CHAPTER

51

Fluid Management & Blood Component Therapy

KEY CONCEPTS

1. Although the intravascular half-life of a crystalloid solution is 20–30 min, most colloid solutions have intravascular half-lives between 3 and 6 h.
2. Patients with a normal hematocrit should generally be transfused only after losses greater than 10–20% of their blood volume. The exact point is based on the patient's medical condition and the surgical procedure.
3. The most severe transfusion reactions are due to ABO incompatibility; naturally acquired antibodies can react against the transfused (foreign) antigens, activate complement, and result in intravascular hemolysis.
4. In anesthetized patients, an acute hemolytic reaction is manifested by a rise in temperature, unexplained tachycardia, hypotension, hemoglobinuria, and diffuse oozing in the surgical field.
5. Allogeneic transfusion of blood products may diminish immunoresponsiveness and promote inflammation.
6. Immunocompromised and immunosuppressed patients (eg, premature infants, organ transplant recipients, and cancer patients) are particularly susceptible to severe transfusion-related cytomegalovirus (CMV) infections. Ideally, such patients should receive only CMV-negative units.
7. The most common cause of nonsurgical bleeding following massive blood transfusion is dilutional thrombocytopenia.
8. Clinically important hypocalcemia, causing cardiac depression, will not occur in most normal patients unless the transfusion rate exceeds 1 unit every 5 min, and intravenous calcium salts should rarely be required in the absence of measured hypocalcemia.
9. Once adequate tissue perfusion is restored, the most consistent acid-base abnormality following massive blood transfusion is metabolic alkalosis, caused by the rapid hepatic metabolism of citric acid and lactic acid to bicarbonate.

Almost all patients undergoing surgical procedures require venous access for administration of intravenous fluids and medication, and some patients will require transfusion of blood components. The anesthesia provider should be able to assess intravascular volume with sufficient accuracy to correct existing fluid or electrolyte deficits and replace ongoing losses. Errors in fluid and electrolyte replacement or transfusion may result in morbidity or death.

Evaluation of Intravascular Volume

Clinical estimation of intravascular volume must be relied upon because objective measurements of fluid compartment volumes are not practical in the clinical environment. Intravascular volume can be estimated using patient history, physical examination,

and laboratory analysis, often with the aid of sophisticated hemodynamic monitoring techniques. Regardless of the method employed, serial evaluations are necessary to confirm initial impressions and to guide fluid, electrolyte, and blood component therapy. Multiple modalities should complement one another, because all parameters are indirect, nonspecific measures of volume; reliance upon any one parameter may lead to erroneous conclusions.

PATIENT HISTORY

The patient history is an important tool in preoperative volume status assessment. Important factors include recent oral intake, persistent vomiting or diarrhea, gastric suction, significant blood loss or wound drainage, intravenous fluid and blood administration, and recent hemodialysis if the patient has kidney failure.

PHYSICAL EXAMINATION

Indications of hypovolemia include abnormal skin turgor, dehydration of mucous membranes, thready peripheral pulses, increased resting heart rate and decreased blood pressure, orthostatic heart rate and blood pressure changes from the supine to sitting or standing positions, and decreased urinary flow rate (Table 51–1). Unfortunately, many medications administered during anesthesia, as well as the neuroendocrine stress response to operative procedures, alter these signs and render them unreliable in the immediate postoperative period. Intraoperatively, the fullness of a peripheral pulse, urinary flow rate, and indirect signs such as the response of blood pressure to positive-pressure ventilation and to the vasodilating or negative inotropic effects of anesthetics, are most often used.

Pitting edema—presacral in the bedridden patient or pretibial in the ambulatory patient—and increased urinary flow are signs of excess extracellular water and likely hypervolemia in patients with normal cardiac, hepatic, and renal function. Late signs of hypervolemia in settings such as congestive heart failure may include tachycardia, elevated jugular pulse pressure, pulmonary crackles and rales, wheezing, cyanosis, and pink, frothy pulmonary secretions.

TABLE 51–1 Signs of fluid loss (hypovolemia).

	Fluid Loss (Expressed as Percentage of Body Weight)		
Sign	***5%***	***10%***	***15%***
Mucous membranes	Dry	Very dry	Parched
Sensorium	Normal	Lethargic	Obtunded
Orthostatic changes In heart rate In blood pressure	None	Present	Marked >15 bpm ↑[1] >10 mm Hg ↓
Urinary flow rate	Mildly decreased	Decreased	Markedly decreased
Pulse rate	Normal or increased	Increased >100 bpm	Markedly increased >120 bpm
Blood pressure	Normal	Mildly decreased with respiratory variation	Decreased

[1]bpm, beats per minute.

LABORATORY EVALUATION

Several laboratory measurements may be used as surrogates of intravascular volume and adequacy of tissue perfusion, including serial hematocrits, arterial blood pH, urinary specific gravity or osmolality, urinary sodium or chloride concentration, serum sodium, and the blood urea nitrogen (BUN) to serum creatinine ratio. However, these measurements are only indirect indices of intravascular volume, and they often cannot be relied upon intraoperatively because they are affected by many perioperative factors and because laboratory results are often delayed. Laboratory signs of dehydration may include rising hematocrit and hemoglobin, progressive metabolic acidosis (including lactic acidosis), urinary specific gravity greater than 1.010, urinary sodium less than 10 mEq/L, urinary osmolality greater than 450 mOsm/L, hypernatremia, and BUN-to-creatinine ratio greater than 10:1. The hemoglobin and hematocrit are usually unchanged in patients with acute hypovolemia

secondary to acute blood loss because there is insufficient time for extravascular fluid to shift into the intravascular space. Radiographic indicators of volume overload include increased pulmonary vascular and interstitial markings (Kerley "B" lines) or diffuse alveolar infiltrates.

HEMODYNAMIC MEASUREMENTS

Hemodynamic monitoring is discussed in Chapter 5. Central venous pressure (CVP) monitoring has been used in patients with normal cardiac and pulmonary function when volume status is difficult to assess by other means or when rapid or major alterations are expected. However, static CVP readings do not provide an accurate or reliable indication of volume status.

Pulmonary artery pressure monitoring has been used in settings where central venous pressures do not correlate with the clinical assessment or when the patient has primary or secondary right ventricular dysfunction; the latter is usually due to pulmonary or left ventricular disease, respectively. Pulmonary artery occlusion pressure (PAOP) readings of less than 8 mm Hg indicate hypovolemia in the presence of confirmatory clinical signs; however, values less than 15 mm Hg may be associated with relative hypovolemia in patients with poor ventricular compliance. PAOP measurements greater than 18 mm Hg are elevated and generally imply left ventricular volume overload. The normal relationship between PAOP and left ventricular end-diastolic volume is altered by the presence of mitral valve disease (particularly stenosis), severe aortic stenosis, or a left atrial myxoma or thrombus, as well as by increased thoracic and pulmonary airway pressures (see Chapters 5, 20, 21, and 22). All PAOP measurements should be obtained at end expiration and interpreted in the context of the clinical setting. Finally, one should recognize that multiple studies have failed to show that pulmonary artery pressure monitoring leads to improved outcomes in critically ill patients, and that echocardiography provides a much more accurate and less invasive estimate of cardiac filling and function.

