Index
Transfusion Practices in Critical Care
Chapter 36 Anemia and Red Blood Cell Transfusions in the ICU
Chapter 37 Platelets in Critical Illness

Chapter 36

ANEMIA AND RED BLOOD CELL TRANSFUSIONS IN THE ICU

One if *the important discoveries, I believe* ... is *the realization that anemia* is *well tolerated* ... providing *blood volume* is *maintained.*
Daniel j. Ullyot, M.D. (J 992)

Anemia is almost universal in patients who spend more than a few days in the ICU (1), and about half of ICU patients with anemia are given one or more transfusions of concentrated erythrocytes (packed red blood cells) to correct the problem (2). This practice of transfusing red blood cells to correct anemia is one of the most fickle and arbitrary interventions in critical care medicine. Few ICUs employ practice guidelines to standardize transfusion therapy (2), and in most cases blood transfusions are given without documented evidence of need or benefit. The fear of anemia is pervasive but unfounded, because (as indicated in the introductory quote) anemia does not compromise tissue oxygenation as long as the intravascular volume (and hence cardiac output) is maintained. The relative importance of blood volume over blood cells is demonstrated by the fact that hypovolemia is a recognized cause of circulatory shock (impaired tissue oxygenation), whereas anemia is not. The important role of blood volume in supporting tissue oxygenation is often overlooked, even by the American Red Cross, whose popular slogan, *blood saves lives,* deserves a more accurate update like the one shown in Figure 36.1.
This chapter presents the current knowledge on the indications, methods, and complications of erythrocyte transfusions (3-6). Transfusion practices that are physiologically unsound or unproven are highlighted to emphasize the shortcomings that continue to plague this area of clinical practice.

ANEMIA IN THE ICU

Surveys have consistently shown that anemia is common on admission to the ICU (60% of patients in one study) and is almost universal by the end of the first week after admission (1,2). However, these results can be misleading because they are based on the hemoglobin concentration in blood as a marker of anemia. This is explained in the next section.

The Definition of Anemia

Anemia is defined as a *decrease in the oxygen carrying capacity of blood.* The oxygen carrying capacity of blood is a function of the total volume of circulating red blood cells, so anemia can be defined as a *decrease in the total red cell volume.* This parameter can be measured using chromium-tagged erythrocytes (see Table 36.1 for the normal values), but the methodology is not readily available in the clinical setting. Therefore, clinicians use an alternative definition of anemia that is based on the hematocrit and hemoglobin concentration in blood (see Table 36.1 for the reference ranges of these measurements). However, this practice is problematic, as described next.

The Problem

The problem with the clinical definition of anemia is the influence of the plasma volume on the hematocrit and hemoglobin concentration. This is demonstrated in Figure 36.2, which shows the postural changes in hematocrit and plasma volume in a group of healthy adults (7). When changing from the standing to supine positions, interstitial fluid in the lower extremities moves into the bloodstream and increases the plasma volume. The hematocrit then decreases by dilution. The absolute changes

TABLE 36.1 Reference Ranges for Red Cell Parameters in Adults

Red Blood Cell Count	*Mean Cell Volume (MCV)*
Males: 4.6 - 6.2 x 10^{12} */L*	Males: 80 - 100 x 10-^{15}L
Females: 4.2 - 5.4 x 10^{12} */L*	Females: same
Reticulocyte Count	*Hematocrit*
Males: 25 - 75 x 10^{9} */L*	Males: 40 - 54%
Females: same	Females: 38 - 47%
*Red Blood Cell Volume**	*Hemoglobin*t
Males: 26 mL/kg	Males: 14 - 18 gldL
Females: 24mL/kg	Females: 12 - 16 *g/dL*

*Normal values are 10% lower in the elderly (65 yrs of age).

tNormal values are 0.5 gldL lower in blacks.

Sources: (1) Walker RH (ed). Technical Manual of the American Association Banks. 10th ed. Arlington, VA: American Association of Blood Banks, (2) Hillman RS, Finch CA. Red cell manual. 6th ed. Philadelphia: FA Davis.

in hematocrit (4.1 %) and plasma volume (420 mL) in Figure 36.2 are equivalent to one unit of whole blood. The dilutional decrease in hematocrit could therefore be misinterpreted as indicating a red blood cell deficit, and this could lead to the inappropriate transfusion of one unit of blood (packed red blood cells).

Changes in plasma volume are expected in critically ill patients for the following reasons: (1) These patients are often hemodynamically unstable, and this is often associated with fluid shifts between the extravascular and intravascular compartments, (2) hypoalbuminemia is common in critically ill patients, and this will shift fluid out of the vascular compartment, and (3) intravenous fluids (which will increase plasma volume) and diuretics (which will decrease plasma volume) are used frequently in critically **ill** patients. Because of the risk that plasma volume is changing, the hematocrit and hemoglobin are unreliable markers of anemia in critically **ill** patients. This has been confirmed in clinical studies (8,9).

Common Causes of Anemia in the ICU

There are two conditions that are recognized for favoring the development of anemia in ICU patients: (1) systemic inflammation, and (2) repeated phlebotomy for laboratory studies. Failure of erythropoiesis could also occur without these two predisposing conditions if the energy needs of erythropoiesis are not satisfied.

The Burden of Erythropoiesis

The average adult has as many as 6 trillion(6 X 10^{12}) RBCs per liter of blood (see Table 36.1) (10). Using a blood volume of 5 liters, this corresponds to a total of about 30 trillion RBCs in circulating blood. The average turnover of circulating RBCs is 1 % per day (11), which means

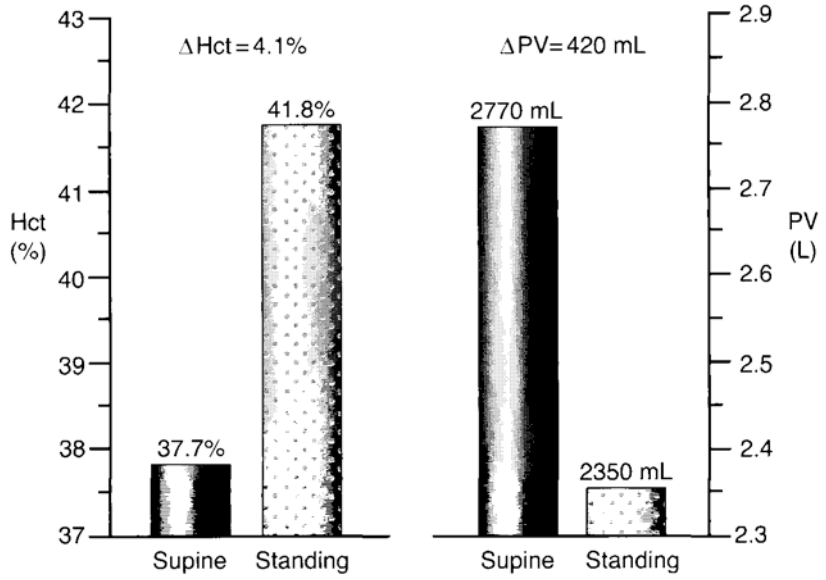

FIGURE 36.2 Postural changes in hematocrit (*Hct*) and plasma volume (*PV*) in a group of healthy adults. The numbers in parenthesis are the mean values of each parameter for the entire study group. (From Jacob G, Raj SR, Ketch T, et al. Postural pseudoanemia: posture-dependent change in hematocrit. Mayo Clin Proc 2005;80:611–614.)

that (0.01 X 30 trillion) 300 *billion* RBCs must be produced daily to maintain a constant pool of circulating erythrocytes. Failure to meet the energy requirements of this effort could lead to failure of erythropoiesis and subsequent anemia.

This daily production of RBCs (which takes place in the marrow cavities of the axial skeleton in adults) is regulated by *enjthropoietin,* a hormone produced in the peritubular capillary endothelium in the kidneys that stimulates erythropoiesis in marrow cavities. The cells that manufacture erythropoietin can respond to decreases in the arterial 02 content (either hemoglobin or arterial $P0_2$) by increasing the secretion of erythropoietin. The subsequent actions of erythropoietin on marrow erythropoiesis would then help to correct the deficit in the 02 content of blood. Interruption of the erythropoietin regulatory system is considered one of the major mechanisms for ICU-acquired anemia (12).

