75 units of red cell transfusion per 1,000 population as compared to 44.93 units of red cell transfusion per 1,000 population in England, 28 units of red cell transfusion per 1,000 population in Australia, and 54.8 units of red cell transfusion per 1,000 population in Denmark (9).

As anemia in critical care illness is common, 25% to 37% of patients receive at least one blood transfusion during their intensive care unit (ICU) stay (10–12). In one study (10), 85%...
of patients with an ICU length of stay greater than 1 week re-
ceived at least one blood transfusion. Notably, blood transfu-
sion was not associated with acute blood loss in over two thirds of 
these cases. Phlebotomy and decreased production of blood 
cells have been implicated as significant contributors to anemia 
in the ICU. Since many studies have estimated daily blood loss 
from phlebotomy to be at least 40 mL/day (10,11,13), crit-
ical care practitioners should carefully consider the need for 
frequent blood draws in the ICU.

Collection and Preparation 
of Blood Products

Modern-day blood banks have adopted component therapy 
to optimize management of the blood supply. Blood is col-
lected from donors and is then separated into its individual 
components—packed RBCs, plasma, platelets, and proteins— 
to maximize the benefits of each donated unit while minimiz-
ing the risk to recipients of blood products. Blood is collected 
from donors into plastic bags containing a citrate solution that 
binds calcium, thus preventing coagulation. These solutions in-
clude citrate phosphate dextrose (CPD), citrate phosphate dou-
ble dextrose (CPDD), and citrate phosphate dextrose adenine 
(CPDA-1). Additional solutions are now available that extend 
the shelf life of packed RBCs, and contain dextrose, adenine, 
sodium chloride, and either phosphate (AS-3) or mannitol (AS-
1 and AS-5). After collection, each unit is gently centrifuged to 
pack the RBCs, leaving approximately 70% of the platelets 
suspended in plasma; the platelet-rich plasma is removed and 
centrifuged again to pack the platelets. All but a small 
amount of the resulting supernatant plasma is removed 
and rapidly frozen. The platelets are then reuspended, yielding 
a platelet concentrate. When the frozen plasma is stored at less 
than 18°C, it is referred to as fresh frozen plasma. If the frozen 
plasma is allowed to thaw at 4°C, the precipitate that remains 
can be collected to yield cryoprecipitate. Albumin and other 
proteins can then be extracted from the remaining plasma.

Another option for the collection of blood leukocytes, 
platelets, or plasma is through automated cell separators (apheresis). Blood is withdrawn from a donor and separated by 
centrifuge, and the desired component is removed. The remain-
ing blood is returned to the donor. Using this technique, many 
units of leukocytes or platelets can be quickly removed, allow-
ing blood banks to offer products such as single-donor platelet 
packs. The administration of a single-donor unit of platelets is 
advantageous since it exposes the recipient to only one person’s 
antigens, whereas an equivalent dose of pooled platelet trans-
fusion (“six pack” or “ten pack”) exposes the patient to six or 
ten sets of antigens, respectively, making subsequent platelet 
transfusion less effective since antibodies are formed against 
the wide array of foreign antigens. In addition, bacterial con-
tamination is less likely with single-donor apheresis platelets.

Storage Lesion

Storage and refrigeration create progressive changes in packed 
RBCs, known as the storage lesion (14). These changes include 
an increase in the concentration of potassium, phosphate, and 
ammonia; decrease in pH; altered affinity of hemoglobin for 

globin; changes in RBC deformability; hemolysis; develop-
ment of microaggregates; release of vasoactive substances; and 
denaturation of proteins. In addition, the life span of RBCs 
becomes shorter the longer cells are stored. This is associated 
with a decrease in both intracellular 2,3-diphosphoglycerate 
(2,3-DPG) and adenosine triphosphate (ATP). The transfusion 
of large volumes of cold blood contributes to the development 
of hypothermia, one of the most clinically significant effects of 
storage on subsequent transfusion. With the exception of hy-
pothemia, it is important to realize that many of these changes 
may be reversed shortly after transfusion, and may, in some 
cases, cause metabolic effects that are different from those pre-
dicted based on the above ex vivo observations. It is therefore 
critical not to empirically treat the theoretically anticipated ef-
fects of blood transfusions using “cookbook” approaches (such 
as giving one ampule of bicarbonate and one ampule of calcium 
with every “x” units of blood). Some of these treatments may, 
in fact, be harmful to the patient in hemorrhagic shock.

Administration of Blood Products

Transfusion based on sound physiologic principles and an un-
derstanding of relative risks and benefits should give maximal 
benefit to the patient, with efficient use of a valuable and finite 
resource. Utilizing data from recent studies, it is increasingly 
possible to base transfusion practice on scientific grounds. The 
most prominent example is the progressive abandonment of 
the “10/30” transfusion “trigger” for red cell transfusion in 
favor of lower transfusion triggers and, even more appropri-
ately, transfusion practice based on patient physiology (10,13). 
The 10/30 transfusion trigger for red cell transfusion likely re-
sulted from a recommendation in a 1942 publication that it 
was “wise” to maintain hemoglobin levels “between 8 and 10 
grams per cubic centimeter” for patients who were poor sur-
gical risks by giving a preoperative transfusion (16). No data 
were available to support this recommendation, but it stood 
relatively unchallenged for about 50 years. An expanding body 
of literature now suggests that arbitrary transfusion for a set 
transfusion trigger (e.g., the “10/30 rule”) is ill-advised, and 
that purported cardiac risks with anemia are overemphasized 
(17). The following transfusion guidelines are presented based 
on the best evidence currently available. Given the active ongo-
ing investigations in this area, it is likely that frequent updates 
will be forthcoming.

Whole Blood

There have been few widely accepted indications for whole 

blood in modern transfusion practice. Storage of whole blood 
precludes the extraction of components and, from a systems 
perspective, is highly inefficient. As such, whole blood is not 
available from most blood banks in the United States. In the-
ory, the goals of oxygen delivery and volume expansion can be 
achieved with packed RBCs and crystalloid solutions. Recent 
experience with the use of whole blood by the U.S. military (18) 
has rejuvenated the cause of whole blood. This accumulating 
experience, especially with fresh whole blood having poten-
tially beneficial effects on coagulopathy and hypothermia, may 
result in some modification of civilian practices in the future.

Red Blood Cells

Packed RBCs are the most commonly utilized blood product, 
providing oxygen-carrying capacity in cases of acute or chronic 


blood loss. The longest storage life currently allowed by the U.S. Food and Drug Administration (FDA) is 42 days. Longer storage times result in fewer than 75% of the RBCs remain-
ing viable in circulation 24 hours after transfusion. Platelets
degenerate at refrigerator temperatures, so refrigerated packed
RBCs contain essentially no functioning platelets. The levels of
factors V and VIII decrease significantly at 1°C to 6°C, while
levels of other factors remain essentially unchanged. There are
insignificant amounts of plasma in a unit of AS red cells.

packed RBCs provide oxygen-carrying capacity and main-
tain oxygen delivery provided that intravascular volume and
cardiac function are adequate. The decision to transfuse, and
the amount of packed RBCs transfused, depend on the clini-
cal situation. As noted previously, the use of a hemoglobin
of 30% (or a hemoglobin of 10 g/dL) as a transfusion trigger
is no longer acceptable. One or more units of blood may be
transfused with no predetermined number of units applicable.
Each unit of packed RBCs typically raises the hematocrit 2%
to 3% in a 70-kg adult, although this varies depending on
the donor, the recipient’s fluid status, the method of storage, and
its duration.