Intravascular volume status is often difficult to assess, and goal-directed hemodynamic and fluid therapy utilizing arterial pulse contour analysis and estimation of stroke volume variation (eg, LIDCOrapid, Vigileo FloTrak), esophageal Doppler, or transesophageal echocardiography should be considered when accurate determination of hemodynamic and fluid status is important. Stroke volume variation (SVV) is calculated as follows:

$$SVV = SV_{max} - SV_{min}/SV_{mean}$$

The maximum, minimum and mean SV are calculated for a set period of time by the various measuring devices. During spontaneous ventilation the blood pressure decreases on inspiration. During positive pressure ventilation the opposite occurs. Normal SVV is less than 10–15% for patients on controlled ventilation. Patients with greater degrees of SVV are likely to be responsive to fluid therapy. In addition to providing a better assessment of the patient's volume and hemodynamic status than that obtained with CVP monitoring, these modalities avoid the multiple risks associated with central venous and pulmonary artery catheters.

Intravenous Fluids

Intravenous fluid therapy may consist of infusions of crystalloids, colloids, or a combination of both. Crystalloid solutions are aqueous solutions of ions (salts) with or without glucose, whereas colloid solutions also contain high-molecular-weight substances such as proteins or large glucose polymers. Colloid solutions help maintain plasma colloid oncotic pressure (see Chapter 49) and for the most part remain intravascular, whereas crystalloid solutions rapidly equilibrate with and distribute throughout the entire extracellular fluid space.

Controversy exists regarding the use of colloid versus crystalloid fluids for surgical patients. Proponents of colloids justifiably argue that by maintaining plasma oncotic pressure, colloids are more efficient (ie, a smaller volume of colloids than crystalloids is required to produce the same effect) in restoring normal intravascular volume and cardiac output. Crystalloid proponents, on the other hand, maintain that the crystalloid solutions are equally effective when given in appropriate amounts. Concerns that

colloids may enhance the formation of pulmonary edema fluid in patients with increased pulmonary capillary permeability appear to be unfounded (see Chapter 23). Several generalizations can be made:

1. Crystalloids, when given in sufficient amounts, are just as effective as colloids in restoring intravascular volume.
2. Replacing an intravascular volume deficit with crystalloids generally requires three to four times the volume needed when using colloids.
3. Surgical patients may have an extracellular fluid deficit that exceeds the intravascular deficit.
4. Severe intravascular fluid deficits can be more rapidly corrected using colloid solutions.
5. The rapid administration of large amounts of crystalloids (>4–5 L) is more frequently associated with tissue edema.

Some evidence suggests that marked tissue edema can impair oxygen transport, tissue healing, and return of bowel function following major surgery.

CRYSTALLOID SOLUTIONS

Crystalloids are usually considered as the initial resuscitation fluid in patients with hemorrhagic and septic shock, in burn patients, in patients with head injury (to maintain cerebral perfusion pressure), and in patients undergoing plasmapheresis and hepatic resection. Colloids may be included in resuscitation efforts following initial administration of crystalloid solutions depending upon anesthesia provider preferences and institutional protocols.

A wide variety of solutions is available (Table 51–2), and choice is according to the type of

TABLE 51–2 Composition of crystalloid solutions.

Solution	Toxicity (mOsm/L)	Na^+ (mEq/L)	Cl^- (mEq/L)	K^+ (mEq/L)	Ca^{2+} (mEq/L)	Mg^{2+} (mEq/L)	Glucose (g/L)	Lactate (mEq/L)	HCO_3^- (mEq/L)	Acetate (mEq/L)	Gluconate (mEq/L)
5% dextrose in water (D_5W)	Hypo (253)–						50				
Normal saline (NS)	Iso (308)	154	154								
D_5 ¼NS	Iso (355)	38.5	38.5				50				
D_5 ½NS	Hyper (432)	77	77				50				
D_5NS	Hyper (586)	154	154				50				
Lactated Ringer's injection (LR)	Iso (273)	130	109	4	3			28			
D_5LR	Hyper (525)	130	109	4	3		50	28			
½NS	Hypo (154)	77	77								
3% S	Hyper (1026)	513	513								
5% S	Hyper (1710)	855	855								
7.5% $NaHCO_3$	Hyper (1786)	893							893		
Plasmalyte	Iso (294)	140	98	5		3				27	23

fluid loss being replaced. For losses primarily involving water, replacement is with hypotonic solutions, also called maintenance-type solutions. If losses involve both water and electrolytes, replacement is with isotonic electrolyte solutions, also called replacement-type solutions. Glucose is provided in some solutions to maintain tonicity, or prevent ketosis and hypoglycemia due to fasting, or based on tradition. Children are prone to developing hypoglycemia (<50 mg/dL) following 4- to 8-h fasts.

Because most intraoperative fluid losses are isotonic, replacement-type solutions are generally used. The most commonly used fluid is lactated Ringer's solution. Although it is slightly hypotonic, providing approximately 100 mL of free water per liter and tending to lower serum sodium, lactated Ringer's generally has the least effect on extracellular fluid composition and appears to be the most physiological solution when large volumes are necessary. The lactate in this solution is converted by the liver into bicarbonate. **When given in large volumes, normal saline produces a dilutional hyperchloremic acidosis because of its high sodium and chloride content (154 mEq/L): plasma bicarbonate concentration decreases as chloride concentration increases.** Normal saline is the preferred solution for hypochloremic metabolic alkalosis and for diluting packed red blood cells prior to transfusion. Five percent dextrose in water (D_5W) is used for replacement of pure water deficits and as a maintenance fluid for patients on sodium restriction. Hypertonic 3% saline is employed in therapy of severe symptomatic hyponatremia (see Chapter 49). Hypotonic solutions must be administered slowly to avoid inducing hemolysis.

COLLOID SOLUTIONS

The osmotic activity of the high-molecular-weight substances in colloids tends to maintain these solutions intravascularly. Although the intravascular half-life of a crystalloid solution is 20–30 min, most colloid solutions have intravascular half-lives between 3 and 6 h. The relatively greater cost and occasional complications associated with colloids may limit their use. Generally accepted indications for colloids include (1) fluid resuscitation in patients with severe intravascular fluid deficits (eg, hemorrhagic shock) prior to the arrival of blood for transfusion, and (2) fluid resuscitation in the presence of severe hypoalbuminemia or conditions associated with large protein losses such as burns. For burn patients, colloids are not included in most initial resuscitation protocols (and we strongly recommend that burn surgeons and anesthesia personnel develop a resuscitation protocol and follow it), but may be considered following initial resuscitation with more extensive burn injuries during subsequent operative procedures.

Many clinicians also use colloid solutions in conjunction with crystalloids when fluid replacement needs exceed 3–4 L prior to transfusion. It should be noted that colloid solutions are prepared in normal saline (Cl^- 145–154 mEq/L) and thus can also cause hyperchloremic metabolic acidosis (see above). Some clinicians suggest that during anesthesia, maintenance (and other) fluid requirements be provided with crystalloid solutions and blood loss be replaced on a milliliter-per-milliliter basis with colloid solutions (including blood products).

Several colloid solutions are generally available. All are derived from either plasma proteins or synthetic glucose polymers and are supplied in isotonic electrolyte solutions.