Inflammation and Anemia

Inflammatory cytokines (e.g., tumor necrosis factor) have several effects that can promote anemia, including inhibition of erythropoietin release from the kidneys, reduced marrow responsiveness to erythropoietin, iron sequestration in macrophages, and increased destruction of RBCs (12,13). The anemia associated with inflammation has the same characteristics as the *anemia of chronic disease:* i.e., a decrease in iron, total iron binding capacity, and transferrin levels in plasma, combined with increased

ferritin levels in plasma and iron sequestration in reticuloendothelial cells. This is the most common pattern observed in the anemia that develops in ICU patients, so inflammatory cytokines are believed to playa major role in ICU-acquired anemia.

Phlebotomy and Anemia

The volume of blood withdrawn from ICU patients to perform laboratory tests averages 40 mL to 70 mL daily (14,15). Cumulative increases in this phlebotomy volume can reach 500 mL (1 unit of whole blood) after one week, and this volume can augment the severity of anemia from other causes (by removing iron that is needed for erythrocyte production), or can itself become a source of anemia if allowed to continue.

The daily phlebotomy volume is at least 4 times higher in ICU patients than in other hospitalized patients (14), and the difference is not entirely due to increased diagnostic testing in ICU patients. Blood samples for laboratory analysis are usually withdrawn through indwelling vascular catheters, and the initial aliquot of blood (usually 5 mL) withdrawn through the catheter is discarded because it contains fluid from the catheter lumen instead of the bloodstream. Returning the initial aliquot of blood to the patient (using a closed system) reduced the total phlebotomy volume by 50% in one study (16). Of course, decreasing the number of laboratory tests performed daily is always the better choice.

Anemia and Oxygen Transport

The uptake of oxygen into peripheral tissues ($V0_2$) is described in Chapter 2 using the equation shown below (where Q is cardiac output, Hb is hemoglobin concentration in blood, and $Sa0_2$ - $Sv0_2$ is the arteriovenous oxyhemoglobin saturation difference).

$$V0_2 = Q \times 13.4 \times Hb \times (Sa0_2 - Sv0_2) \qquad (36.1)$$

The oxygen transport system operates to maintain a constant $V0_2$ in the face of changes in any of the variables in Equation 36.1. In the case of anemia, $V0_2$ remains constant because the decrease in hemoglobin (Hb) is accompanied by increases in both cardiac output (Q) and peripheral 02 extraction (SaO2 – SvO2). These compensatory responses to anemia are described next.

Cardiac Output

The influence of anemia on circulatory blood flow is described at the end of Chapter 1. The hematocrit is the principal determinant of blood viscosity (see Table 1.2 in Chapter 1), and thus a decrease in hematocrit will decrease the viscosity of blood. According to the Hagen-Poiseuille equation shown below, a decrease in viscosity (μ) will result in an increase in circulatory blood flow (Q) as long as the pressure gradient along the circulation (deltaP) and the dimensions of the blood vessels (r for radius

and L for length) remain constant. (This equation is described in detail in Chapter 1.)

$Q = \text{deltaP X pi radius}^4/8\mu L$ (36.2)

A decrease in blood viscosity augments cardiac stroke output by reducing ventricular afterload.
Anemia can also be accompanied by activation of the sympathetic nervous system (4,12), which will augment cardiac output by increases in both myocardial contractility and heart rate. However, this response is not prominent, and thus **tachycardia is not a prominent finding in anemia** (at least at rest) (4).
When considering the isolated effects of anemia on cardiac output, the blood volume should be normal or unchanged (this condition is referred to as *isovolemic anemia).* The changes in cardiac output associated with progressive, isovolemic anemia are shown in Figure 1.8 (Chapter 1). Note that the increase in cardiac output is proportionally much greater than the decrease in hematocrit. This response is attributed to the flow-dependency of blood viscosity; i.e., an increase in blood flow (cardiac output) will decrease bloop viscosity. Thus, anemia decreases blood viscosity, which then increases cardiac output, which then decreases blood viscosity, and so on. Ketchup is another fluid with a flow-dependent viscosity, so if you can picture what happens when you pour ketchup (the flow is sluggish at first, then increases as you continue to pour), you will get the idea. Blood viscosity is described at the end of Chapter 1.
In addition to the global changes in cardiac output, anemia can preferentially increase flow in the cardiac and cerebral circulations, and decrease flow in the splanchnic circulation (5). This will have a protective effect on myocardial and cerebral metabolism in the presence of anemia.

Peripheral Oxygen Extraction
The effects of progressive isovolemic anemia on systemic oxygen transport is summarized in the graphs in Figure 36.3 (17). The initial decrease in hematocrit is accompanied by a decrease in systemic oxygen delivery ($D0_2$), and this is counterbalanced by an increase in 02 extraction ($Sa0_2$ $Sv0_2$). The reciprocal changes in D02 and 02 extraction keep the $V0_2$ constant ($V0_2$ = D02 X 02 extraction). However, when the hematocrit falls below 10%, the increase in 02 extraction is no longer able to match the decreasing 002' and the $V0_2$ begins to fall. The decrease in $V0_2$ is a sign of dysoxia (defined in Chapter 2 as oxygen-limited aerobic metabolism), and is accompanied by an increase in lactate production. The point at which the $V0_2$ begins to fall is thus the threshold for tissue dysoxia, and it usually occurs when the 02 extraction reaches a maximum level of 50 to 60%. This means that an 02 extraction ($Sa0_2$ - $Sv0_2$) that is 50% or higher is a sign of inadequate tissue oxygenation.

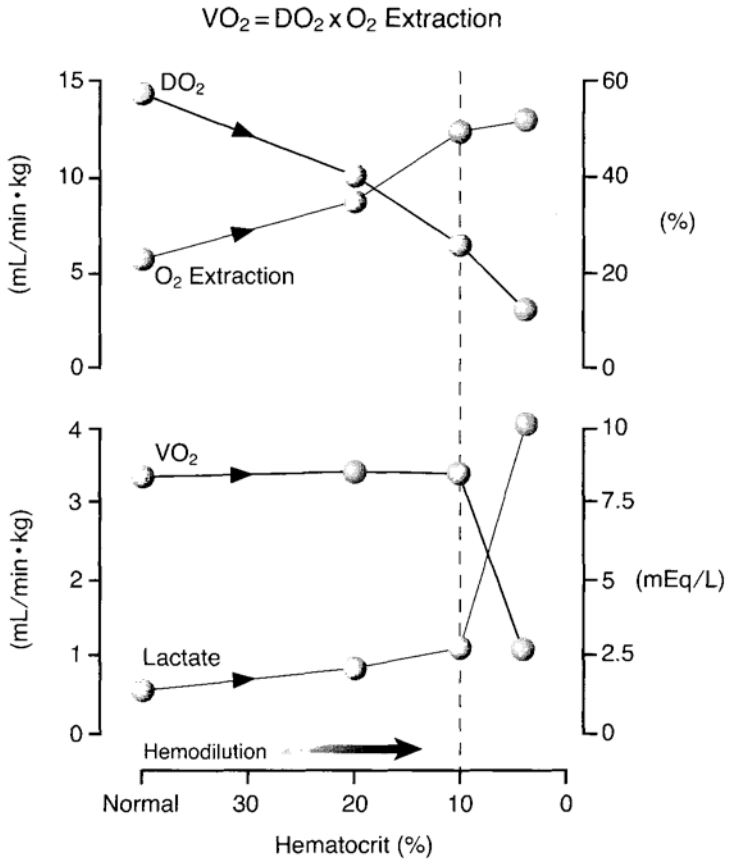

FIGURE 36.3 The effects of progressive isovolemic anemia on oxygen delivery (DO_2), oxygen extraction ratio (O_2ER), oxygen uptake (VO_2), and blood lactate levels in experimental animals. (From Wilkerson DK, Rosen AL, Gould SA, et al. Oxygen extraction ratio: a valid indicator of myocardial metabolism in anemia. J Surg Res 1987;42:629–634.)

Thus, because of the compensatory changes in cardiac output and peripheral 02 extraction, progressive anemia will not impair tissue oxygenation until the hemoglobin and hematocrit reach dangerously low levels. In the results of the animal study shown in Figure 36.3, the hematocrit had to fall below 10% (corresponding to a hemoglobin concentration of 3 g/ dL) before tissue oxygenation was compromised. The experimental animals in this study were anesthetized and breathing pure oxygen (which could favor tolerance to severe anemia), but similar results have been reported in awake animals breathing room air (18). The lowest hemoglobin or hematocrit that is capable of supporting tissue oxygenation in humans in not known, but one study of isovolemic anemia in healthy adults showed that hemoglobin levels of 5 g/ dL had no deleterious effects on tissue oxygenation (19).