With blood loss, oxygen delivery is maintained through a
series of complex interactions and compensatory mechanisms.
This includes increased cardiac output, increased extraction ra-
tio, rightward shift of the oxyhemoglobin curve, and expansion
of volume. Many anemic patients tolerate hemoglobin levels of
7 to 9 g/dL or less, as has been demonstrated in chronic renal
failure and Jehovah’s Witnesses (17). In general, cardiac output
does not increase significantly until hemoglobin falls below ap-
proximately 7 g/dL. Young healthy patients tolerate acute ane-
mia to hemoglobin levels of 7 g/dL or less through increases
in cardiac output, provided they have a normal intravascular
volume and high arterial oxygen saturation.

In a multicenter, randomized controlled study of transfusion
in 838 patients in the critical care setting, a liberal transfu-
sion strategy (transfusion for hemoglobin <10 g/dL) was com-
pared with a restrictive strategy (transfusion for hemoglobin
<7 g/dL). The restrictive strategy was found to be at least as
effective as the liberal strategy, with the possible exception of
patients with acute myocardial infarction and unstable angina
(19). Suggested guidelines for RBC transfusion are listed in Ta-
ble 171.1.

Leukocyte-reduced Red Blood Cells

The transfusion of RBCs has been associated with immuno-
suppression. This effect is thought to be related to exposure
to leukocytes. Therefore, the use of leukocyte-reduced compo-
nents has been proposed as a means of minimizing immuno-
suppression; the majority of red cells and platelet transfusions
in the United States are currently leukocyte reduced. The ef-
ficacy of these preparations remains controversial, however,
and compelling data are lacking. Recent recommendations
for transfusion of leukocyte-reduced blood components are listed
in Table 171.2 (20).

Platelets

Platelet transfusions are indicated for patients who are at a sig-
nificant risk of bleeding because of quantitative or qualitative
platelet deficits. A unit of platelets can be prepared from indi-
vidual (or “random”) donors or by apheresis, whereby a donor
provides the equivalent of 6 to 10 single “random” donor units.
In selected cases, human leukocyte antigen (HLA)-matched
platelets can be obtained by apheresis from HLA-matched
donors. The efficacy of platelet transfusion may be assessed
both by clinical parameters (improved hemostasis) and by fol-
lowing the platelet counts at 1 hour and 24 hours as an estimate
of platelet survival. The platelet count at 1 hour post transfu-
sion of a unit of platelets should increase by 5,000 to 10,000
platelets/μL. Less pronounced responses should be expected
with repeated transfusion and the development of alloimmunu-
nization, or in the presence of fever, sepsis, or splenomegaly. If
alloimmunization is thought to be the cause of a poor response,
platelets from an HLA-matched donor may be needed.

The prophylactic transfusion of platelets in the absence of
microvascular bleeding, a low platelet count in a patient under-
going a surgical procedure, or a platelet count that has fallen
below 10,000 platelets/μL, in most medical patients, should
be considered inappropriate. Disease state-specific triggers for
platelet transfusion have been proposed and are listed in Table
171.3 (21). It is crucial to recognize that hypothermia depresses
platelet function, and platelet transfusion is generally ineffec-
tive with depressed temperatures. Restoration of a normal tem-
perature returns platelet function to normal and ameliorates
microvascular bleeding.

PLASMA

Plasma is used as a source of clotting factors in patients with
coagulopathy and documented factor deficiency. This may oc-
cur with liver dysfunction, congenital absence of factors, and
transfusion of factor-deficient blood products, or after the use
of warfarin. A unit of plasma contains near-normal levels of all
factors, including about 400 mg of fibrinogen, and generally

<table>
<thead>
<tr>
<th>TABLE 171.1</th>
<th>GUIDELINES FOR TRANSFUSION OF PACKED RED BLOOD CELLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing bleeding with hemodynamic instability unresponsive (or incompletely responsive) to infusion of 2,000 to 3,000 ml crystallloid</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin &lt;7 g/dL</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE 171.2</th>
<th>INDICATIONS FOR TRANSFUSION OF LEUKOCYTE-REDUCED BLOOD COMPONENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>To decrease the incidence of subsequent refractoriness to platelet transfusion caused by human leukocyte antigen (HLA) alloimmunization in patients requiring long-term platelet support</td>
<td></td>
</tr>
<tr>
<td>To provide blood components with reduced risk for cytomegalovirus transmission</td>
<td></td>
</tr>
<tr>
<td>To prevent future febrile nonhemolytic transfusion reactions (FNHTRs) in patients who have had a documented FNHTR</td>
<td></td>
</tr>
<tr>
<td>To decrease the incidence of HLA alloimmunization in nonhepatic solid-organ transplant candidates</td>
<td></td>
</tr>
</tbody>
</table>

about 200 mg of fibrinogen. These relatively high concentrations are usually administered as a transfusion of 10 single units.

Indications for the use of cryoprecipitate include factor deficiencies (hemophilia A), von Willebrand disease, and hypofibrinogenemia (Table 171.4). Some patients with uremic bleeding increases factor levels by about 3%. Adequate clotting can usually be achieved with factor levels greater than 30%, although higher levels are advisable in patients undergoing operative or invasive procedures. The prothrombin time (PT) and the activated partial thromboplastin time (aPTT) can be used to assess patients for plasma transfusion and to follow the efficacy of administered plasma. Recent experience suggests that the use of thromboelastography may provide advantages over the PT as a guide for the treatment of coagulopathy (22,23). Plasma can be frozen and stored for up to 1 year.

Plasma should not be given routinely or prophylactically by “cookbook” formula after RBC transfusion—for example, 2 units of plasma for every 5 units of packed RBCs—or “prophylactically” after cardiac bypass or other procedures. Plasma should not be used as a volume expander since crystalloids are cheaper, safer, and at least as effective. Broadly accepted guidelines for transfusion of plasma are listed in Table 171.4 (24).

Cryoprecipitate

Indications for the use of cryoprecipitate include factor deficiency (hemophilia A), von Willebrand disease, and hypofibrinogenemia (Table 171.5). Some patients with uremic bleeding may also benefit from cryoprecipitate transfusion. Cryoprecipitate is usually administered as a transfusion of 10 single units. Each 5- to 15-mL unit contains over 80 units of factor VIII and about 200 mg of fibrinogen. These relatively high concentrations allow the use of a smaller volume of cryoprecipitate than would be required if plasma were administered.