Blood-derived colloids include albumin (5% and 25% solutions) and plasma protein fraction (5%). Both are heated to 60°C for at least 10 h to minimize the risk of transmitting hepatitis and other viral diseases. Plasma protein fraction contains α- and β-globulins in addition to albumin and has occasionally resulted in hypotensive reactions. These reactions are allergic in nature and may involve activators of prekallikrein.

Synthetic colloids include dextrose starches and gelatins. Gelatins are associated with histamine-mediated allergic reactions and are not available in the United States. **Dextran** is available as dextran 70 (Macrodex) and dextran 40 (Rheomacrodex), which have average molecular weights of 70,000 and 40,000, respectively. Although dextran 70 is a better volume expander than dextran 40, the latter also improves blood flow through the microcirculation, presumably by decreasing blood viscosity, and is often administered to take advantage of these rheological properties rather than to meet "fluid

requirements." Antiplatelet effects are also described for dextrans. Infusions exceeding 20 mL/kg per day can interfere with blood typing, may prolong bleeding time, and have been associated with kidney failure. Dextrans can also be antigenic, and both mild and severe anaphylactoid and anaphylactic reactions are described. Dextran 1 (Promit) may be administered prior to dextran 40 or dextran 70 to prevent severe anaphylactic reactions; it acts as a hapten and binds any circulating dextran antibodies.

Hetastarch (hydroxyethyl starch) is available in multiple formulations, which are designated by concentration, molecular weight, degree of starch substitution (on a molar basis), and ratio of hydroxylation between the C2 and the C6 positions. Thus in some countries a wide variety of formulations are available with concentrations between 6% and 10%, molecular weights between 200 and 670, and degree of molar substitution between 0.4 and 0.7. A greater ratio of C2 versus C6 substitution leads to longer persistence in plasma. The starch molecules are derived from plants. Smaller starch molecules are eliminated by the kidneys, whereas large molecules must first be broken down by amylase. Hetastarch is highly effective as a plasma expander and is less expensive than albumin. Moreover, hetastarch is nonantigenic, and anaphylactoid reactions are rare. Coagulation studies and bleeding times are generally not significantly affected following infusions of older, higher molecular weight formulations up to 1.0 L in adults. Newer, lower molecular weight formulations can safely be given in larger volumes.

Perioperative Fluid Therapy

Perioperative fluid therapy includes replacement of normal losses (maintenance requirements), of preexisting fluid deficits, and of surgical wound losses including blood loss.

NORMAL MAINTENANCE REQUIREMENTS

In the absence of oral intake, fluid and electrolyte deficits can rapidly develop as a result of continued urine formation, gastrointestinal secretions, sweating, and insensible losses from the skin and lungs. Normal maintenance requirements can be estimated from Table 51–3.

TABLE 51–3 Estimating maintenance fluid requirements.[1]

Weight	Rate
For the first 10 kg	4 mL/kg/h
For the next 10 kg	Add 2 mL/kg/h
For each kg above 20 kg	Add 1 mL/kg/h

[1]Example: What are the maintenance fluid requirements for a 25-kg child? Answer: 40 + 20 + 5 = 65 mL/h.

PREEXISTING DEFICITS

Patients presenting for surgery after an overnight fast without any fluid intake will have a preexisting deficit proportionate to the duration of the fast. The deficit can be estimated by multiplying the normal maintenance rate by the length of the fast. For the average 70-kg person fasting for 8 h, this amounts to (40 + 20 + 50) mL/h × 8 h, or 880 mL. In fact, the real deficit is less as a result of renal conservation. (After all, how many of us would feel the need to consume nearly 1L of fluid upon awakening after 8 hours of sleep?)

Abnormal fluid losses frequently contribute to preoperative deficits. Preoperative bleeding, vomiting, diuresis, and diarrhea are often contributory. Occult losses (really redistribution; see below) due to fluid sequestration by traumatized or infected tissues or by ascites can also be substantial. Increased insensible losses due to hyperventilation, fever, and sweating are often overlooked.

Ideally, deficits should be replaced preoperatively in surgical patients. The fluids used should be similar in composition to the fluids lost (Table 51–4).

SURGICAL FLUID LOSSES

Blood Loss

One of the most important, yet difficult, tasks of anesthesia personnel is to monitor and estimate blood loss. Although estimates are complicated by

TABLE 51–4 Electrolyte content of body fluids.

Fluid	Na^+ (mEq/L)	K^+ (mEq/L)	Cl^- (mEq/L)	HCO_3^- (mEq/L)
Sweat	30–50	5	45–55	
Saliva	2–40	10–30	6–30	30
Gastric juice				
High acidity	10–30	5–40	80–150	
Low acidity	70–140	5–40	55–95	5–25
Pancreatic secretions	115–180	5	55–95	60–110
Biliary secretions	130–160	5	90–120	30–40
Ileal fluid	40–135	5–30	20–90	20–30
Diarrheal stool	20–160	10–40	30–120	30–50

occult bleeding into the wound or under the surgical drapes, accuracy is important to guide fluid therapy and transfusion.

The most commonly used method for estimating blood loss is measurement of blood in the surgical suction container and visual estimation of the blood on surgical sponges ("4 by 4's") and laparotomy pads ("lap sponges"). A fully soaked 4 × 4 sponge is said to hold 10 mL of blood, whereas a soaked "lap" holds 100–150 mL. More accurate estimates are obtained if sponges and "laps" are weighed before and after use, which is especially important during pediatric procedures. Use of irrigating solutions complicates estimates, but their use should be noted and an attempt made to compensate. Serial hematocrits or hemoglobin concentrations reflect the ratio of blood cells to plasma, not necessarily blood loss, and rapid fluid shifts and intravenous replacement affect measurements.

Other Fluid Losses

Many surgical procedures are associated with obligatory losses of fluids other than blood. Such losses are due mainly to evaporation and internal redistribution of body fluids. Evaporative losses are most significant with large wounds and are proportional to the surface area exposed and to the duration of the surgical procedure.

Internal redistribution of fluids—often called *third-spacing*—can cause massive fluid shifts and severe intravascular depletion. Everything related to "third-space" fluid loss is controversial, including whether it actually exists in patients other than those with peritonitis, burns, and similar situations characterized by inflamed or infected tissue. Traumatized, inflamed, or infected tissue can sequester large amounts of fluid in the interstitial space and can translocate fluid across serosal surfaces (ascites) or into bowel lumen. Shifting of intravascular fluid into the interstitial space is especially important; protein-free fluid shift across an intact vascular barrier into the interstitial space is exacerbated by hypervolemia, and pathological alteration of the vascular barrier allows protein-rich fluid shift.

INTRAOPERATIVE FLUID REPLACEMENT

Intraoperative fluid therapy should include supplying basic fluid requirements and replacing residual preoperative deficits as well as intraoperative losses (blood loss, fluid redistribution, and evaporation). Selection of the type of intravenous solution depends on the surgical procedure and the expected blood loss. For minor procedures involving minimal blood loss, dilute maintenance solutions can be used. For all other procedures, lactated Ringer's solution or Plasmalyte is generally used even for maintenance requirements.

Replacing Blood Loss

Ideally, blood loss should be replaced with crystalloid or colloid solutions to maintain intravascular volume (normovolemia) until the danger of anemia outweighs the risks of transfusion. At that point, further blood loss is replaced with transfusions of red blood cells to maintain hemoglobin concentration (or hematocrit) at that level. There are no mandatory transfusion triggers. The point where the benefits of transfusion outweigh its risks must be considered on an individual basis.