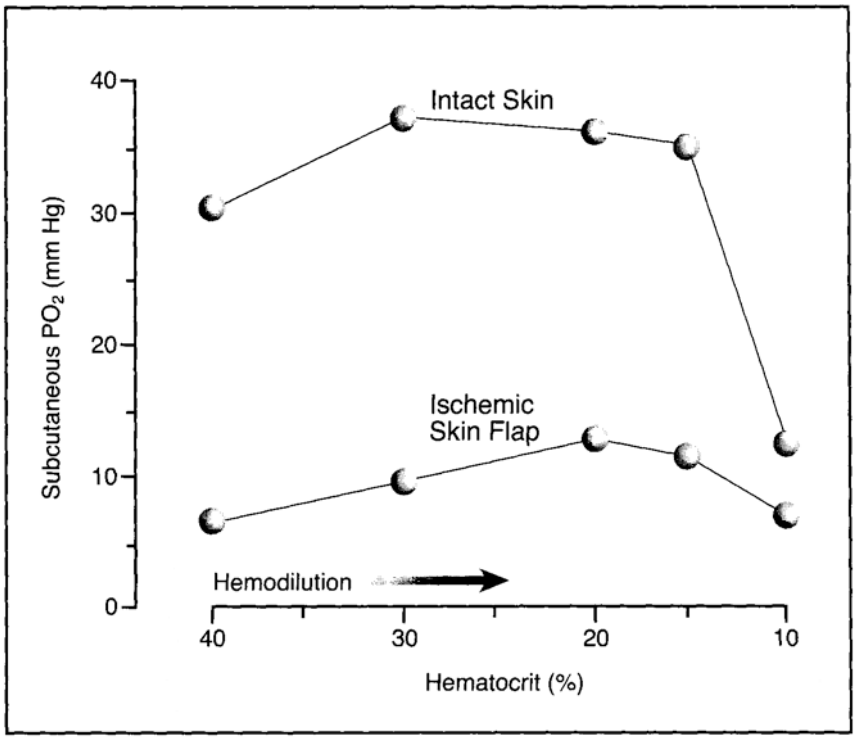

FIGURE 36.4 Paradoxical increase in tissue (subcutaneous) PO_2 during progressive isovolemic anemia in normal and ischemic regions of skin. (From Hansen ES, Gellett S, Kirkegard L, et al. Tissue oxygen tension in random pattern skin flaps during normovolemic hemodilution. J Surg Res 1989;47:24–29.)

Paradoxical Effect

Isovolemic anemia can have a paradoxical effect that **increases** tissue oxygenation. This is shown in Figure 36.4, which is from an animal study that evaluated the effects of isovolemic anemia on skin flaps using a specialized oxygen electrode to measure the $P0_2$ in subcutaneous tissues below the skin. (20). As indicated in the graph, reductions in hematocrit were associated with increases in the subcutaneous $P0_2$ in both normal and ischemic skin regions. Furthermore, the increase in tissue $P0_2$ persisted until the hematocrit fell to 10 to 15% (which is about the same hematocrit where tissue oxygenation became compromised in the study shown in Fig. 36.3).

The improvement in tissue oxygenation shown in Figure 36.4 can be explained **if** the cardiac output response to anemia is so exaggerated that the oxygen delivery increases despite the decrease in serum hemoglobin. Anemia can preferentially increase flow in certain regional circulations, as mentioned earlier, and the skin may be one of these regions. In fact, the beneficial effects of isovolemic anemia on blood flow to the skin has

led to the use of isovolemic anemia as a clinical tool for promoting the viability of skin flaps.

Erythrocyte Transfusions

The most recent survey of blood use in ICUs in the United States (reported in 2004) revealed that close to half of all ICU patients receive an average of 4 to 5 units of blood (packed red blood cells), and 90% of blood transfusions are given to correct anemia (2). As stated earlier, the use of erythrocyte transfusions in the ICU is arbitrary and without scientific basis, and the survey just mentioned found no change in this behavior over the past decade.

Transfusion Triggers

Few topics in critical care medicine have received as much attention over the past decade as the use of erythrocyte transfusions to correct anemia. Yet there continues to be no standardized or even appropriate set of indications for these transfusions.

Hemoglobin: Popular but Inappropriate

The use of hemoglobin as a *transfusion trigger* began in 1942 with the recommendation that a hemoglobin of 10 g/ dL be used as an indication for erythrocyte transfusions (21). This continues to be the most popular transfusion trigger today. Two clinical trials have shown that a lower hemoglobin of 7 g/ dL is safe in most patients (except those with acute myocardial infarction and unstable angina) and also reduces the number of RBC transfusions (22,23). The lower hemoglobin level of 7 g/ dL is gaining popularity as a transfusion trigger for all patients who do not have active coronary artery disease, but a recent survey showed that only 25% of RBC transfusions are based on the lower hemoglobin threshold of 7 g/ dL (2). This threshold can probably be reduced further because a previously mentioned study has shown that acute isovolemic anemia with hemoglobin levels of 5 g/ dL is well tolerated and without adverse consequences (19). This study was conducted in healthy adults, and needs to be repeated using ICU patients as subjects.

The popularity of the hemoglobin level as a transfusion trigger is disturbing because this measurement provides absolutely no information about the state of tissue oxygenation. In fact, according to Figure 36.4, a low serum hemoglobin could be a sign of improved tissue oxygenation in some situations! Furthermore, as mentioned earlier, the hemoglobin is not even an accurate measure of anemia in critically **ill** patients. An example of the folly of the hemoglobin as a transfusion trigger is shown in the example below.

A patient is admitted to the ICU with a severe pneumonia and a hemoglobin of 11 g/ dL. One week later, when the patient is improved and ready for transfer to the medical floor, the hemoglobin is noted to

be 7 g/dL. There has been no evidence of bleeding, but the patient's weight has increased from 170 to 185 lbs. Does this patient need a blood transfusion?

(I will let you answer the question yourself.) Two practice guidelines published about 15 to 20 years ago recommended abandoning the hemoglobin as a transfusion trigger and adopting more physiologic measures of tissue oxygenation '(24,25). Instead of abandoning the hemoglobin, physicians have abandoned the recommendation!

O_2 Extraction: A Better Transfusion Trigger
The graphs in Figure 36.3 (and also in Figs. 2.4 and 11.4) show that the peripheral 02 extraction, which is equivalent to the ($Sa0_2$ - $Sv0_2$), increases to a maximum level of about 50% in response to a decrease in 02 delivery (e.g., from anemia), and thus this maximum level of O_2 extraction is a sign of impending or actual tissue dysoxia. This means that an 02 extraction, or ($Sa0_2$ - $Sv0_2$), that is 50% or higher can be used as a transfusion trigger (17,26) because it identifies the threshold for impaired tissue oxygenation. Oxygen extraction can be monitored continuously in the ICU by using pulse oximetry (for arterial 02 saturation) combined with venous oximetry (for venous 0, saturation), as described in Chapter 20.

Monitoring the Effects of Erythrocyte Transfusions
The standard end-point of RBC transfusions is an increase in hemoglobin and hematocrit, but these are inappropriate because they provide no information about oxygen transport or tissue oxygenation. The appropriate end-points are an increase in both 02 delivery and 02 uptake into tissues.

Cardiac Output
Just as anemia can increase the cardiac output by reducing blood viscosity, infusing red blood cells to increase hematocrit can reduce the cardiac output by increasing blood viscosity (27). The decrease in cardiac output can cancel the benefit of an increased hemoglobin on oxygen transport.

Systemic Oxygenation
Erythrocyte transfusions have a variable effect on systemic oxygenation (28-30). This is demonstrated in Figure 36.5. Each line in this graph shows the effects of erythrocyte transfusions on the hemoglobin concentration and systemic oxygen uptake ($V0_2$) in individual postoperative patients. The number of units of packed cells transfused in each patient is indicated by the numbers intersecting each line in the graph. Of the six patients who were transfused, all showed an increase in hemoglobin concentration, but only three patients showed an increase in $V0_2$, while three patients showed a decrease in $V0_2$. This graph demonstrates that an increase in hemoglobin concentration after erythrocyte transfusions does not necessarily indicate that tissue oxygenation has also improved.