Risks of Blood Transfusion

Even though a blood transfusion is a potentially life-saving intervention, significant risks are still involved in the administration of these products. Risks range from minor febrile transfusion reactions to the transmission of viral infection to a potentially fatal transfusion of incompatible blood (Table 171.6). Blood banks in the United States generally conduct over ten individual tests or checks on donated units of blood in addition to the screening interview. Most (nine) are for infectious diseases. Screening of donors and the introduction of increasingly effective tests for hepatitis and human immunodeficiency virus (HIV) have reduced the transmission of viral infections by about 90%.

| TABLE 171.3 |
| Indications for Transfusion of Platelets |
| ■ Disseminated intravascular coagulation: 20,000–50,000 platelets/μL |
| ■ Major surgery in leukemia: 50,000 platelets/μL |
| ■ Thrombocytopenia with massive transfusion: 50,000 platelets/μL |
| ■ Invasive procedures in cirrhosis: 50,000 platelets/μL |
| ■ Cardiopulmonary bypass: 50,000–40,000 platelets/μL |
| ■ Liver biopsy: 50,000–100,000 platelets/μL |
| ■ Neurosurgical procedures: 100,000 platelets/μL |

| TABLE 171.4 |
| Indications for Transfusion of Plasma |
| ■ International normalized ratio (INR) > 1.5 with an anticipated invasive procedure or surgery |
| ■ Massive hemorrhage (over one blood volume) with an INR > 1.5 |
| ■ Treatment of thrombotic thrombocytopenia purpura |
| ■ Inherited coagulopathies where a specific factor concentrate is not available |
| ■ Emergent reversal of antiocoagulant therapy |

| TABLE 171.5 |
| Indications for Transfusion of Cryoprecipitate |
| ■ Hemophilia A |
| ■ von Willebrand disease |
| ■ Hypofibrinogenemia |
| ■ Uremic bleeding |
| ■ As substrate for plasma if lower volume is desired |

| TABLE 171.6 |
| Risks of Blood Transfusion |
| ■ Transfusion-related acute lung injury |
| ■ Bacterial contamination of blood products |
| ■ Administrative error leading to transfusion of ABO-incompatible blood |
| ■ Viral infection transmission |
| □ Hepatitis B |
| □ Hepatitis C |
| □ Human immunodeficiency virus 1 and 2 |
| □ Human T-cell leukemia virus 1 and 2 |
| □ Epstein-Barr virus |
| □ Cytomegalovirus |
| □ Parovirus B19 |
| □ Human herpesvirus 8 |
| □ Transfusion-transmitted virus |
| □ Mad cow disease (bovine spongiform encephalopathy) |
| □ West Nile virus |
| ■ Bacterial/pseudomonal infection transmission |
| □ Syphilis |
| □ Malaria |
| □ Babesia microti |
| □ Trypanosoma cruzi |
| □ Yersinia enterocolitica |
| □ Serratia marcescens |
| □ Staphylococcus aureus |
| □ Staphylococcus epidermidis |
| □ Klebsiella pneumoniae |
| □ Trypanosoma cruzi |
| ■ Transfusion reactions |
| □ Acute |
| □ Delayed |
| □ Immunosuppression |
virus (HIV) have dramatically reduced the risks of transmission of these infections. The public has historically been most concerned about the transmission of HIV; however, recent data reveal that the leading causes of fatalities after blood transfusion continue to be administrative error, leading to transfusion of ABO-incompatible blood, bacterial contamination, and transfusion-related acute lung injury (TRALI). Overall, infectious risks of blood transfusion are far outweighed by non-infectious risks (Fig. 171.1). According to the FDA, TRALI was the leading cause of transfusion-related mortality in 2003 (24). An average of 11.7 deaths from bacterial sepsis per year in the United States was reported to the FDA from 2001 to 2003. This decreased to 7.3 deaths per year in 2004 and 2005, due at least in part to the mandating of bacterial screening of platelets, which began in 2004 (24,25). Transfusion of blood to the wrong person continues to be a serious threat to patients. In a review of a 10-year experience in New York State, Linden et al. estimated the risk of an ABO-incompatible transfusion at 1 in 38,000 units of red cells, with the risk of a fatal reaction at 1 in 1.8 million transfusions (26). A rate of ABO-incompatible transfusion of 1 in 12,000 units of red cells transfused has been reported from the hemovigilance program in Quebec, Canada (27).

Transfusion Reactions

The classification of the American Association of Blood Banks for transfusion reactions is shown in Table 171.8. Hemolytic transfusion reactions can be categorized broadly into acute (<24 hours) and delayed (>24 hours) reactions. Hemolytic

### TABLE 171.7

INFORMATION FOR PATIENTS: COMMONLY ASKED QUESTIONS ABOUT BLOOD TRANSFUSION

<table>
<thead>
<tr>
<th>Complication</th>
<th>Risk from blood product transfusion</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile nonhemolytic transfusion reactions</td>
<td>Occurs in 0.5%–38% of all transfusions</td>
<td>Usually mild fever only. More common with platelet transfusions.</td>
</tr>
<tr>
<td>Severe acute hemolytic reaction</td>
<td>Fatal in 1 of 600,000 transfusions</td>
<td>Stop transfusion immediately and initiate supportive measures.</td>
</tr>
<tr>
<td>Delayed hemolytic reaction</td>
<td>1 in 260,000 transfusions</td>
<td>Suspect when unexplained fever, fall in hematocrit, or jaundice occur.</td>
</tr>
<tr>
<td>Bacterial contamination</td>
<td>1 in 15,000 platelet transfusions</td>
<td>Among leading causes of transfusion-related fatalities.</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Of concern in low-birth-weight infants and immunocompromised patients (e.g., transplant)</td>
<td>Between 50% and 85% of adults in the United States are carriers.</td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td>&lt;1 in 137,000</td>
<td>25% of carriers have active hepatitis and may progress to cirrhosis.</td>
</tr>
<tr>
<td>Hepatitis C virus</td>
<td>&lt;1 in 1 million</td>
<td>Most infected persons asymptomatic, but 80% become chronic.</td>
</tr>
<tr>
<td>Human immunodeficiency virus</td>
<td>&lt;1 in 1.9 million</td>
<td>Potentially fatal. Rarely found in U.S. blood donors.</td>
</tr>
<tr>
<td>Human T-cell leukemia virus 1 and 2</td>
<td>Very small</td>
<td>80% of those infected remain asymptomatic.</td>
</tr>
<tr>
<td>West Nile virus</td>
<td>Very small when donors are properly screened.</td>
<td>20% develop mild symptoms, and 1 in 150–200 infected people develop severe disease that may be fatal.</td>
</tr>
<tr>
<td>Transfusion-related lung injury</td>
<td>1 in 5,000 units (estimated)</td>
<td>5%–10% fatal.</td>
</tr>
</tbody>
</table>


BASIC INFORMATION...

YOUR PHYSICIAN FEELS THAT YOU MAY NEED A TRANSFUSION OF A BLOOD PRODUCT...

Please realize you will be given blood or blood products only if necessary. This brochure has been offered to help you understand the benefits, risks of, and alternatives to a blood transfusion and is not inclusive of all information. Your physician is the best source for additional information related to blood transfusions.

**Blood products could include:**
- Red blood cells (known as “blood”)
- Platelets
- Fresh frozen plasma (known as “plasma”)
- Cryoprecipitate (a specific part of plasma)

**Blood products are prepared from carefully screened, healthy, human volunteers.**

Any treatment in medicine involves weighing the benefits and risks for each particular patient. In your case, your physician has recommended the benefits and risks for each particular patient. However, you need to understand the potential complications that you receive a blood product. However, you need to understand the potential complications of transfusions, and also the consequences of NOT receiving that blood product.