Below a hemoglobin concentration of 7 g/dL, the resting cardiac output increases to maintain a normal oxygen delivery. An increased hemoglobin concentration may be appropriate for older and sicker patients with cardiac or pulmonary disease, particularly when there is clinical evidence (eg, a reduced mixed venous oxygen saturation and a persisting tachycardia) that transfusion would be useful.

In settings other than massive trauma, most clinicians administer lactated Ringer's solution or Plasmalyte in approximately three to four times the volume of the blood lost, or colloid in a 1:1 ratio, until the transfusion point is reached. At that time, blood is replaced unit-for-unit as it is lost, with reconstituted packed red blood cells.

The transfusion point can be determined preoperatively from the hematocrit and by estimating blood volume (Table 51–5). Patients with a normal hematocrit should generally be transfused only after losses greater than 10–20% of their blood volume. The exact point is based on the patient's medical condition and the surgical procedure. The amount of blood loss necessary for the hematocrit to fall to 30% can be calculated as follows:

1. Estimate blood volume from Table 51–5.
2. Estimate the red blood cell volume (RBCV) at the preoperative hematocrit ($RBCV_{preop}$).
3. Estimate RBCV at a hematocrit of 30% ($RBCV_{30\%}$), assuming normal blood volume is maintained.
4. Calculate the RBCV lost when the hematocrit is 30%; $RBCV_{lost} = RBCV_{preop} - RBCV_{30\%}$.
5. Allowable blood loss = $RBCV_{lost} \times 3$.

Example

An 85-kg woman has a preoperative hematocrit of 35%. How much blood loss will decrease her hematocrit to 30%?

Estimated blood volume = 65 mL/kg × 85 kg
= 5525 mL.
$RBCV_{35\%} = 5525 \times 35\% = 1934$ mL.
$RBCV_{30\%} = 5525 \times 30\% = 1658$ mL.
Red cell loss at 30% = 1934 − 1658 = 276 mL.
Allowable blood loss = 3 × 276 mL = 828 mL.

Therefore, transfusion should be considered only when this patient's blood loss exceeds 800 mL. Increasingly, transfusions are not recommended until the hematocrit decreases to 24% or lower (hemoglobin <8.0 g/dL), but it is necessary to take into account the rate of blood loss and comorbid conditions (eg, cardiac disease, in which case transfusion might be indicated if only 800 mL of blood is lost).

Clinical guidelines commonly used include: (1) one unit of red blood cells will increase hemoglobin 1 g/dL and the hematocrit 2–3% in adults; and (2) a 10-mL/kg transfusion of red blood cells will increase hemoglobin concentration by 3 g/dL and the hematocrit by 10%.

TABLE 51–5 Average blood volumes.

Age	Blood Volume
Neonates	
Premature	95 mL/kg
Full-term	85 mL/kg
Infants	80 mL/kg
Adults	
Men	75 mL/kg
Women	65 mL/kg

Replacing Redistributive & Evaporative Losses

Because redistributive and evaporative losses are primarily related to wound size and the extent of surgical dissections and manipulations, procedures can be classified according to the degree of tissue trauma. These additional fluid losses can be replaced

TABLE 51–6 Redistribution and evaporative surgical fluid losses.

Degree of Tissue Trauma	Additional Fluid Requirement
Minimal (eg, herniorrhaphy)	0–2 mL/kg
Moderate (eg, cholecystectomy)	2–4 mL/kg
Severe (eg, bowel resection)	4–8 mL/kg

according to Table 51–6, based on whether tissue trauma is minimal, moderate, or severe. These values are only guidelines, and actual needs vary considerably from patient to patient.

Transfusion

BLOOD GROUPS

Human red cell membranes are estimated to contain at least 300 different antigenic determinants, and at least 20 separate blood group antigen systems are known. Fortunately, only the ABO and the Rh systems are important in the majority of blood transfusions. Individuals often produce antibodies (alloantibodies) to the alleles they lack within each system. Such antibodies are responsible for the most serious reactions to transfusions. Antibodies may occur "naturally" or in response to sensitization from a previous transfusion or pregnancy.

The ABO System

ABO blood group typing is determined by the presence or absence of A or B red blood cell (RBC) surface antigens: Type A blood has A RBC antigen, type B blood has B RBC antigen, type AB blood has both A and B RBC antigens, and type O blood has neither A nor B RBC antigen present. Almost all individuals not having A or B antigen "naturally" produce antibodies, mainly immunoglobulin (Ig) M, against those missing antigens within the first year of life.

The Rh System

There are approximately 46 Rhesus group red cell surface antigens, and patients with the D Rhesus antigen are considered Rh-positive. Approximately 85% of the white population and 92% of the black population has the D antigen, and individuals lacking this antigen are called Rh-negative. In contrast to the ABO groups, Rh-negative patients usually develop antibodies against the D antigen only after an Rh-positive transfusion or with pregnancy, in the situation of an Rh-negative mother delivering an Rh-positive baby.

Other Red Blood Cell Antigen Systems

Other red cell antigen systems include Lewis, P, Ii, MNS, Kidd, Kell, Duffy, Lutheran, Xg, Sid, Cartright, YK, and Chido Rodgers. Fortunately, with some exceptions (Kell, Kidd, Duffy, and Ss), alloantibodies against these antigens rarely cause serious hemolytic reactions.

COMPATIBILITY TESTING

The purpose of compatibility testing is to predict and to prevent antigen–antibody reactions as a result of red cell transfusions.

ABO–Rh Testing

3 The most severe transfusion reactions are due to ABO incompatibility; naturally acquired antibodies can react against the transfused (foreign) antigens, activate complement, and result in intravascular hemolysis. The patient's red cells are tested with serum known to have antibodies against A and against B to determine blood type. Because of the almost universal prevalence of natural ABO antibodies, confirmation of blood type is then made by testing the patient's serum against red cells with a known antigen type.

The patient's red cells are also tested with anti-D antibodies to determine Rh status. If the subject is Rh-negative, the presence of anti-D antibody is checked by mixing the patient's serum against Rh-positive red cells. The probability of developing anti-D antibodies after a single exposure to the Rh antigen is 50–70%.

Antibody Screen

The purpose of this test is to detect in the serum the presence of the antibodies that are most commonly

associated with non-ABO hemolytic reactions. The test (also known as the indirect Coombs test) requires 45 min and involves mixing the patient's serum with red cells of known antigenic composition; if specific antibodies are present, they will coat the red cell membrane, and subsequent addition of an antiglobulin antibody results in red cell agglutination. Antibody screens are routinely done on all donor blood and are frequently done for a potential recipient instead of a crossmatch (below).

Crossmatch

A crossmatch mimics the transfusion: donor red cells are mixed with recipient serum. Crossmatching serves three functions: (1) it confirms ABO and Rh typing, (2) it detects antibodies to the other blood group systems, and (3) it detects antibodies in low titers or those that do not agglutinate easily.

Type & Crossmatch versus Type & Screen

In the situation of negative antibody screen without crossmatch, the incidence of serious hemolytic reaction with ABO- and Rh-compatible transfusion is less than 1:10,000. Crossmatching, however, assures optimal safety and detects the presence of less common antibodies not usually tested for in a screen. Because of the expense and time involved (45 min), crossmatches are often now performed before the need to transfuse only when the patient's antibody screen is positive, when the probability of transfusion is high, or when the patient is considered at risk for alloimmunization.