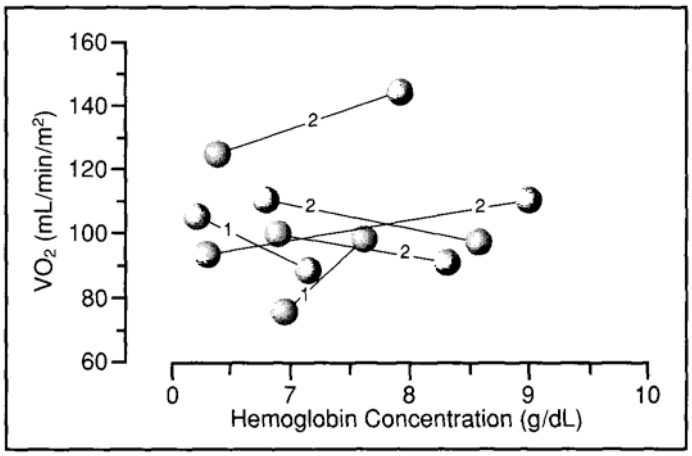

FIGURE 36.5 The effects of erythrocyte transfusions on hemoglobin levels and systemic oxygen uptake (VO_2) in postoperative patients with isovolemic anemia. Each line on the graph represents the changes recorded in a single patient. The numbers that transect each line represent the units of RBCs transfused in each case. (Data from personal observations.)

Erythrocyte Products

All blood products containing erythrocytes are stored at 4°C using a liquid anticoagulant preservative that contains citrate, phosphate, and dextrose (CPD). The citrate binds ionized calcium and acts as an anticoagulant. The phosphate helps retard the breakdown of 2,3diphosphoglycerate, and the dextrose serves as a fuel source for the erythrocytes. Erythrocytes stored in CPD at 4° C are viable for at least 21 days **(O)**.

Whole Blood

A unit of whole blood contains an average of 510 mL (blood plus CPD solution) (31). Most blood banks will store whole blood only on request. Otherwise, the blood is fractionated into erythrocyte and plasma fractions within a few hours of collection. The separation of whole blood into its component fractions allows more efficient use of blood products to achieve specific transfusion goals.

Packed Red Cells

Erythrocyte concentrates, or *packed red cells,* are prepared by centrifuging whole blood and removing 250 mL of the plasma supernatant (20). Each unit of packed cells contains approximately 200 mL of cells (mostly erythrocytes) and 50 to 100 mL of plasma and CPD solution. The hematocrit is usually between 60 and 80%, and the hemoglobin concentration is between 23 and 27 *g*/dL **(O)**.

Leukocyte-Poor Red Cells
Removal of the Leukocytes in packed red cells is recommended when transfusing patients with a history of febrile, nonhemolytic transfusion reactions (which are caused by antibodies to Leukocytes in donor blood) (31). The Leukocytes can be separated by centrifugation or filters, but separation is never complete and up to 30% of the Leukocytes remain in the sample.

Washed Red Cells
Packed cells can be washed with isotonic saline to remove Leukocytes and residual plasma. The removal of plasma helps prevent allergic reactions caused by prior sensitization to plasma proteins in donor blood. Washed red cells are therefore used for transfusing patients with a history of hypersensitivity transfusion reactions.

Infusing Erythrocyte Products
A standard infusion system for transfusing erythrocyte products is shown in Figure 36.6. Each of the numbered components in the system is described briefly in the following paragraphs.

Pressurized Infusions
The gravity-driven flow of whole blood and packed cells is shown in Table 36.2 (32). Because these flow rates do not approach the 250 *ml/* min or greater flow rates needed for the resuscitation of trauma victims, pressure-generating devices are used to speed infusion rates. The most common device used for this purpose is a standard blood pressure cuff that is wrapped around the collapsible plastic blood containers. When the cuff is inflated to a pressure of 200 mm Hg, the infusion rate of whole blood and packed cells increases approximately threefold, as shown in Table 36.2. Manual hand pumps are also available for increasing infusion rates. These hand pumps are not as effective as the blood pressure cuff (at 200 mm Hg) for infusing whole blood but are equivalent to the pressure cuffs for infusing packed cells (Table 36.2).

Saline Dilution
Packed cells infuse at approximately one-third the rate of whole blood. Special Y-configured tubing in blood infusion sets allows packed cells to be diluted with an equal volume of isotonic saline. When this is done, the infusion rate of packed cells is comparable to that of whole blood. Only isotonic saline should be used as a diluent for packed red cells. Ringer's solutions are not advised for diluting erythrocyte products because the calcium in Ringer's solutions can promote clotting in the blood sample (33).

Blood Filters
Erythrocyte products are infused through filters that trap small clots and other cellular debris (e.g., decomposed platelets and fibrin-coated

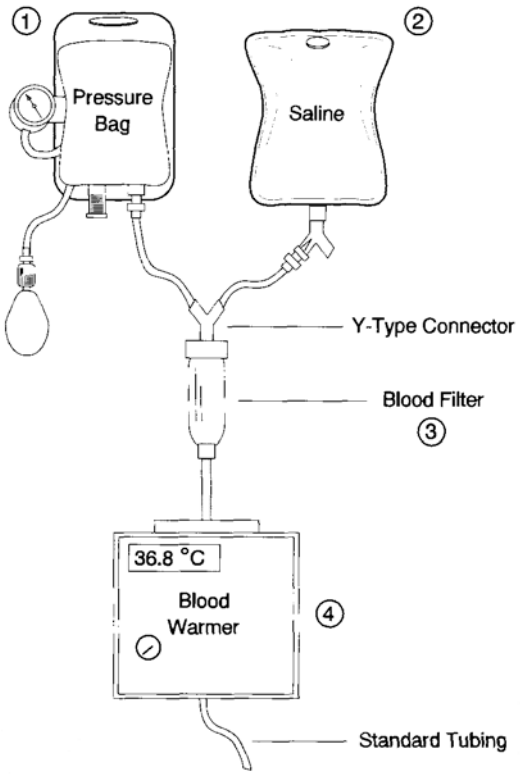

FIGURE 36.6 An infusion system for transfusing erythrocyte products. Each of the numbered components is described in the text.

leukocytes). These filters can become an impediment to flow as they collect trapped debris, and thus they should be replaced periodically (e.g., after every 4 units of blood). The standard filters have a pore size of 170 to 260 microns (23), which allows small fibrin microaggregates to pass freely. These microaggregates can become lodged in the pulmonary capillaries and create abnormalities in gas exchange. Smaller microaggregate filters are available, but their value in preventing pulmonary complications has not been proven (34).

Blood Warmers

Warming reduces the viscosity of refrigerated blood and can increase infusion rates by 30 to 50% (see footnote in Table 36.2). However, the major value of warming blood is considered to be the prevention of hypothermia from rapid transfusions (when 1 unit of blood is transfused every 5 to 10 minutes) (35). The recommended temperature for infused blood is 33° to 35° C (35). Temperatures of 37> C or higher can promote hemolysis.

A simple method for warming blood is to immerse the blood storage bags in hot water before transfusion. However, this rewarming method can take up to 30 minutes, and can produce hemolysis from overheating.

TABLE 36.2 Pressurized Infusion of Erythrocyte Products

		Infusion Rate (mUmin)*		
Fluid	Catheter Size	Gravity Flow	Hand Pump	Pressure Cuff (200 mm Hg)
Tap water	16-gauge 2" length	100	180	285
Whole blood		65	125	185
Packed cells		20	80	70

*Infusion rates for fluids at room temperature. Refrigerated blood products 50% slower

Data from Dula DJ et al. Flow rate variance of commonly used IV infusion J Trauma 1981 :21 :48D--482.

Controlled warming devices that can warm blood to the desired infusion temperatures at flow rates slightly in excess of 100 mL/minute are available (36). However, at the infusion rates often used to resuscitate trauma victims (Le., greater than 250 mL/minute), blood warming devices are often unable to warm blood to the desired temperature (36).

ADVERSE EFFECTS OF ERYTHROCYTE TRANSFUSIONS

Complications are reported in 2 to 4% of erythrocyte transfusions (2,37). The most notable of these are listed in Table 36.3, along with the frequency of each expressed in relation to the number of units transfused. Note that transfusion errors are much more frequent than transmission of HIV and other infections. The following is a brief description of the acute transfusion reactions (37-41).

TABLE 36.3 Adverse Events Associated with RBC Transfusions (per units transfused)

Immune Reactions	**Other Risks**
Acute hemolytic reaction (1 per 35,000)	**Infections**
Fatal hemolytic reaction (1 per million)	Bacterial (1 per 500,000)
Acute lung injury (1 per 5,000)	Hepatitis B virus (1 per 220,000)
Allergic reactions	Hepatitis C virus (1 per 1.6 million)
Urticaria (1 per 100)	HIV (1 per 1.9 million)
Anaphylaxis (1 per 1,000)	**Transfusion Errors**
Anaphylactic shock (1 per 50,000)	Wrong person transfused (1 per 15,000)
Non-hemolytic fever (1 per 200)	Incompatable transfusion (1 per 33,000)

From References 37-39.