**RISKS OF BLOOD PRODUCT TRANSFUSION...**

All blood products have a minimal risk of transmitting an infectious disease.

All blood products are tested for transfusion-transmitted diseases according to federal regulations. Yes, some risks remain present; no screen can be 100% effective. Viruses are not commonly transmitted but may cause serious diseases.

March 2004 estimates from the American Association of Blood Banks show that the risk of getting:

- HIV is <1 in 3.8 million transfused units
- Hepatitis C is <1 in million transfused units
- Hepatitis B is <1 in 137,000 transfused units

Other risks include, but are not limited to:

- **Fever and/or chills**
  - Temperature elevation ≥1°C, chills and/or rigor, headache, vomiting

- **Hemolytic**
  - Chills, fever, hypotension, renal failure, back pain, hemoglobinuria

- **Urticarial**
  - Urticaria, urticaria, bronchospasm, respiratory distress, wheezing, local edema, anxiety

- **Anaphylactic**
  - Hypotension, urticaria, bronchospasm, respiratory distress, wheezing, local edema, anxiety

- **Transfusion-associated acute lung injury**
  - Hypoxemia, respiratory failure, hypotension, fever

- **Nonhemorrhagic**
  - Flushing, hypotension

- **Hypotension (associated with angiotensin-converting enzyme inhibition)**
  - Droppea, orthopnea, cough, tachycardia, hypertension, headache

- **Circulatory overload**
  - Fluid overload, cardiac output, congestion, pulmonary edema

- **Nonimmune hemolysis**
  - Hemoglobinuria, headache

- **Air embolus**
  - Sudden dyspnea, cyanosis, chest pain, cough, hypotension, cardiac arrhythmia

- **Hypocalemia**
  - Paresthesia, tetany, arrhythmia

- **Hypothermia**
  - Cardiac arrhythmia

- **Transfusion-associated sepsis**
  - Bacterial contamination of transfused blood

**Transfusion reactions, which are unpredictable, may occur.** Their symptoms vary,

- Some reactions may present as fever and chills.
- Some reactions are mild immunologic reactions that manifest 10–14 days after red-cell transfusion and may shorten the life of the transfused red cells.
- Allergic reactions may be caused by plasma proteins and typically cause itching and hives. Some reactions may be serious.
- Severe reactions are extremely rare but may include life-threatening disorders such as shortness of breath or hemolysis (destruction of the transfused red cells). They can in turn cause jaundice or kidney problems.

**BENEFITS OF BLOOD PRODUCT TRANSFUSION...**

Blood may be transfused to treat anemia or acute blood loss.

- Anemia: A deficiency in the oxygen-carrying material of the blood, also known as low blood count or low blood level.
- **Symptoms** that might improve after blood transfusion include weakness, shortness of breath, chest pain, or light-headedness.
- **Conditions** that may be prevented with appropriate use of blood include strokes, heart attacks, kidney failure, and other serious problems, including death.
- **Platelets, plasma, or cryoprecipitate may be prescribed for the prevention or treatment of bleeding problems.**

**TABLE 17.1.8**

<table>
<thead>
<tr>
<th>Type</th>
<th>Clinical features</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infectious</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemolytic</td>
<td>Chills, fever, hypotension, renal failure, back pain, hemoglobinuria</td>
<td>Caused by red blood cell mismatch</td>
</tr>
<tr>
<td>Fever and/or chills, nonhemolytic</td>
<td>Temperature elevation ≥1°C, chills and/or rigors, headache, vomiting</td>
<td></td>
</tr>
<tr>
<td>Urticarial</td>
<td>Urticaria, urticaria, bronchospasm, respiratory distress, wheezing, local edema, anxiety</td>
<td>Varies from isolated urticaria to fatal anaphylaxis</td>
</tr>
<tr>
<td>Anaphylactic</td>
<td>Hypotension, urticaria, bronchospasm, respiratory distress, wheezing, local edema, anxiety</td>
<td>Leading cause of transfusion-associated mortality</td>
</tr>
<tr>
<td>Transfusion-associated acute lung injury</td>
<td>Hypoxemia, respiratory failure, hypotension, fever</td>
<td></td>
</tr>
<tr>
<td>Nonhemorrhagic</td>
<td>Flushing, hypotension</td>
<td></td>
</tr>
<tr>
<td>Hypotension (associated with angiotensin-converting enzyme inhibition)</td>
<td>Droppea, orthopnea, cough, tachycardia, hypertension, headache</td>
<td></td>
</tr>
<tr>
<td>Circulatory overload</td>
<td>Fluid overload, cardiac output, congestion, pulmonary edema</td>
<td></td>
</tr>
<tr>
<td>Nonimmune hemolysis</td>
<td>Hemoglobinuria, headache</td>
<td>Caused by physical destruction of blood (heating, freezing, etc.)</td>
</tr>
<tr>
<td>Air embolus</td>
<td>Sudden dyspnea, cyanosis, chest pain, cough, hypotension, cardiac arrhythmia</td>
<td></td>
</tr>
<tr>
<td>Hypocalemia</td>
<td>Paresthesia, tetany, arrhythmia</td>
<td></td>
</tr>
<tr>
<td>Hypothermia</td>
<td>Cardiac arrhythm</td>
<td></td>
</tr>
<tr>
<td>Transfusion-associated sepsis</td>
<td>Bacterial contamination of transfused blood</td>
<td>Consider in patients with fever &gt;40°C and/or cardiovascular collapse</td>
</tr>
</tbody>
</table>
transplant patients during their anhepatic phase in the operation is compromised and/or they are hypothermic (e.g., liver large volumes of citrated blood, especially if their liver function is compromised and/or they are hypothermic. The "prophylactic" use of calcium follow-

When a hemolytic or anaphylactic transfusion reaction is suspected, the infusion should be stopped immediately and the unit checked against the recipient's identification band to de-
termine whether the wrong unit has been administered to the patient. The unit, including all intravenous solutions and tub-
ing, should be sent promptly to the blood bank for examina-
tion. Blood should be drawn from a remote site and tested for free hemoglobin. The urine should also be tested for free hemoglobin. A direct antiglobulin test is indicated. Aggressive fluid resuscitation should be initiated, and urine output should be monitored at high levels. The early development of hy-

Delayed hemolytic reactions tend to present 5 to 10 days after transfusion (28), with approximately 1 in 200,000 pa-
tients developing a significant hemolytic reaction (30). The de-
gree of hemolysis may be significant in the patient whose total RBC mass has been replaced by massive transfusion. A trans-

Allergic nonhemolytic reactions are generally believed to be caused by recipient antibodies to infusing donor plasma pro-
teins. The manifestations vary from a slight rash or urticaria to hemodynamic instability, with bronchospasms and anaphy-
laxis. Allergic reactions may be prevented by pretreatment with antihistamines (e.g., diphenhydramine). Recipient anti-
bodies against antigens on donor leukocytes or platelets will prime and activate the recipient's neutrophils, with resultant nonhemolytic reactions. Reactions occur when destruction of transfused RBCs occurs because of preformed antibodies, and is mediated by com-

The acute onset of pulmonary edema associated with transfu-
sion should also be given a diuretic.