EMERGENCY TRANSFUSIONS

When a patient is exsanguinating, the urgent need to transfuse may arise prior to completion of a crossmatch, screen, or even blood typing. If the patient's blood type is known, an abbreviated crossmatch, requiring less than 5 min, will confirm ABO compatibility. **If the recipient's blood type and Rh status is not known with certainty and transfusion must be started before determination, type O Rh-negative (universal donor) red cells may be used.**

BLOOD BANK PRACTICES

Blood donors are screened to exclude medical conditions that might adversely affect the donor or the recipient. Once the blood is collected, it is typed, screened for antibodies, and tested for hepatitis B, hepatitis C, syphilis, and human immunodeficiency virus (HIV). A preservative–anticoagulant solution is added. The most commonly used solution is **CPDA-1,** which contains citrate as an anticoagulant (by binding calcium), phosphate as a buffer, dextrose as a red cell energy source, and adenosine as a precursor for adenosine triphosphate (ATP) synthesis. CPDA-1-preserved blood can be stored for 35 days, after which the viability of the red cells rapidly decreases. Alternatively, use of either AS-1 (Adsol) or AS-3 (Nutrice) extends the shelf-life to 6 weeks.

Nearly all units collected are separated into their component parts (ie, red cells, platelets, and plasma). In other words, whole blood units are rarely available for transfusion in civilian practice. When centrifuged, one unit of whole blood yields approximately 250 mL of packed red blood cells (PRBCs) with a hematocrit of 70%; following the addition of saline preservative, the volume of a unit of PRBCs often reaches 350 mL. Red cells are normally stored at 1–6°C, but may be frozen in a hypertonic glycerol solution for up to 10 years. The latter technique is usually reserved for storage of blood with rare phenotypes.

The supernatant is centrifuged to yield platelets and plasma. The unit of platelets obtained generally contains 50–70 mL of plasma and can be stored at 20–24°C for 5 days. The remaining plasma supernatant is further processed and frozen to yield fresh frozen plasma; rapid freezing helps prevent inactivation of labile coagulation factors (V and VIII). Slow thawing of fresh frozen plasma yields a gelatinous precipitate (cryoprecipitate) that contains high concentrations of factor VIII and fibrinogen. Once separated, this cryoprecipitate can be refrozen for storage. One unit of blood yields about 200 mL of plasma, which is frozen for storage; once thawed, it must be transfused within 24 h. Most platelets are now obtained from donors by apheresis, and a single platelet apheresis unit is equivalent to the amount of platelets derived from 6–8 units of whole blood.

The use of leukocyte-reduced (*leukoreduction*) blood products has been rapidly adopted by many countries, including the United States, in order to decrease the risk of transfusion-related febrile reactions, infections, and immunosuppression.

INTRAOPERATIVE TRANSFUSION PRACTICES

Packed Red Blood Cells

Blood transfusions should be given as PRBCs, which allows optimal utilization of blood bank resources. Surgical patients require volume as well as red cells, and crystalloid or colloid can be infused simultaneously through a second intravenous line for volume replacement.

Prior to transfusion, each unit should be carefully checked against the blood bank slip and the recipient's identity bracelet. The transfusion tubing should contain a 170-μm filter to trap any clots or debris. Blood for intraoperative transfusion should be warmed to 37°C during infusion, particularly when more than 2–3 units will be transfused; failure to do so can result in profound hypothermia. The additive effects of hypothermia and the typically low levels of 2,3-diphosphoglycerate (2,3-DPG) in stored blood can cause a marked leftward shift of the hemoglobin–oxygen dissociation curve (see Chapter 23) and, at least theoretically, promote tissue hypoxia.

Fresh Frozen Plasma

Fresh frozen plasma (FFP) contains all plasma proteins, including most clotting factors. Transfusions of FFP are indicated in the treatment of isolated factor deficiencies, the reversal of warfarin therapy, and the correction of coagulopathy associated with liver disease. Each unit of FFP generally increases the level of each clotting factor by 2–3% in adults. The initial therapeutic dose is usually 10–15 mL/kg. The goal is to achieve 30% of the normal coagulation factor concentration.

FFP may also be used in patients who have received massive blood transfusions (see below) and continue to bleed following platelet transfusions. Patients with antithrombin III deficiency or thrombotic thrombocytopenic purpura also benefit from FFP transfusions.

Each unit of FFP carries the same infectious risk as a unit of whole blood. In addition, occasional patients may become sensitized to plasma proteins. ABO-compatible units should generally be given but are not mandatory. As with red cells, FFP should generally be warmed to 37°C prior to transfusion.

Platelets

Platelet transfusions should be given to patients with thrombocytopenia or dysfunctional platelets in the presence of bleeding. Prophylactic platelet transfusions are also indicated in patients with platelet counts below $10{,}000–20{,}000 \times 10^9$/L because of an increased risk of spontaneous hemorrhage.

Platelet counts less than $50{,}000 \times 10^9$/L are associated with increased blood loss during surgery. Thrombocytopenic patients often receive prophylactic platelet transfusions prior to surgery or invasive procedures. Vaginal delivery and minor surgical procedures may be performed in patients with normal platelet function and counts greater than $50{,}000 \times 10^9$/L. Administration of a single unit of platelets may be expected to increase the platelet count by $5000–10{,}000 \times 10^9$/L, and with administration of a platelet apheresis unit, by $30{,}000–60{,}000 \times 10^9$/L.

ABO-compatible platelet transfusions are desirable but not necessary. Transfused platelets generally survive only 1–7 days following transfusion. ABO compatibility may increase platelet survival. Rh sensitization can occur in Rh-negative recipients due to the presence of a few red cells in Rh-positive platelet units. Moreover, anti-A or anti-B antibodies in the 70 mL of plasma in each platelet unit can cause a hemolytic reaction against the recipient's red cells when a large number of ABO-incompatible platelet units is given. Administration of Rh immunoglobulin to Rh-negative individuals can protect against Rh sensitization following Rh-positive platelet transfusions.

Granulocyte Transfusions

Granulocyte transfusions, prepared by leukapheresis, may be indicated in neutropenic patients with bacterial infections not responding to antibiotics. Transfused granulocytes have a very short circulatory life span, so that daily transfusions of 10^{10} granulocytes are usually required. Irradiation of

these units decreases the incidence of graft-versus-host reactions, pulmonary endothelial damage, and other problems associated with transfusion of leukocytes (see below), but may adversely affect granulocyte function. The availability of granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) has greatly reduced the use of granulocyte transfusions.

Indications for Procoagulant Transfusions

Blood products can be misused in surgical settings. Use of a transfusion algorithm, particularly for components such as plasma, platelets, and cryoprecipitate, and particularly when the algorithm is guided by appropriate laboratory testing, will reduce unnecessary transfusion of these precious (but dangerous) resources (see Chapter 22). Derived from military experience, there is a trend in major trauma care towards transfusing blood products in equal ratios early in resuscitation in order to preempt or correct trauma-induced coagulopathy. This balanced approach to transfusion of blood products, 1:1:1 (one unit of FFP and one unit of platelets with each unit of PRBCs) is termed damage control resuscitation (see Chapter 39).