Acute Hemolytic Reactions

Acute hemolytic reactions are caused by transfusion of ABO-incompatible RBCs, and are usually the result of human error. Fortunately, they are uncommon, and rarely fatal (one fatality per million units transfused). These reactions are the result of antibodies in the recipient binding to ABO surface antigens on donor RBCs. The ensuing lysis of donor RBCs is rapid, and incites a systemic inflammatory response that can be accompanied by hypotension and multiorgan failure.

Clinical Manifestations

Symptoms can appear after infusion of only 5 mL of donor blood (37), and include fever, dyspnea, chest pain, and low back pain. Hypotension can develop suddenly, and may be the only sign of a hemolytic reaction in comatose patients. Severe reactions are accompanied by a consumptive coagulopathy and progressive multiorgan dysfunction.

Bedside Approach

The following approach is recommended for any patient who develops a fever soon after the start of a blood transfusion.

Stop the transfusion immediately. This is imperative because the morbidity and mortality in hemolytic reactions is a function of the volume of incompatible blood transfused (37).

Check the blood pressure immediately. **If** the pressure is dropping, do the following:

Infuse volume (colloids may be preferred because of their ability to rapidly expand the vascular volume).

Start dopamine (at 5 μg/kg/minute). This agent has been preferred for its renal vasodilating effects because renal failure is a poor prognostic sign in hemolytic transfusion reactions (29). However, the relative benefits of dopamine over other pressor agents is unproven.

Once the patient is stabilized, do the following:

Obtain a blood sample and inspect the plasma for the pink-toned hue of hemoglobin.

Obtain a freshly voided urine specimen and perform a dipstick test for blood.

Send a blood sample for a direct Coomb's test. A positive test confirms a hemolytic transfusion reaction. However, a negative test is possible if most of the donor erythrocytes have already lysed.

Febrile Nonhemolytic Reactions

Fever that is not related to an acute hemolytic reaction occurs in only 0.5% of RBC transfusions (or once per 200 units transfused) (38). This

reaction is the result of antibodies in the recipient to Leukocytesin donor blood. The antileukocyte antibodies are produced in response to prior transfusions or prior pregnancies, so this type of response is often seen in multiparous women or in patients with a history of prior transfusions. Fever is more of a problem with platelet transfusions, where the incidence of fever is as high as 30% (38).

Clinical Manifestations
The fever usually appears 1 to 6 hours after starting the transfusion (later than the onset of fever associated with hemolytic transfusion reactions), and it is not usually accompanied by signs of systemic illness. However, severe reactions can occur, and patients can have a toxic appearance.

Bedside Approach
The approach to this fever is the same as outlined for hemolytic transfusion reactions, although the transfusion may be completed before the fever appears. The diagnosis of a nonhemolytic febrile reaction is confirmed by excluding the presence of hemolysis with the tests described previously. Bacterial contamination of RBC products is rare (one per 500,000 units), and is much more common in platelet transfusions (one per 2,000 units) (38). The need for routine cultures of donor and recipient blood is usually dictated by local blood bank policies. Many blood banks require cultures for all febrile reactions accompanied by other signs of systemic illness (e.g., rigors, dyspnea). The organism most often isolated in RBC products is *Yersinia enterocolitica,* and transfusions contaminated with this organism are fatal in 60% of cases (38).

Future Transfusions
More than 75% of patients with a nonhemolytic febrile transfusion reaction will not experience a similar reaction during subsequent blood transfusions (38). Therefore, no special precautions are necessary for future transfusions. If a second febrile reaction develops, leukocyte-poor red cell preparations are advised for all further erythrocyte transfusions.

Allergic Reactions
The most common hypersensitivity reaction is urticaria, which is reported in one of every 100 units transfused (39). More severe anaphylactic reactions (e.g., wheezing) are much less common, and anaphylactic shock is rare 0 per 50,000 units) (39). These reactions are the sensitization to plasma proteins in prior transfusions. Patients with IgA deficiency are particularly prone to hypersensitivity reactions, and they do not require prior exposure to plasma products.

Clinical Manifestations
The usual manifestation is mild urticaria that appears during the transfusion and is not accompanied by fever. The sudden onset of wheezing is

a clue for anaphylaxis, and sudden hypotension (which is rare) can be mistaken for an acute hemolytic reaction.

Bedside Approach
Mild urticaria without fever does not require interruption of the transfusion. However, the common practice is to stop the transfusion temporarily and administer antihistamines (diphenhydramine, 25 to 50 mg orally or intramuscularly every 6 hours). This practice might provide some symptomatic relief, but is otherwise useless. Transfusion-related anaphylaxis should be managed as described in Chapter 40. Patients who develop anaphylaxis should be tested for an underlying IgA deficiency.

Future Transfusions
Future transfusions should be avoided if possible for all cases of transfusion-associated anaphylaxis. For less severe allergic reactions, washed red cell preparations (plasma removed) are advised for subsequent transfusions. Antihistamine premedication is a popular but unproven practice.

Acute Lung Injury
Transfusion-associated acute lung injury (TRALI) is an inflammatory lung injury that is first apparent during or within 6 hours after the start of transfusion (40). The reported incidence is 1 per 5,000 transfusions (38). The prevailing theory is that antileukocyte antibodies in donor blood bind to circulating granulocytes in the recipient and promote leukocyte sequestration in the pulmonary microcirculation (41). This leads to granulocyte-mediated lung injury, which presents as acute respiratory distress syndrome (ARDS). Although this form of lung injury is fatal in fewer than 10% of patients (40), it is considered the leading cause of death from blood transfusions (37,38).

Clinical Manifestations
Signs of respiratory compromise (dyspnea, hypoxemia) begin to develop during or within a few hours after the transfusion begins. Fever is common, and hypotension has been reported. The chest x-ray film eventually shows diffuse pulmonary infiltrates, and intubation with mechanical ventilation is often necessary. Although the acute syndrome can be severe, the process usually resolves within a week.

Bedside Approach
The transfusion should be stopped (if still running) at the first signs of respiratory compromise. Distinguishing TRALI from hydrostatic pulmonary edema is often mentioned, but this is not necessary because RBC transfusions are a viscous load, not a fluid load, and they do not produce hydrostatic pulmonary edema (the RBCs can't get out of the pulmonary capillaries!). Even when combined with an equal volume of isotonic saline, the total volume of exchangeable fluid that is infused (250 mL) is not enough to produce hydrostatic pulmonary edema.

Therefore, what appears to be pulmonary edema shortly after a blood transfusion is ARDS, and the management is similar to that described for ARDS in Chapter 22.

Future Transfusions
There are no firm recommendations regarding future transfusions in patients who develop TRALI. Some recommend using washed RBCs to remove antibodies from the preparation, but the efficacy of this measure is not known.

Transfusion-Associated Immunomodulation
Patients who receive blood transfusions have an increased incidence of nosocomial infections (41), and this, combined with the observation that blood transfusions improve the survival of renal allografts, has led to the proposal that blood transfusions promote immunosuppression in the recipient. The mechanisms for this effect are not known, but one possibility is that antigenic substances or Leukocytes in transfused blood persist in the recipient and induce a down-regulation of the recipient's immune system. Removing Leukocytesfrom RBC products is one consideration, but universalICUkoreduction for RBC preparations is not currently practiced. Until this problem is resolved, the increased risk of infection associated with RBC transfusions is reason to avoid transfusions whenever possible.

BLOOD CONSERVATION IN THE ICU

A variety of blood conservation strategies have been proposed, but only a few can be applied to patient care in the ICU.

Postoperative Blood Salvage
For surgical procedures involving median sternotomy (such as coronary artery bypass surgery), blood collected from mediastinal drainage tubes can be reinfused (42). Chest tube drainage from the mediastinum is passed through a filter at the bedside to trap large clots and cellular debris, and the filtered blood is then reinfused. Because the blood has undergone endogenous defibrination in the chest, no anticoagulants need to be added. Traumatic disruption of cells is common, and the hematocrit of the reinfused blood is only 15 to 25%. This low hematocrit may explain why reinfusion of shed mediastinal blood does not always reduce the number of homologous transfusions (43).