Transfusion-related Acute Lung Injury

The acute onset of pulmonary edema associated with transfu-
sion and leading to death was first described in 1951 by Barnard (31). The term, TRALI, was introduced by Popovsky in 1983 (32). It is currently the leading cause of death after transfusion, with an estimated rate of 1 in 5,000 units transfused, although higher rates have been reported (33). TRALI is associated with an acute lung injury is likely underappreciated and underdiagnosed due to other more commonly recognized conditions (such as acute lung injury [ALI] and the acute respiratory distress syn-
drome [ARDS]) being often associated with blood transfu-
sion, making the diagnosis of TRALI more difficult. The mor-
tality rate associated with TRALI is in the range of 5% to 10% (34). These data suggest that all patients receiving blood products should be appropriately monitored, including pulse oximetry.

Transfusion-related acute lung injury occurs with the trans-

Hypocalcemia rarely occurs in patients receiving 1 unit of blood at a time. The "prophylactic" use of calcium follow-

Numerous viral and bacterial diseases may be transmitted by blood transfusion (Table 171.6). Since March 1999, pooled
nucleic acid amplification testing (NAT) has been used to test for HIV and hepatitis C virus (HCV), which involves pooling of 16 to 24 individual blood samples and polymerase chain reaction or other amplification techniques to test for HIV and HCV nucleic sequences. Bacterial and protozoal diseases include syphilis, malaria, and infection with *Babesia microti*, *Trypanosoma cruzi*, *Yersinia enterocolitica*, *Serratia marcescens*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, or *Klebsiella pneumoniae*. *Trypanosoma cruzi* causes Chagas disease, but transmission of this infection is very rare in the United States.

**Bacterial Contamination**

Bacterial contamination of blood is the most frequent cause of transfusion-transmitted infectious disease (35). After hemolytic reactions and TRALI, bacterial contamination is the most frequently reported cause of transfusion-related fatalities to the FDA (36). The agents most often implicated in packed RBC bacteremia were *Serratia* and *Yersinia*. For platelets, *S. aureus*, *Escherichia coli*, *Enterobacter*, and *Serratia* species were more frequently identified. Fever, chills, hypotension, tachycardia, and shock after transfusion should raise the suspicion of bacterial contamination, and blood cultures of the patient and unit should be obtained. Platelets, which are stored at 20°C to 24°C, are a good growth medium for bacteria. Platelets are now screened for bacterial contamination in the United States.

**Hepatitis**

Transmission of the infectious agents for hepatitis is among the most serious risks of blood transfusion. Past estimates of posttransfusion hepatitis were approximately 10%. Current data suggest that the incidence of hepatitis B virus (HBV), with tests for HBsAg and anti-Hbc, is <0.01% per unit transfused (30). All blood is screened for the hepatitis B virus (HBV), with tests for HBsAg and anti-Hbc. In addition, blood is screened for HCV with anti-HCV testing. The risk of transfusion-associated HBV infection is approximately 1 in 30,000 to 1 in 250,000 per unit. With the development of pooled NAT tests for HCV, the window period has decreased, and the risk of HCV transmission is now as low as 1 in 1 million (37). No new case of transfusion-associated HCV infection has been detected by the Centers for Disease Control and Prevention Sentinel Counties Viral Hepatitis Surveillance System since 1994 in the United States.

Approximately half of the blood recipients who contract HBV infection develop symptoms; a much smaller percentage requires hospitalization. Approximately half of patients who contract posttransfusion HCV infection develop a chronic form of the disease. Many of those patients eventually develop significant liver dysfunction, including cirrhosis.

**Human Immunodeficiency Virus**

The risk of HIV transmission from blood transfusion has decreased dramatically since the early 1980s despite an increasing incidence of HIV infection in the general population. The window period from initial infection to the development of antibody to the virus poses a problem with the ability to detect all seropositive donors. With pooled NAT, the window period for detection of HIV has been reduced by 30% to 50%, and the risk of HIV transmission is estimated to be as low as 1 in 2 million units (37).

**Human T-cell Leukemia Virus**

In addition to the transmission of cytomegalovirus (CMV), hepatitis infection, and HIV, blood transfusion carries the risk of transmission of human T-cell leukemia virus (HTLV) 1 and 2 infection. Transmission of the virus, especially to immunocompromised patients, may cause illnesses such as T-cell leukemia, spastic paraparesis, and myelopathy, and has prompted routine screening of donors in the United States since 1989. The risk of HTLV 1 and 2 transmission is estimated to be 1 in 641,000 units.

**Herpesviruses**

CMV infection is endemic, so routine screening is not performed in the United States. About 20% of blood donors are infected with CMV by 20 years of age, and approximately 70% are infected by 70 years of age. The infection is carried in white blood cells (WBCs). Most patients who encounter problems with CMV are immunocompromised, especially transplant recipients on immunosuppressive drugs. Such patients require transfusion with CMV-reduced risk—leukocyte-reduced or seronegative—blood products to avoid the transmission of this viral infection. Human herpesvirus 8 causes Kaposi sarcoma and lymphoma in patients with acquired immunodeficiency syndrome (AIDS) and other immunosuppressed states.

**Graft Versus Host Reaction**

Blood transfusion exposes the recipient to many cells and proteins from the donor. When immunologically competent lymphocytes are introduced into an immunocompromised patient, a graft versus host reaction can occur (28). The functional donor lymphocytes attack recipient tissues, notably the bone marrow, causing aplasia. Patients present with fever, rash, nausea, vomiting, diarrhea, liver function test abnormalities, and depressed cell counts. This complication is fatal in as many as 90% of the cases. The prevalence of this complication in the United States is not known but is thought to be rare. Rare cases have also been reported from familial directed donations and with HLA-matched platelets. γ-Irradiation of blood products eliminates this risk.

**Immunomodulation**

Allogeneic blood transfusion may alter the immune response in individuals and susceptibility to infection, tumor recurrence, and reactivation of latent viruses. It has been known since 1974 that the transfusion of packed RBCs depresses the immune response in patients undergoing renal transplantation; however, it is unclear to what extent these immunosuppressive effects exist in other recipients. Contradictory evidence exists concerning increased infections in patients given allogeneic blood transfusions. Similar controversy also exists regarding the exact relationship of blood transfusions to increased recurrence of tumor and poor prognosis. Early studies on colorectal cancer showed decreased survival and increased tumor recurrence in patients who were heavily transfused. Since then, studies on many tumors have been performed that have not yielded a decisive answer. The possibility exists that blood transfusion may represent a covariable, because very ill patients and those undergoing more difficult procedures for more extensive disease are more likely to receive blood transfusion. In light of the immunomodulating effects of allogeneic blood transfusion, leukocyte-depleted transfusions have been suggested as an
alternative. In view of the data on immunosuppression from blood transfusion, it would seem reasonable to adopt a policy of blood conservation in the perioperative period in the absence of clear indications and acute symptoms. Leukocyte reduction of blood products is thought to decrease the risk of immunomodulation (38).