Complications of Blood Transfusion

IMMUNE COMPLICATIONS

Immune complications following blood transfusions are primarily due to sensitization of the recipient to donor red cells, white cells, platelets, or plasma proteins. Less commonly, the transfused cells or serum may mount an immune response against the recipient.

1. Hemolytic Reactions

Hemolytic reactions usually involve specific destruction of the transfused red cells by the recipient's antibodies. Less commonly, hemolysis of a recipient's red cells occurs as a result of transfusion of red cell antibodies. Incompatible units of platelet concentrates, FFP, clotting factor concentrates, or cryoprecipitate may contain small amounts of plasma with anti-A or anti-B (or both) alloantibodies. Transfusions of large volumes of such units can lead to intravascular hemolysis. Hemolytic reactions are commonly classified as either acute (intravascular) or delayed (extravascular).

Acute Hemolytic Reactions

Acute intravascular hemolysis is usually due to ABO blood incompatibility, and the reported frequency is approximately 1:38,000 transfusions. The most common cause is misidentification of a patient, blood specimen, or transfusion unit. These reactions are often severe, and may occur after infusion of as little as 10–15 mL of ABO-incompatible blood. The risk of a fatal hemolytic reaction is about 1 in 100,000 transfusions. In awake patients, symptoms include chills, fever, nausea, and chest and flank pain. 4 In anesthetized patients, an acute hemolytic reaction may be manifested by a rise in temperature, unexplained tachycardia, hypotension, hemoglobinuria, and diffuse oozing in the surgical field. Disseminated intravascular coagulation, shock, and kidney failure can develop rapidly. The severity of a reaction often depends upon the volume of incompatible blood that has been administered.

Management of hemolytic reactions can be summarized as follows:

1. If a hemolytic reaction is suspected, the transfusion should be stopped immediately and the blood bank should be notified.
2. The unit should be rechecked against the blood slip and the patient's identity bracelet.
3. Blood should be drawn to identify hemoglobin in plasma, to repeat compatibility testing, and to obtain coagulation studies and a platelet count.
4. A urinary catheter should be inserted, and the urine should be checked for hemoglobin.
5. Osmotic diuresis should be initiated with mannitol and intravenous fluids.

Delayed Hemolytic Reactions

A delayed hemolytic reaction—also called extravascular hemolysis—is generally mild and is caused by antibodies to non-D antigens of the Rh system or

to foreign alleles in other systems such as the Kell, Duffy, or Kidd antigens. Following an ABO and Rh D-compatible transfusion, patients have a 1–1.6% chance of forming antibodies directed against foreign antigens in these other systems. By the time significant amounts of these antibodies have formed (weeks to months), the transfused red cells have been cleared from the circulation. Moreover, the titer of these antibodies subsequently decreases and may become undetectable. Reexposure to the same foreign antigen during a subsequent red cell transfusion, however, triggers an anamnestic antibody response against the foreign antigen. The hemolytic reaction is therefore typically delayed 2–21 days after transfusion, and symptoms are generally mild, consisting of malaise, jaundice, and fever. The patient's hematocrit typically fails to rise, or rises only transiently, in spite of the transfusion and the absence of bleeding. The serum unconjugated bilirubin increases as a result of hemoglobin breakdown.

Diagnosis of delayed antibody-mediated hemolytic reactions may be facilitated by the antiglobulin (Coombs) test. The direct Coombs test detects the presence of antibodies on the membrane of red cells. In this setting, however, this test cannot distinguish between recipient antibodies coated on donor red cells and donor antibodies coated on recipient red cells. The latter requires a more detailed reexamination of pretransfusion specimens from both the patient and the donor.

The treatment of delayed hemolytic reactions is primarily supportive. The frequency of delayed hemolytic transfusion reactions is estimated to be approximately 1:12,000 transfusions. Pregnancy (exposure to fetal red cells) can also be responsible for the formation of alloantibodies to red cells.

2. Nonhemolytic Immune Reactions

Nonhemolytic immune reactions are due to sensitization of the recipient to the donor's white cells, platelets, or plasma proteins; the risk of these reactions may be minimized by the use of leukoreduced blood products.

Febrile Reactions

White cell or platelet sensitization is typically manifested as a febrile reaction. Such reactions are relatively common (1–3% of transfusion episodes) and are characterized by an increase in temperature without evidence of hemolysis. Patients with a history of repeated febrile reactions should receive leukoreduced transfusions only.

Urticarial Reactions

Urticarial reactions are usually characterized by erythema, hives, and itching without fever. They are relatively common (1% of transfusions) and are thought to be due to sensitization of the patient to transfused plasma proteins. Urticarial reactions can be treated with antihistaminic drugs (H_1 and perhaps H_2 blockers) and steroids.

Anaphylactic Reactions

Anaphylactic reactions are rare (approximately 1:150,000 transfusions). These severe reactions may occur after only a few milliliters of blood has been given, typically in IgA-deficient patients with anti-IgA antibodies who receive IgA-containing blood transfusions. The prevalence of IgA deficiency is estimated to be 1:600–800 in the general population. Such reactions require treatment with epinephrine, fluids, corticosteroids, and H_1 and H_2 blockers. Patients with IgA deficiency should receive thoroughly washed packed red cells, deglycerolized frozen red cells, or IgA-free blood units.

Transfusion-Related Acute Lung Injury

Transfusion-related acute lung injury (TRALI) presents as acute hypoxia and noncardiac pulmonary edema occurring within 6 h of blood product transfusion. It may occur as frequently as 1:5000 transfused units, and with transfusion of any blood component, but especially platelets and FFP. It is thought that transfusion of antileukocytic or anti-HLA antibodies results in damage to the alveolar–capillary membrane. Treatment is similar to that for acute respiratory distress syndrome (see Chapter 57), with the important difference that TRALI may resolve within a few days with supportive therapy.

Graft-Versus-Host Disease

This type of reaction may be seen in immunocompromised patients. Cellular blood products contain lymphocytes capable of mounting an immune

response against the compromised (recipient) host. Use of special leukocyte filters alone does not reliably prevent graft-versus-host disease; irradiation (1500–3000 cGy) of red cell, granulocyte, and platelet transfusions effectively eliminates lymphocytes without altering the efficacy of such transfusions.

Post-Transfusion Purpura

Rarely, profound thrombocytopenia may occur following blood transfusions. This post-transfusion purpura results from the development of platelet alloantibodies. For unknown reasons, these antibodies also destroy the patient's own platelets. The platelet count typically drops precipitously 5–10 days following transfusion. Treatment includes intravenous IgG and plasmapheresis.

Transfusion-Related Immunomodulation

5 Allogeneic transfusion of blood products may diminish immunoresponsiveness and promote inflammation. Post-transfusion immunosuppression is clearly evident in renal transplant recipients, in whom preoperative blood transfusion improves graft survival. Recent studies suggest that perioperative transfusion may increase the risk of postoperative bacterial infection, cancer recurrence, and mortality, all of which emphasize the need to avoid unnecessary administration of blood products.

INFECTIOUS COMPLICATIONS

Viral Infections

A. Hepatitis

The incidence of post-transfusion viral hepatitis varies greatly, from approximately 1:200,000 transfusions (for hepatitis B) to approximately 1:1,900,000 (for hepatitis C). Most acute cases are anicteric. Hepatitis C is the more serious infection; most cases progress to chronic hepatitis, with cirrhosis developing in 20% of chronic carriers and hepatocellular carcinoma developing in up to 5% of chronic carriers.