Erythropoietin
Because the anemia that develops in ICU patients is associated with reduced levels of circulating erythropoietin (as described earlier), exogenously administered erythropoietin has been evaluated as a possible

means of reducing RBC transfusions in the ICU. About seven clinical studies have been reported (44), and each shows that patients who receive erythropoietin require fewer RBC transfusions (a subcutaneous dose of 40,000 units once weekly is adequate, and the effects can take 3 weeks to become evident). However, none of the studies have proven that the decreased transfusion requirements from erythropoietin are associated with fewer adverse events or better outcomes. Furthermore, the cost of erythropoietin is a concern: in one analysis, the estimated cost of erythropoietin therapy to prevent one transfusion-related adverse event was $5 million, and the cost of preventing one transfusion-related death was more than $25 million (44). At these prices, erythropoietin will have to do a lot better before it is embraced in the ICU.

A FINAL WORD

The single most important point to remember from this chapter is that anemia is well tolerated as long as intravascular volume is maintained. When blood volume is normal, hemoglobin levels have to drop to 3 g/ dL to demonstrate evidence of impaired tissue oxygenation. What this means to me is that cardiac output is more important for tissue oxygenation than the hemoglobin level in blood. The importance of cardiac output over hemoglobin is evident when you consider that hypovolemic shock and cardiogenic shock are recognized entities, while "anemic shock" is not. Since shock is a condition of impaired tissue oxygenation, the fact that anemia is not a recognized cause of shock is proof that anemia does not impair tissue oxygenation (at least not until the anemia reaches dangerously low levels). If this is the case, then most RBC transfusions to correct anemia will not improve tissue oxygenation (and thus are not warranted).

The second point that deserves emphasis is the nonvalue of the hemoglobin for assessing transfusion needs. A better measurement for evaluating systemic oxygenation is the peripheral 02 extraction, which can be measured as the ($Sa0_2$ - $Sv0_2$) difference. All you need is an indwelling central venous catheter to measure $Sv0_2$, and a pulse oximeter to measure $Sa0_2$. When the ($Sa0_2$ - $Sv0_2$) approaches 50%, and there is no reason to suspect a low cardiac output (which can also increase peripheral 02 extraction), then transfusion of RBCs is a reasonable consideration.

REFERENCES

Chapter 37

PLATELETS IN CRITICAL ILLNESS

Platelet disorders fall into two categories: those characterized by abnormal numbers of circulating platelets and those characterized by abnormal platelet function. This chapter introduces the common causes of both types of platelet disorders in the reu population. This is followed by a brief description of the indications, methods, and complications of platelet transfusion therapy 0-3).

PLATELETS AND HEMOSTASIS

Platelets are cytoplasmic remnants of megakaryocytes and are not true cells because they have no nucleus and cannot synthesize proteins. The normal adult has an average of 250 billion platelets per liter of blood. Assuming a normal blood volume of 5.5 L, the total number of platelets in the bloodstream is slightly in excess of 1 trillion. Platelets have a normal life span of 10 days, and each day about 45 billion new platelets must be added to each liter of blood to maintain a constant pool of circulating platelets (4).

Thrombosis

When the vascular endothelium is damaged, platelets adhere to exposed collagen in the subendothelium. The platelets then release calcium, and this activates glycoprotein (IIb-IIIa) receptors on the platelet surface. These receptors bind irreversibly to von Willebrand factor in the surrounding endothelium, and this anchors the developing platelet plug. The glycoprotein IIb-rna receptors also bind fibrinogen, and fibrinogen bridges

between platelets result in platelet aggregation. The released calcium also activates the coagulation cascade, and this results in the production of fibrin strands that form an interlacing meshwork with the platelets to produce a thrombus.

Thrombocytopenia

Thrombocytopenia is defined as a platelet count below 150,000/μL (5), but the ability to form a hemostatic plug is retained until the platelet count falls below 100,000/μL. Therefore, thrombocytopenia that is clinically significant corresponds to a platelet count below 100,000/μL. rn this range, the bleeding tendency is determined primarily by the presence or absence of a structural lesion that is prone to bleeding. rn the absence of such a lesion, platelet counts down to 5000/μL can be tolerated without evidence of bleeding (6).

Pseudothrombocytopenia

Pseudothrombocytopenia is a condition where the anticoagulant EDTA (used in collection tubes for routine blood counts) promotes clumping of platelets in vitro. The clumped platelets are then misread as leukocytes by automated machines that perform cell counts, and this results in a spuriously low platelet count (2). This phenomenon tends to occur in patients who have antiplatelet antiboDICs that do cause thrombocytopenia in vivo (e.g., cold agglutinins), and it has been reported in as many as 2% of hospitalized patients (7). The diagnosis can be confirmed by observation of platelet clumps on blood smears obtained with EDTA, or by repeating the platelet counts on blood samples collected with sodium citrate as the anticoagulant (2).

Platelet Adhesion

When the ability of platelets to adhere to the sub endothelium is diminished (e.g., as in uremia), the risk of hemorrhage can be increased despite platelet counts that exceed 100,000/μL. Defects in platelet adhesion can be detected by a prolonged bleeding time. However, there is no correlation between the bleeding time and the tendency for bleeding from altered platelet adhesion (8), and thus the bleeding time is not a useful test for detecting clinically significant defects in platelet adhesion. The recognition of abnormal platelet adhesion usually involves simple recognition of conditions that alter platelet adhesiveness in individual patients. These conditions are described later in the chapter.

THROMBOCYTOPENIA IN THE ICU

The incidence of clinically significant thrombocytopenia (<100,000/μL) is 13 to 35% in medical and surgical reus (9,10), and the most common predisposing conditions are sepsis and disseminated intravascular coagulation (DIC). The causes of thrombocytopenia most likely to be encountered in the reu are listed in Table 37.1. The conditions you must be aware of are described next.

Heparin-Induced Thrombocytopenia

Heparin can combine with a heparin-binding protein (platelet factor 4) on platelets to form an antigenic complex that induces the formation of IgG antiboDICs. These antiboDICs then bind to platelets and form cross-bridges that result in platelet aggregation. If severe enough, this

TABLE 37.1 Causes of Significant Thrombocytopenia in the ICU

Conditions	Drugs·
Systemic sepsis	Acetaminophen
Disseminated intravascular coagulation	Heparin
	Quinidine
Thrombotic thrombocytopenia purpura	Rifampin
HELLP syndrome	Trimethoprim-sulfamethoxazole

'Includes only drugs reported to cause bleeding or thrombosis. From Reference 2.

process can result in a consumptive thrombocytopenia and clinically apparent thrombosis (11).

Clinical Features

Heparin-induced thrombocytopenia (HIT) typically appears as a 50% or greater reduction in the platelet count that begins 5 to 10 days after the first exposure to heparin (the onset is earlier in patients with a prior exposure to heparin). Five to ten percent of patients with HIT from subcutaneous heparin will develop erythematous lesions surrounding the injection site, and 25% of patients with HIT from intravenous heparin will develop systemic reactions that include fever, chills, tachypnea, tachycardia and shortness of breath **(1)**.

The major complication of HIT is thrombosis, not bleeding.

Approximately **75% of cases of HIT are accompanied by symptomatic thrombosis**, including deep vein thrombosis of the lower extremities (50% of cases) and upper extremities 00% of cases), acute pulmonary embolism (25% of cases), arterial thrombosis involving a limb (5 to 10% of cases, thrombotic stroke.(3 to 5% of cases), acute myocardial infarction (3 to 5% of cases), and adrenal vein thrombosis with adrenal hemorrhagic necrosis (3% of cases) (1).

Risk Factors

The risk of HIT is greater with unfractionated heparin (UFH) than with low molecular weight heparin (LMWH). The risk of HIT from UFH is greatest following orthopedic surgery (3 to 5%) and cardiac surgery 0 to 3%), while about 1 % of medical patients who receive UFH develop HIT (1). The risk of HIT from LMWH is about 1 % in orthopedic surgery cases, and is less than 1 % in other clinical settings (1).

One of the important features of HIT is the fact that it can appear with very low doses of heparin. This includes heparin flushes and the small amounts on heparin-coated pulmonary artery catheters, which can induce thrombocytopenia (2).

Diagnosis

The diagnosis of HIT requires a high-probability clinical scenario (e.g., thrombocytopenia that develops 5 to 10 days after starting heparin and is accompanied by symptomatic thrombosis) combined with serologic evidence of IgG antiboDICs to the heparin-platelet factor 4 complex (3). The antibody assay measures the release of 14e-labeled serotonin from platelets that are added to a sample of the patient's serum. A positive

TABLE 37.2 Anticoagulation with Direct Thrombin Inhibitors

	Lepirudin	Argatroban
Clearance	Renal	Hepatic
Prophylactic Dose	0.10 mg/kg/hr IV or 25 mg SC every 12 h.	–
Therapeutic Dose	0.4 mg/kg IV bolus, then 0.15 mg/kg/hr (max wt = 110 kg). Adjust dose to PTT = 1.5-3 x control.	Start at 2 μg/kg/min & adjust dose to PIT = 1 .5-3 x control. Max. rate = 10 μg/kg/min.
Dose Adjustments:		
Renal insufficency	See Appendix 4	No dose adjustment
Liver Failure	No dose adjustment	.t initial dose rate to 0.5 μg/kg/min

antibody assay does not secure the diagnosis of HIT because this assay also detects non-pathogenic IgG antiboDICs to heparin-platelet-factor-4 complex (3). For this reason, the antibody assay must be combined with a suggestive clinical scenario to make the diagnosis of HIT.