**Decision Making in Blood Transfusion**

**Blood Transfusion in Hemorrhagic Shock**

During World War I, it was believed that toxins caused vascular collapse in injured patients (39). Experiments in the 1930s by Dallas B. Phemister and Alfred Blalock showed that fluid was lost from the circulation into damaged tissues; the concept of fluid loss into a “third space.” During World War II, plasma was the resuscitation solution of choice, as blood was rarely available. British forces in the North African campaign did utilize blood for casualties and noted improved outcome. Although solutions containing electrolytes were used for children with diarrhea, and advances in research had increased the understanding of metabolic and endocrine changes seen with injury, the use of plasma solutions prevailed until the Korean conflict. Subsequent experimental work indicated that extracellular fluids shifted into the intracellular space after significant hemorrhage with shock (40). Providing volume resuscitation in excess of shed blood became standard practice to maintain adequate circulation and to refill the “third space.”

During World War II, acute tubular necrosis (ATN) was a common consequence of hypovolemic shock. As fluid resuscitation became more prevalent during the Korean and Vietnam conflicts, the incidence of ATN decreased. Yet, posthemorrhagic shock ATN became less common with better fluid resuscitation, the acute—initially termed the adult, to differentiate it from the neonatal syndrome—respiratory distress syndrome became increasingly common. The lung injury in ARDS was shown to be a function of the shock state rather than the resuscitation solution used.

The goal of resuscitation from shock is prompt restoration of adequate tissue and end-organ perfusion and oxygen transport. The American College of Surgeons Committee on Trauma developed a classification of hemorrhagic shock that permits useful guidelines for resuscitation (Table 171.9). Crystalloid is infused at a 3:1 ratio for every unit of RBCs administered, and therapy is monitored primarily by hemodynamic response. Because crystalloid solutions are ubiquitously available, and some delay is required to prepare blood products, crystalloid is the proper initial resuscitation fluid. Resuscitation proceeds with the use of blood products, depending on the patient’s response.

Although controversy existed in the past regarding the choice of a colloid solution (e.g., albumin, plasma) or a crystalloid solution (e.g., lactated Ringer [LR] solution or saline), recent evidence has confirmed that colloid solutions offer no advantages over crystalloids for fluid resuscitation in critically ill patients (41). Crystalloid solutions should be considered the solutions of choice because they are less expensive, need not be cross-matched, do not transmit disease, and probably result in less fluid accumulation in the lung. No experimental data indicate that using colloids rather than crystalloid solutions can prevent pulmonary edema. An updated review of randomized controlled trials of albumin resuscitation yielded no suggestion of a reduction in mortality when the colloid was used in hypovolemia or in critically ill patients with burns and hypoalbuminemia (42).

Several crystalloid solutions are available for resuscitation, but isotonic solutions should be used to avoid free water overload. While lactated Ringer solution is recommended as initial therapy, metabolic alkalosis is common after subsequent resuscitation with this solution and blood products because the lactate in LR solution and the citrate in banked blood are both converted to bicarbonate in the liver. LR solution contains calcium and, if it is mixed with a blood product, the blood may, in theory, clot in the bag. Normal (0.9%) saline solution is an acceptable alternative to LR solution but large volumes can produce a hyperchloremic metabolic acidosis, which may complicate the use of base deficit in resuscitation. Since normal saline is compatible with all blood products, its use is sometimes preferred if transfusion is a possibility.

The decision to transfuse blood is highly dependent on the acuity of blood loss. Patients with acute, massive hemorrhage, such as those with trauma or gastrointestinal bleeding, show signs of hemodynamic instability early in their presentation. The clinical picture depends on the amount of blood loss (Table 171.9). For example, acute loss of 40% of the total blood volume (about 2,000 mL in a 70-kg patient) is associated with severe tachycardia, hypotension, depressed mental status, and

**TABLE 171.9**  
**CLASSES OF HEMORRHAGIC SHOCK**

<table>
<thead>
<tr>
<th>Class of hemorrhage</th>
<th>Blood volume loss</th>
<th>Characteristics</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>15% (750 mL)</td>
<td>Vital signs essentially normal, Tachycardia, decreased pulse pressure, anxiety, pallor, diaphoresis, acidosis</td>
<td>No resuscitation generally needed</td>
</tr>
<tr>
<td>II</td>
<td>15%–30% (750–1,500 mL)</td>
<td>Tachycardia, decreased pulse pressure, anxiety, pallor, diaphoresis, acidosis</td>
<td>Crystalloid resuscitation needed. Blood transfusion given if no response to fluids (or if response is transient)</td>
</tr>
<tr>
<td>III</td>
<td>30%–40% (1,500–2,000 mL)</td>
<td>Hypotension, tachycardia, decreased mental status, oliguria</td>
<td>Blood transfusion generally needed, with crystalloids in 3:1 ratio</td>
</tr>
<tr>
<td>IV</td>
<td>&gt;40% (&gt;2,000 mL)</td>
<td>Severe tachycardia and hypotension, lethargy</td>
<td>Massive resuscitation with fluids and blood products needed</td>
</tr>
</tbody>
</table>

Adapted from the American College of Surgeons, Advanced Trauma Life Support.
oliguria. On the other hand, blood loss of up to 15% of the blood volume (750 mL) may not have any obvious physiologic effects.

It is important to remember that the diagnosis of hemorrhagic shock and the decision to administer blood transfusion should not be based solely on hypotension, tachycardia, or anemia. Hypotension does not generally occur until more than 30% of the blood volume has been lost. This is particularly the case in children who, due to very effective compensatory mechanisms, maintain their blood pressure despite severe blood loss. Conversely, elderly patients on β-blocking agents may not manifest significant tachycardia. Hemoglobin levels obtained early in the course of hemorrhagic shock do not reflect the severity of blood loss, as there has not been enough time for fluid shifts to occur. Therefore, blood transfusion should be based on a comprehensive assessment of the patient, including vital signs and estimation of the amount of blood loss, as well as clinical and laboratory evaluation of end-organ perfusion.

Acute, massive hemorrhage is managed initially with aggressive volume replacement using crystalloid solutions. After administering 2,000 to 3,000 mL of crystalloid solution, blood transfusion should be initiated in patients who continue to manifest unstable vital signs. This should occur concomitantly with expeditious surgical control of the bleeding sites. Cross-matched blood should be given as soon as it is available. If needed, type O negative blood can be given to women of childbearing age, and type O positive blood can be given to men of all ages and women older than 50 years of age until cross-matched blood is available. Correction of coagulopathy and hypothermia is paramount. A “damage control” surgical approach, aimed at rapid control of bleeding while delaying less urgent procedures, should be utilized. This helps reduce transfusion requirements and allows the patient to recover more quickly from shock.

### Blood Transfusion in the Normovolemic Patient

Anemic patients with a normal blood volume, such as patients who have recovered from hemorrhagic shock and those with subacute or chronic anemia, are generally hemodynamically intact. Concerns regarding the diminished oxygen-carrying capacity of the blood may persist in some of these patients, especially those in the critical care setting. For many years, the standard of care dictated that a hematocrit level of at least 30% should be maintained; the rationale included faster recovery and prevention of myocardial ischemia, especially in patients with coronary artery disease. Recent data indicate that lower hematocrit levels are well tolerated, even in patients at risk for myocardial ischemia (10, 43–47). Combined with the current understanding of blood transfusion risks, this has resulted in lowering the trigger level for transfusion.