B. Acquired Immunodeficiency Syndrome (AIDS)

The virus responsible AIDS, HIV-1, is transmissible by blood transfusion. HIV-2 is a similar, but less virulent virus. All blood is tested for the presence of anti-HIV-1 and anti-HIV-2 antibodies. The requirement for nucleic acid testing by the Food and Drug Administration (FDA) has decreased the risk of transfusion-transmitted HIV to approximately 1:1,900,000 transfusions.

C. Other Viral Infections

Cytomegalovirus (CMV) and Epstein–Barr virus usually cause asymptomatic or mild systemic illness. Some individuals infected with these viruses become asymptomatic infectious carriers; the white cells in blood units from such donors are capable of transmitting either virus. Immunocompromised and immunosuppressed patients (eg, premature infants, organ transplant recipients, and cancer patients) are particularly susceptible to severe transfusion-related CMV infections. Ideally, such patients should receive only CMV-negative units. However, recent studies indicate that the risk of CMV transmission from transfusion of leukoreduced blood products is equivalent to CMV test-negative units. Human T-cell lymphotropic viruses 1 and 2 (HTLV-1 and HTLV-2) are leukemia and lymphoma viruses, respectively, that have been reported to be transmitted by blood transfusion; the former has also been associated with myelopathy. Parvovirus transmission has been reported following transfusion of coagulation factor concentrates and can result in transient aplastic crises in immunocompromised hosts. West Nile virus infection may result in encephalitis with a fatality rate of up to 10%, and transmission of this virus by transfusion has been reported.

6

Parasitic Infections

Parasitic diseases that can be transmitted by transfusion include malaria, toxoplasmosis, and Chagas' disease. Such cases are very rare.

Bacterial Infections

Bacterial contamination of blood products is the second leading cause of transfusion-associated mortality. The prevalence of positive bacterial cultures in blood products ranges from 1:2000 for platelets to 1:7000 for PRBCs and may be due to transient donor bacteremia or inadequate antisepsis during phlebotomy. The prevalence of sepsis due to blood transfusion ranges from 1:25,000 for platelets to 1:250,000

for PRBCs. Both gram-positive (*Staphylococcus*) and gram-negative (*Yersinia* and *Citrobacter*) bacteria can contaminate blood transfusions and transmit disease. To avoid the possibility of significant bacterial contamination, blood products should be administered over a period shorter than 4 h. Specific bacterial diseases rarely transmitted by blood transfusions from donors include syphilis, brucellosis, salmonellosis, yersiniosis, and various rickettsioses.

MASSIVE BLOOD TRANSFUSION

Massive transfusion is most often defined as the need to transfuse one to two times the patient's blood volume. For most adult patients, that is the equivalent of 10–20 units. The approach to massive transfusion (and to lesser degrees of transfusion) after trauma injury has been greatly influenced by military experience in recent Middle Eastern and Central Asian wars in which outcomes have improved with concurrent transfusion of packed red cells, plasma, and platelets to avoid dilutional coagulopathy (see Chapter 39).

Coagulopathy

7 The most common cause of nonsurgical bleeding following massive blood transfusion is dilutional thrombocytopenia, although clinically significant dilution of coagulation factors may also occur. **Coagulation studies and platelet counts, if readily available, should guide platelet and FFP transfusion.** Although most clinicians will be familiar with "routine" coagulation tests (eg, prothrombin time [PT], activated partial thromboplastin time [aPTT], international normalized ratio [INR], platelet count, fibrinogen), multiple studies show that viscoelastic analysis of whole blood clotting (thromboelastography, rotation thromboelastometry, and Sonoclot analysis) may be more useful in resuscitation, liver transplantation, and cardiac surgical settings.

Citrate Toxicity

Calcium binding by the citrate preservative can rise in importance following transfusion of large volumes of blood or blood products. Clinically important hypocalcemia, causing cardiac depression, will not occur in most normal patients unless the transfusion rate exceeds 1 unit every 5 min, and intravenous calcium salts should rarely be required in the absence of measured hypocalcemia. Because citrate metabolism is primarily hepatic, patients with hepatic disease or dysfunction (and possibly hypothermic patients) may demonstrate hypocalcemia and require calcium infusion during massive transfusion, as may small children and others with relatively impaired parathyroid–vitamin D function.

8

Hypothermia

Massive blood transfusion is an absolute indication for warming all blood products and intravenous fluids to normal body temperature. Ventricular arrhythmias progressing to fibrillation often occur at temperatures close to 30°C, and hypothermia can hamper cardiac resuscitation. The use of rapid infusion devices with efficient heat transfer capability has decreased the incidence of transfusion-related hypothermia.

Acid–Base Balance

Although stored blood is acidic due to the citric acid anticoagulant and accumulation of red cell metabolites (carbon dioxide and lactic acid), metabolic acidosis due to transfusion is uncommon because citric acid and lactic acid are rapidly metabolized to bicarbonate by the normal liver. In the situation of massive blood transfusion, acid-base status is largely dependent upon tissue perfusion, rate of blood transfusion, and citrate metabolism. Once normal tissue perfusion is restored, any metabolic acidosis typically resolves, and metabolic alkalosis commonly occurs as citrate and lactate contained in transfusions and resuscitation fluids are converted to bicarbonate by the liver.

9

Serum Potassium Concentration

The extracellular concentration of potassium in stored blood steadily increases with time. The amount of extracellular potassium transfused with each unit is typically less than 4 mEq per unit. Hyperkalemia can develop regardless of the age of the blood when transfusion rates exceed 100 mL/min. The treatment of hyperkalemia is discussed in

Chapter 49. Hypokalemia is commonly encountered postoperatively, particularly in association with metabolic alkalosis (see Chapters 49 and 50).

Alternative Strategies for Management of Blood Loss During Surgery

AUTOLOGOUS TRANSFUSION

Patients undergoing elective surgical procedures with a high probability for transfusion can donate their own blood for use during that surgery. Collection is usually started 4–5 weeks prior to the procedure. The patient is allowed to donate a unit as long as the hematocrit is at least 34% or hemoglobin at least 11 g/dL. A minimum of 72 h is required between donations to make certain that plasma volume returns to normal. With iron supplementation and erythropoietin therapy, at least 3 or 4 units can usually be collected prior to operation. Some studies suggest that autologous blood transfusions do not adversely affect survival in patients undergoing operations for cancer. Although autologous transfusions likely reduce the risk of infection and transfusion reactions, they are not risk-free. Risks include those of immunological reactions due to clerical errors in collection, labeling, and administration; bacterial contamination; and improper storage. Allergic reactions can occur due to allergens (eg, ethylene oxide) that dissolve into the blood from collection and storage equipment.

BLOOD SALVAGE & REINFUSION

This technique is used widely during cardiac, major vascular, and orthopedic surgery (see Chapter 22). The shed blood is aspirated intraoperatively into a reservoir and mixed with heparin. After a sufficient amount of blood is collected, the red cells are concentrated and washed to remove debris and anticoagulant and then reinfused into the patient. The concentrates obtained usually have hematocrits of 50–60%. To be used effectively, this technique requires blood losses greater than 1000–1500 mL. Contraindications to blood salvage and reinfusion include septic contamination of the wound and perhaps malignancy. Newer, simpler systems allow reinfusion of shed blood without centrifugation.