Acute Management

When HIT is first suspected heparin exposure must be discontinued. Remember to discontinue heparin flushes and remove any heparincoated intravascular catheters. If anticoagulation is necessary, two direct thrombin inhibitors are available: lepirudin and argatroban 04-16). These agents inhibit clot-bound thrombin, and they do not cross-react with heparin antiboDICs. The dose recommendations for each of these agents are shown in Table 37.2. Lepirudin is a recombinant form of hirudin (a component of leech saliva) that has been used successfully in prophylaxis and treatment of thromboembolism in patients with HIT (14,15). Lepirudin is cleared by the kidneys, and dose adjustments are necessary for renal insufficiency (see Appendix 4 for these dose adjustments). Another thrombin inhibitor, argatroban, may be preferred in renal insufficiency because it does not require dose adjustments (see below). Argatroban has also been used successfully to treat thromboembolism in patients with HIT (15,16). This drug is cleared by the liver, and dose adjustments are necessary in hepatic insufficiency (see Table 37.2). Lepirudin may be preferred in hepatic insufficiency because it does not require dose adjustments.

Long- Term Management

Heparin antiboDICs can persist for longer than 100 days after the initial exposure, long after the thrombocytopenia has resolved (5), and heparin should not be re-introduced as long as these antiboDICs persist in the bloodstream. eoumadin can be used for long-term anticoagulation after the thrombocytopenia has resolved, but coumadin should never be used during the active phase of HIT because there is an increased risk of limb gangrene from coumadin 05).

Infections

Thrombocytopenia is almost universal in patients with systemic sepsis, and is presumably due to increased phagocytosis of platelets by macrophages (17). Increased platelet destruction is also responsible for the thrombocytopenia that is reported in 50% of patients with acquired immunodeficiency syndrome (AIDS), but the platelet destruction is immune-mediated in this condition **(8)**. Bleeding is not common in either condition unless the thrombocytopenia is accompanied by other coagulation abnormalities.

Disseminated Intravascular Coagulation

Widespread endothelial damage, as can occur with septicemia or multiple trauma, releases a protein known as *tissue factor* that activates the endogenous coagulation cascade and the fibrinolytic system. This can result in a severe coagulopathy characterized by widespread microvascular thrombosis accompanied by depletion of circulating platelets and procoagulant proteins **(8)**. This condition is called *disseminated intravascular coagulation* (DIC). rn addition to sepsis and trauma, the other major causes of DIC are obstetric emergencies (amniotic fluid embolism, abruptio placentae, eclampsia, and retained fetus syndrome).

Clinical Features

The microvascular thrombosis in DIC produces multiorgan dysfunction. The lungs are commonly involved, and the clinical picture is similar to the acute respiratory distress syndrome, which is described in Chapter 22. Advanced cases are accompanied by acute oliguric renal failure and progressive hepatocellular injury. Depletion of platelets and coagulation factors can be accompanied by bleeding from multiple sites, particularly the gastrointestinal tract.

DIC can also be accompanied by symmetrical necrosis and ecchymosis involving the limbs; a condition known as *purpura fulminans.* This condition can develop in any case of overwhelming sepsis, but it is most characteristic of meningococcemia 0).

Diagnosis

The diagnosis of DIC is based on the presence of a predisposing condition (e.g., severe sepsis) combined with laboratory evidence of widespread coagulation deficits. Table 37.3 shows a scoring system for the

TABLE 37.3 Scoring System for Disseminated Intravascular Coagulation*

Points	0	1	2	3
Platelet Count InL	>100	>=50	<50	
D-dimer *(µg/mL)*	<=1		1-5	>5
Fibrinogen (giL)	>1	<=1		
Prothrombin Index (%)	>70	40-70	<40	

'A score of 5 or greater is consistent with the diagnosis of disseminated coagulation. From Reference

diagnosis of DIC proposed by the International Society on Thrombosis and Haemostasis (9). There are four laboratory abnormalities used in this scoring system. Three of the abnormalities (thrombocytopenia, reduced fibrinogen levels, and prolongation of the prothrombin times) are the result of depletion caused by widespread microvascular thrombosis, and one of the abnormalities (elevated d-dimer levels) is a manifestation of enhanced fibrinolysis. Because the laboratory abnormalities reflect consumption of coagulation factors, DIC is often referred to as a *consumptive coagulopathy.*

Management
Advanced cases of DIC have a mortality rate in excess of 80%, and there is no specific treatment other than that directed against the predisposing conditions. Bleeding often prompts the replacement of platelets and coagulation factors 00 units of cryoprecipitate provides about 2.5 grams of fibrinogen), but this rarely helps, and consumption of the platelets and coagulation proteins can aggravate the microvascular thrombosis. Heparin is usually ineffective in retarding the microvascular thrombosis, probably because of depletion of antithrombin-III (20). Antithrombin-III concentrates can be given with heparin (the AT-III dosage is 90 to 120 Units as a load, then 90 to 120 Units daily for 4 days), but there is no evidence that this practice improves survival (21,22).

Thrombotic Thrombocytopenia Purpura
Thrombotic thrombocytopenia purpura (TTP) is a rare but life-threatening condition caused by immune-mediated platelet aggregation with widespread microvascular thrombosis. Like DIC, it is classified as one of the thrombotic microangiopathies.

Clinical Features
TTP often occurs in young adults, particularly women, and usually follows a nonspecific illness like a viral syndrome. The clinical presentation of TTP is characterized by five clinical features (pentad): fever, change in mental status, acute renal failure, thrombocytopenia, and microangiopathic hemolytic anemia. All 5 clinical features are required for the diagnosis.
Patients usually experience fever and depressed consciousness that can progress rapidly to coma and generalized seizures. Thrombocytopenia is not associated with other coagulation abnormalities, which distinguishes TTP from DIC. The microangiopathic hemolytic anemia is detected by the presence of schistocytes in the blood smear. Prompt diagnosis is mandatory because the treatment for this condition is most effective early in the course of the illness.

Management
The treatment of choice for TTP is plasma exchange (23,24). This can be performed with plasmapheresis equipment that removes blood and separates the plasma from the red cells. The plasma is discarded and the red cells are reinfused with fresh frozen plasma. This is continued until 1.5 times the plasma volume has been exchanged (the normal plasma volume is 40 mL/kg in adult men and 36 mL/kg in adult women). This is repeated daily for approximately 1 week.

If plasmapheresis equipment is unavailable, a "poor man's" plasma exchange can be performed by inserting an arterial catheter into *the* femoral artery and withdrawing 500 mL aliquot", of blood (equivalent to *1 Unit* of whole blood) into a blood collection bag. This is then sent to the blood bank for centrifugation to separate the plasma from the blood cells. The cells are then returned to the patient, and one unit of fresh frozen plasma is infused with every unit of packed red blood celb This is continued until at least one plasma volume has been exchanged.

Acute, fulminant TTP is almost always fatal if untreated. **With prompt use of plasma exchange, as many as 90% of patients can survive** the acute episode (23,24). Platelet transfusiuns are contraindIcated m TTP because they can aggravate the underlying thrombosis

Blood Transfusions

The viability of platelets in whole blood and erythrocyte concentrates (packed cells) is almost completely lost after 24 hours ot storage Therefore, large-volume transfusions can produce dilutional thrombocytopenia. This effect becomes prominent when the transfusIOn volume exceeds 1.5 times the blood volume (25).

A rare type of posttransfusion thrombocytopenia appears approxImately 1 week after transfusion, usually m multiparous women, and is caused by antiplatelet antibodies. This condItion is called *po;.ttrallsjll*sion *purpura,* and thrombocytopenia is often severe and prolonged (26). Platelet counts can fall to 1O,000/μL or lower for as long as 40 days If hemorrhage ensues, plasma exchange is the treatment of choice.