There are now many reports demonstrating that blood transfusion is an independent risk factor for worse outcome, including increased mortality, especially in trauma patients (48–53). In a landmark study, Hebert et al. demonstrated that maintaining the hemoglobin at or above 10 g/dL (liberal strategy) in euvolemic critically ill patients—as compared to maintaining the hemoglobin at 7 g/dL (conservative strategy)—was not associated with any improvement in overall mortality (19). In fact, mortality was significantly lower with the conservative strategy (hemoglobin at 7 g/dL) among patients who were less acutely ill and in those who were younger than 55 years of age. Patients with active myocardial ischemia, defined as unstable angina and acute myocardial infarction, were excluded from the study. In the latter group of patients, maintaining the hemoglobin at or above 10 g/dL remains the standard of care, although there are conflicting data on that subject.

In a study of Medicare discharge records, elderly patients with acute myocardial infarction had a lower mortality if their hematocrit was 30% or higher (54). Another study suggested that a higher hematocrit upon admission to the ICU after coronary artery bypass grafting was associated with a higher rate of myocardial infarction (55). Despite the large body of evidence against empiric blood transfusion in normovolemic patients, physicians continue to transfuse patients with hematocrit levels between 21% and 30% (56). Finally, there have also been reports advocating a hematocrit level of 30% in septic patients (57), although these reports do not establish blood transfusion to a hematocrit of 30% as an independent factor contributing to improved outcome. The general trend, overall, appears to be that of an increasingly restrictive strategy of blood transfusion (11, 12, 58).

### MINIMIZING TRANSFUSIONS IN THE INTENSIVE CARE UNIT

#### Immediate Concerns

- Given the known risks and the costs associated with blood transfusions, a comprehensive strategy of blood conservation should be followed. The need to correct anemia should be assessed, sources of ongoing blood loss should be controlled, and measures to enhance erythropoiesis should be entertained.

#### Minimizing Unnecessary Blood Loss

A significant amount of blood can be lost with repeated phlebotomy in the ICU. This is particularly significant in children. Routine serial “blood draws” should be avoided. A policy of obtaining laboratory results only when clinically indicated should be followed. Microsampling techniques, including bedside point-of-care testing, limit the amount of blood lost with each blood draw. Since the estimated daily blood loss from phlebotomy is at least 40 mL/day (10, 11, 13), critical care practitioners should carefully consider the need for frequent phlebotomy in the ICU.

#### Optimization of Red Cell Production

**Iron**

Iron is essential for properly functioning hemoglobin, as it is the site of attachment of the oxygen molecule. Other oxygen-carrying proteins, such as myoglobin and cytochrome a-a3, also depend on iron. Many enzymes in the Kreb cycle contain iron in their functional groups. In the critically ill patient, iron deficiency anemia may be multifactorial, for example, poor gastrointestinal absorption, nutrient antagonism, and concomitant copper and vitamin A deficiencies (59). Patients with the systemic inflammatory response syndrome (SIRS) have circulating cytokines that impair the release of iron stored in the reticuloendothelial system. This creates a situation
where total body iron levels are normal but iron is not avail-
able for incorporation into red cell precursors (functional iron deficiency anemia).

Despite the central role that iron plays in oxygen delivery, it is still not known whether iron supplementation in critically ill anemic patients is beneficial (60). Preexisting iron deficiency could also be functional, rather than an absolute reduction in total body iron (61,62). In addition, iron supplementation has been implicated with an increased risk and severity of infection since free iron acts as a chelator of free radicals (63). There is currently no clear indication to administer supplemental iron to critically ill patients who are anemic.

Erythropoietin
Erythropoietin is a circulating glycoprotein secreted primarily by the kidneys in response to hypoxia. Its principal action is to stimulate the production and release of RBCs from the bone marrow (64). This hormone is now commercially available using recombinant DNA technology, and has been approved for use in anemic patients with end-stage renal disease. Its indications were extended to include anemic patients with chronic renal insufficiency, cancer, and AIDS. The indications for erythropoietin therapy are still being expanded. Patients undergoing elective surgical procedures that are typically associated with severe blood loss may benefit from preoperative erythropoietin therapy combined with autologous blood transfusion (65).

The potential therapeutic value of erythropoietin in anemia of critical illness is an area of intense research. Erythropoiesis in critically ill patients can be suppressed for a variety of reasons, including renal and hepatic failure. Circulating cytokines in SIRS suppress erythropoiesis both by blunting the response to and inhibiting the production of erythropoietin (66–72).

Gabriel et al. noted that erythropoietin formation in patients with multiple organ dysfunction was inadequate to stimulate reticulocytosis in what was described as a relative erythropoietin deficit (73). In their study, high doses of recombinant human erythropoietin therapy did stimulate the erythropoietic system, as evidenced by a higher rate of reticulocytosis. There was, however, no increase in hematocrit or reduction in packed RBC transfusion during the 3 weeks of the study.

Studies have focused on the potential of human recombinant erythropoietin therapy to reduce transfusion requirements and improve outcome in critically ill patients (74). Corwin et al., in two randomized controlled trials (75,76), demonstrated a reduction of up to 19% in packed RBC units transfused and a greater increase in hematocrit in the group treated with erythropoietin; there were no differences in morbidity or mortality between the two groups. Georgopoulos et al. showed similar results, with the additional finding that the effects of erythropoietin therapy are dose dependent (77).

More recent studies have shown less favorable results. Another study by Corwin et al. noted that the use of erythropoietin alfa did not reduce the incidence of red cell transfusion among critically ill patients, and treatment with this agent was associated with an increase in the incidence of thrombotic events (78).

A second study concluded that the use of a target hemoglobin level of 13.5 g/dL in chronic kidney disease was associated with free iron acts as a chelator of free radicals (63). There is currently no clear indication to administer supplemental iron to critically ill patients who are anemic.

Adverse effects potentially attributable to erythropoietin therapy include hypertension, thrombotic complications, cardiovascular events, tumor progression in cancer patients, and increased risk of death. In November 2006, the FDA issued an alert to provide new safety information for erythropoiesis-stimulating agents (ESAs) (81). The alert was based on analyses of studies on cancer and orthopedic surgery patients who were found to have a higher chance of serious and life-threatening effects and/or death with the use of ESAs. The FDA recommends using the lowest dose possible to achieve a hemoglobin level that avoids the need for transfusion, and withholding the dose of the ESA if the hemoglobin level exceeds 12 g/dL or rises by 1 g/dL in any 2-week period.

Autotransfusion
Blood lost during surgical procedures can be retrieved, spun, washed, and filtered. The recovered RBCs are then reinfused back into the patient. Similarly, blood from drains such as thoracostomy tubes can be retrieved, collected in containers with citrate solutions to prevent clotting, and reinfused. Relative contraindications include contamination of blood with bacteria, malignant cells, or amniotic or ascitic fluids. Other strategies of blood conservation include preoperative autologous donation and acute normovolemic hemodilution (30).

Hemoglobin-based Oxygen Carriers
The search for a solution that can transport oxygen from the lungs to the tissues started in the early part of the 20th century and continues to the present day (82–84). These solutions are loosely termed “blood substitutes,” although they should be more appropriately described as “oxygen carriers,” since this is the only blood function for which they substitute. A variety of substances have been studied, including perfluorochemicals and porphyrins. Research on the latter two categories of oxygen carriers has been largely abandoned due to problems with manufacturing, ease of use, and adverse effects (85–87).