HELLP Syndrome

HELLP (Hemolysis, Elevated Liver enzymes, Low Platelets) is a thrombotic microangiopathy (like DIC and TTP) that is often associated with preeclampsia. This syndrome is one of the major obstetric emergencies. and develops pre-term in about 80% of cases The clinical manifestations often include hypertension and abdominal pain (epigastric or nght upper quadrant), and the laboratory abnormalties are as mdicated by the name of the condition, The management usually involves platelet transfusions to keep the platelet count above 50,000/μL and prompt delivery (see Reference 27 for a more complete description of the management of this condition)

ABNORMAL PLATELET FUNCTION

Renal Failure

impaired platelet adhesion due to impaired fibrinogen binding to platelets and abnormalities in von Willebrand's factor (whlch anchors the platelets to damaged endothelium) is a well-descnbed complication of acute and chronic renal failure (28). Bleeding times become prolonged when the serum creatinine climbs above 6 mg/dL Dialysls corrects the bleeding time in only 30 to 50% of patients (28) The significance of the impaired platelet adhesion in renal failure is unclear. However, upper gastrointestinal bleeding is the second leading cause of death in acute renal failure (28), so the platelet function

abnormality in renal failure should be of some concern. The measures described next may provide some benefit in the renal failure patient who is bleeding.

Desmopressin
Oesmopressin is a vasopressin analogue (deamino-arginine vasopressin, or DDAVP) that increases the levels of von Willebrand factor, and can correct the bleeding time in 75% of patients with renal failure (28,29). The recommended dose is 0.3 μg/kg intravenously or subcutaneously, or 30 (μglkg intranasally (28,29). The effect lasts only 6 to 8 hours, and repeated dosing leads to tachyphylaxis. Responsiveness is restored if the drug is withheld for 3 to 4 days. Oesmopressin does not have the vasoconstrictor actions or antidiuretic effects of vasopressin.
For patients with renal failure who develop significant bleeding, one dose of desmopressin can be given empirically. A second dose can be given 8 to 12 hours later, but repeated dosing for longer than 24 hours is not advisable because of the tachyphylaxis, and also because it is not possible to determine if the drug has a significant effect in individual patients.

Conjugated Estrogens
Conjugated estrogens can also correct the bleeding time in renal failure (mechanism unknown), but the effect lasts for weeks instead of hours. The recommended dose is **0.6 mg/kg IV every day for 5 consecutive days** (1,28,30). The onset of action takes up to one day, but the effect lasts for 2 weeks (30). This regimen has been recommended for patients with recurrent GI bleeding. Conjugated estrogens are not useful for the management of acute bleeding because of the delayed onset of action.

Cardiopulmonary Bypass
Platelet adhesiveness is impaired by unknown mechanisms when blood passes through the oxygenator apparatus used during cardiopulmonary bypass. The severity of the platelet function defect is directly related to the duration of bypass (31). In most cases, the abnormality resolves within a few hours after bypass is completed. However, defects in platelet adhesion may contribute to troublesome mediastinal bleeding in the immediate postoperative period. The management of bleeding in the immediate postop period usually involves reversal of heparin and normalization of all laboratory measurements of coagulation status. There is no proven treatment for impaired platelet adhesion in this situation. Postoperative bleeding after cardiopulmonary bypass often requires reexploration.

Drug-Induced Platelet Defects
A long list of drugs are capable of impairing platelet adhesion, and the ones most likely to be used in the leU are included in Table 37.4. Clinically significant bleeding is most likely to occur with: 1) aspirin and the other anti platelet agents, 2) ketorolac when combined with heparin, and 3) the plasma expander hetastarch, when given in a daily volume that exceeds 1.5 liters.

TABLE 37.4 Drugs That Can Cause Platelet Function Abnormalities·

Antiplatelet Agents	*Beta-Lactam Antibiotics*
Aspirin	Penicillins
Clopidogrel	Cephalosporins
Dipyridamole	
Glycoprotein Inhibitors	*Cardiovascular Drugs*
Ticlodipine	Calcium channel blockers
	Nitroglycerin
Antihistamines	Nitroprusside
Chlorpheniramine	
Diphenhydramine	*Others*
	Dextrans
Antithrombotic Agents	Haloperidol
Alteplase	Hetastarch
Heparin	Ketorolac

*Includes only drugs that are likely to be used in the ICU. From References

PLATELET TRANSFUSIONS

Random Donor Platelet Concentrates

Platelet concentrates are prepared from fresh whole blood in the following manner (2). First, red blood cells are separated by centrifuging whole blood at low speeds (2,000 rpm). The supernatant, which is called "platelet-rich plasma" is then centrifuged at high speeds (5,000 rpm) to separate the platelets, and the platelet plug is re-suspended in a small volume of plasma. Each platelet concentrate prepared in this fashion contains 50 to 100 billion platelets in 50 mL of plasma (2). These "random donor" platelet concentrates are also rich in leukocytes 10^7 to 10^9 leukocytes per unit), and this is responsible for the high incidence of fever associated with platelet transfusions (see later).

Platelets can be stored for up to 7 days, but viability begins to decline after 3 days. Platelet transfusions are usually given as multiples of 4 to 6 platelet concentrates (units), each one from a different donor. The total volume is 200 to 300 mL.

Effect on Circulating Platelet Counts

In the average-size adult, each platelet concentrate should raise the circulating platelet count by at least 5,000/μL (2). For a routine platelet transfusion of 4 to 6 units, the platelet count should increase 20,000/μL to 30,000/μL, respectively. This effect should be apparent one hour after the transfusion, and it should last approximately 8 days.

Reduced Efficacy

Antibodies to ABO antigens on platelets or to leukocyte (HLA) antigens can cause a less-than-expected rise in platelet counts following platelet

transfusions, and sensitization to these antigens is responsible for the platelet refractoriness that occurs in 30 to 70% of patients who receive multiple platelet transfusions (2). This problem can be alleviated by transfusing ABO-compatible platelets, removing the leukocytes from platelet concentrates, or using single-donor platelet transfusions.

Complications
Because one platelet transfusion involves platelet concentrates from 4 to 6 individual donors, the infectious risks associated with homologous blood transfusions are four to six times higher with platelet transfusions than with red blood cell transfusions. Febrile nonhemolytic reactions are also more common with platelet transfusions (due to the high leukocyte content of random donor platelet concentrates), and fever has been reported in up to 30% of platelet transfusion recipients (2).

INDICATIONS FOR PLATELET TRANSFUSIONS
Active Bleeding
In the presence of active bleeding other than ecchymoses or petechiae, platelet transfusions are indicated when:
The platelet count is below 50,000/μL and there are no contraindications to platelet transfusions (see later).
The platelet count is below 100,000 / μL and the bleeding is intracranial, or there is a condition that impairs platelet adhesion (e.g., renal failure).
For trauma victims who receive multiple transfusions, the platelet count should be kept above 100,000/μL if there is a risk for intracranial hemorrhage (32).

Prophylactic Platelet Transfusions
When there is no evidence of active bleeding other than ecchymotic or petechial hemorrhages, and there is thrombocytopenia from bone marrow suppression, prophylactic platelet transfusions are indicated when 0-3):
The platelet count is below 10, 000/μL.

The platelet count is below 20, 000 /μL and there is a risk of hemorrhage (e.g., peptic ulcer disease).

The platelet count is below 50, 000/μL, and the following procedures are planned: bronchoscopic or endoscopic biopsy, lumbar puncture, percutaneous liver biopsy, and major surgery.

Despite evidence that spontaneous bleeding is uncommon with platelet counts down to 5, 000/μL, most of the experts are reluctant to adopt a threshold as low as 5, 000/μL for platelet transfusions.

Central Venous Catheterization
Several studies have shown that central venous cannulation can be performed safely in patients with platelet counts down to 10,000/μL, and one study showed that the experience of the operator is more important than the presence of coagulopathy in determining the risk of bleeding with central line placement (34). Therefore, special considerations other than the standard threshold for prophylactic platelet transfusions (i.e., 10,000/μL) are not necessary for central venous catheter placement.

Contraindications to Platelet Transfusions
Platelet transfusions are contraindicated in patients with thrombotic thrombocytopenia purpura and heparin-induced thrombocytopenia because transfused platelets can aggravate the tendency for thrombosis in these conditions. DIC is not considered a contraindication to platelet transfusions (2), even though transfused platelets can aggravate the microvascular thrombosis in this condition.

FINAL WORD
The following points deserve emphasis regarding platelets in the critically ill patient:
Don't forget heparin as source of thrombocytopenia in the ICU, and don't forget to remove heparin-coated catheters if heparininduced thrombocytopenia is a possibility.
Central venous catheters can be inserted safely in patients with low platelet counts, but experienced physicians should insert the catheters.

REFERENCES