Current investigation is now focused on the hemoglobin-based oxygen carriers (HBOCs). Hemoglobin can be obtained from three sources: human blood from discarded units of packed RBCs, animal blood, and recombinant DNA technology.

Structure and Function of Normal Human Hemoglobin
Hemoglobin (Hb) is a large molecule made up of four polypeptide chains (two α- and two β-chains), with a molecular weight of 64,450. Each chain is conjugated with a heme moiety, an iron-containing porphyrin derivative to which oxygen attaches, forming oxyhemoglobin. When fully saturated, each Hb molecule has four oxygen molecules attached. Iron has to be in the ferrous state (Fe²⁺) in order for oxygen to attach. When blood is exposed to various drugs and other oxidizing agents, ferrous iron is converted to ferric iron (Fe³⁺), forming methemoglobin (met-Hb), which cannot bind oxygen. An enzyme within red cells, met-Hb reductase, converts met-Hb back to Hb.

The affinity of Hb for oxygen increases exponentially as more oxygen molecules attach, and hence the sigmoid nature...
of the oxygen-Hb dissociation curve. Factors that decrease the affinity of Hb to oxygen (i.e., making off-loading of oxygen easier) include acidosis and 2,3-DPG.

**Characteristics of Cell-free Hemoglobin**

**Dissociation.** When free in the plasma, the Hb tetramer dissociates into two a2-dimers, which are filtered through renal glomeruli and can then precipitate in the renal tubules, causing obstruction. This adverse effect is further compounded by the decreased renal blood flow that results from the vasoconstrictive effect of Hb (88,89). Technologies were developed to produce large stable Hb polymers by cross-linking Hb molecules; the most commonly used cross-linking reagent is glutaraldehyde. This process results in the formation of polymers of varying sizes that do not filter through the glomeruli. Another strategy used to stabilize Hb was intramolecular cross-linking, whereby the cross-link was between a-chains of the same molecule so that neither polymerization nor subunit dissociation occurred; this product was abandoned due to intense vasoconstrictive features.

**Viscosity.** The lower viscosity of Hb solutions, compared to blood, was initially thought to be advantageous, as it provided less systemic vascular resistance. However, deeper insight into the physiology of the vascular endothelium revealed that the reduced shear stresses on the blood vessel wall were associated with decreased secretion of relaxing factors such as prostacyclin and endothelin, with a net vasoconstrictive effect. The resulting decrease in blood flow antagonizes the oxygen delivery function of Hb (90,91).

**Vasoactivity.** Most HBOCs have a systemic pressor effect (92,93), and some have the same effect on the pulmonary circulation as well (94). In addition to the above mechanisms of vasoconstriction, two other mechanisms are described: binding of nitric oxide and stimulation of catecholamine release; these effects have been associated with decreased cardiac output (95).

**Affinity for Oxygen.** Once released from the red cell, Hb loses its 2,3-DPG, and its affinity for oxygen increases. This causes a leftward shift of the oxygen-Hb dissociation curve, thus improving the off-loading of oxygen. Strategies to decrease the affinity of Hb for oxygen include pyridoxalation and the use of bovine Hb. It is not clear whether decreasing the affinity of Hb for oxygen is beneficial. For example, higher levels of oxygen at the tissue level may trigger an autoregulatory response by the blood vessel wall, whereby there is decreased secretion of relaxing factors, resulting in vasoconstriction and decreased flow (96).

**Oxidation.** Deprived of the met-Hb reductase in red cells, free Hb is at higher risk of being oxidized into met-Hb. However, other antioxidants such as glutathione are present in plasma to serve this function. Levels of met-Hb in patients receiving HBOCs may appear to be physiologically significant (97).

**Effects on the Inflammatory Response.** HBOCs, unlike stored blood, lack the ability to stimulate neutrophils and incite an inflammatory response with its attendant systemic manifestations of multiple organ dysfunction (98).

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**Clinical Trials of Hemoglobin-based Oxygen Carriers**

The most widely studied HBOC in clinical practice is a human polymerized hemoglobin product (PolyHeme, Northfield Laboratories, Evanston, IL). The first randomized trial in acute trauma and emergency surgery was published in 1998 (99), showing that PolyHeme maintained total hemoglobin in lieu of red cells despite the marked fall in HbC hemoglobin, and reduced the use of blood transfusion. The study concluded that PolyHeme appears to be a clinically useful blood substitute. A phase III trial involving 720 patients from 32 level I trauma centers was recently completed. The trial randomized trauma patients with evidence of hemorrhagic shock at the scene to either normal saline or PolyHeme. Treatment was started in the field and continued for up to 12 hours after injury. The primary end point was survival at 30 days. Preliminary results showed no statistically significant difference in survival between patients receiving PolyHeme without blood for up to 12 hours following injury and those receiving the standard of care, including early blood replacement. PolyHeme may, therefore, be useful when blood is needed but not available (100).

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**REFUSAL OF BLOOD TRANSFUSION**

Critically ill patients with transfusion preferences present a challenging management problem. For example, Jehovah’s Witnesses’ refusal of blood and blood products is part of their religious beliefs (Genesis 9:3-4, Leviticus 17:10-11) (101). Honoring these beliefs requires modification of medical management strategies, and presents a unique opportunity to question transfusion guidelines and thresholds. The care of these patients requires early identification of transfusion preferences. All patients admitted to the critical care setting should have treatment preferences (including blood transfusion) discussed with them or their legal representative as soon as possible. Although transfusion may need to be administered in some emergent situations without the opportunity to obtain informed consent, in most circumstances the critical care practitioner should be able to discuss the risks, benefits, and potential complications of transfusion with the patient or representative. Moreover, individual patients may have preferences—religious or otherwise—regarding some blood products but not others, so it is important to establish these preferences for each blood product available. Discussion with patients and family members should include a detailed explanation of each blood product, as the origin and technical aspects of these products may affect their acceptance. In the case of the Jehovah’s Witness, or other groups with religious preferences, assistance from a church representative or other religious leaders may be extremely helpful to the family and the physician. Although survival at lower levels of hemoglobin (> 3 g/dL) have been reported, mortality rates exceed 50% when levels fall below 3 g/dL (102). A recent experience with an injured patient who was a Jehovah’s Witness demonstrated that survival without neurologic impairment was possible even at extremely low hemoglobin and hematocrit levels (2.7 g/dL and 7.8%, respectively) (103). The implementation of blood conservation strategies, hormonal stimulation, and the use of red
cell substitutes as they become available are options in the management of these patients. The use of high-dose erythropoietin (40,000 units subcutaneously every other day) and supplemental iron provide accelerated erythropoiesis under extreme circumstances. Table 171.10 lists potential strategies that may be useful in the management of the Jehovah’s Witness and other circumstances. Table 171.10 lists potential strategies that may be useful in the management of the Jehovah’s Witness and other circumstances.

### References

5. Reading FC, Brecher ME. Transfusion-related bacterial sepsis. 1964;88:688–693.
Section XIX: Hematologic and Oncologic Disease and Dysfunction