NORMOVOLEMIC HEMODILUTION

Acute normovolemic hemodilution relies on the premise that if the concentration of red cells is decreased, total red cell loss is reduced when large amounts of blood are shed; moreover, cardiac output remains normal because intravascular volume is maintained. One or two units of blood are typically removed just prior to surgery from a large-bore intravenous catheter and replaced with crystalloid and colloids so that the patient remains normovolemic but has a hematocrit of 21–25%. The blood that is removed is stored in a CPD bag at room temperature (up to 6 h) to preserve platelet function; the blood is given back to the patient after the blood loss or sooner if necessary.

DONOR-DIRECTED TRANSFUSIONS

Patients can request donated blood from family members or friends known to be ABO compatible. Most blood banks discourage this practice and generally require donation at least 7 days prior to surgery in order to process the donated blood and confirm compatibility. Studies comparing the safety of donor-directed units to that of random donor units have found either no difference, or that random units from blood banks are safer than directed units.

CASE DISCUSSION

A Patient with Sickle Cell Disease

A 24-year-old black woman with a history of sickle cell anemia presents with abdominal pain and is scheduled for cholecystectomy.

What is sickle cell anemia?

Sickle cell anemia is a hereditary hemolytic anemia resulting from the formation of an

abnormal hemoglobin (HbS). HbS differs structurally from the normal adult hemoglobin (HbA) only in the substitution of valine for glutamic acid at the sixth position of the β chain. Functionally, sickle hemoglobin has less affinity for oxygen (P_{50} = 31 mm Hg) as well as decreased solubility. Upon deoxygenation, HbS readily polymerizes and precipitates inside red blood cells (RBCs), causing them to sickle. Sickle cell patients produce variable amounts (2–20%) of fetal hemoglobin (HbF). It is likely that cells with large amounts of HbF are somewhat protected from sickling. The continuous destruction of irreversibly sickled cells leads to anemia, and hematocrits are typically 18–30% due to the extravascular hemolysis. RBC survival is reduced to 10–15 days, compared with up to 120 days in normal individuals.

What is the difference between sickle cell anemia and sickle cell trait?

When the genetic defect for adult hemoglobin is present on both the maternally and paternally derived chromosomes (No. 11), the patient is homozygous for HbS and has sickle cell anemia (HbSS). When only one chromosome has the sickle gene, the patient is heterozygous and has *sickle cell trait* (HbAS). Patients with the sickle trait produce variable amounts of HbA (55–60%) and HbS (35–40%). Unlike those with HbSS, they are generally not anemic, are asymptomatic, and have a normal life span. Sickling occurs only under extreme hypoxemia or in low-flow states. Sickling is particularly apt to occur in the renal medulla; indeed, many patients with the sickle trait have impaired renal concentrating ability. Some patients with HbAS have been reported to have renal medullary, splenic, and pulmonary infarcts.

What is the prevalence of the sickle cell gene in black Americans?

Sickle cell anemia is primarily a disease of individuals of Central African ancestry. Approximately 0.2–0.5% of African Americans are homozygous for the sickle gene and approximately 8–10% are heterozygous. Sickle cell anemia is found less commonly in patients of Mediterranean ancestry.

What is the pathophysiology?

Conditions favoring the formation of deoxyhemoglobin (eg, hypoxemia, acidosis, intracellular hypertonicity or dehydration, increased 2,3-DPG levels, or increased temperature) can precipitate sickling in patients with HbSS. Hypothermia may also be detrimental because of the associated vasoconstriction (see below). Intracellular polymerization of HbS distorts red cells, makes them less pliable and more "sticky," increasing blood viscosity. Sickling may initially be reversible but eventually becomes irreversible in some cells. Formation of red cell aggregates in capillaries can obstruct tissue microcirculation. A vicious cycle is established in which circulatory stasis leads to localized hypoxia, which, in turn, causes more sickling.

With what symptoms do patients with sickle cell anemia usually present?

Patients with HbSS generally first develop symptoms in infancy, when levels of fetal hemoglobin (HbF) decline. The disease is characterized by both acute episodic crises and chronic and progressive features (Table 51–7). Children display retarded growth and have recurrent infections. Recurrent splenic infarction leads to splenic atrophy and functional asplenism by adolescence. Patients usually die from recurrent infections or kidney failure. Crises are often precipitated by infection, cold weather, dehydration, or other forms of stress. Crises may be divided into three types:

1. **Vasoocclusive crises:** Depending on the vessels involved, these acute episodes can result in micro- or macroinfarctions. Most painful crises are thought to be due to microinfarcts in the various tissues. Clinically, they present as acute abdominal, chest, back, or joint pain. Differentiation between surgical and nonsurgical causes of abdominal pain is difficult. Most patients form pigmented gallstones by adulthood, and many present with acute cholecystitis. Vasoocclusive phenomena in larger vessels can produce thromboses resulting in splenic, cerebral, pulmonary, hepatic, renal, and, less commonly, myocardial infarctions.

TABLE 51–7 Manifestations of sickle cell anemia.

Neurological
Stroke
Subarachnoid hemorrhage
Coma
Seizures
Ocular
Vitreous hemorrhage
Retinal infarcts
Proliferative retinopathy
Retinal detachment
Pulmonary
Increased intrapulmonary shunting
Pleuritis
Recurrent pulmonary infections
Pulmonary infarcts
Cardiovascular
Congestive heart failure
Cor pulmonale
Pericarditis
Myocardial infarction
Gastrointestinal
Cholelithiasis (pigmented stones)
Cholecystitis
Hepatic infarcts
Hepatic abscesses
Hepatic fibrosis
Hematological
Anemia
Aplastic anemia
Recurrent infections
Splenic infarcts
Splenic sequestration
Functional asplenia
Genitourinary
Hematuria
Renal papillary necrosis
Impaired renal concentrating ability (isosthenuria)
Nephrotic syndrome
Renal insufficiency
Renal failure
Priapism
Skeletal
Synovitis
Arthritis
Aseptic necrosis of femoral head
Small bone infarcts in hand and feet (dactylitis)
Biconcave ("fishmouth") vertebrae
Osteomyelitis
Skin
Chronic ulcers

2. **Aplastic crisis:** Profound anemia (Hb 2–3 g/dL) can rapidly occur when red cell production in the bone marrow is exhausted or suppressed. Infections and folate deficiency may play a major role. Some patients also develop leukopenia.
3. **Splenic sequestration crisis:** Sudden pooling of blood in the spleen can occur in infants and young children and can cause life-threatening hypotension. The mechanism is thought to be partial or complete occlusion of venous drainage from the spleen.

How is sickle cell anemia diagnosed?

RBCs from patients with sickle cell anemia readily sickle following addition of an oxygen-consuming reagent (metabisulfite) or a hypertonic ionic solution (solubility test). Confirmation requires hemoglobin electrophoresis.

What would be the best way to prepare patients with sickle cell anemia for surgery?

Optimal preoperative preparation is desirable for all patients undergoing surgery. Patients should be well hydrated, infections should be controlled, and the hemoglobin concentration should be at an acceptable level. Preoperative transfusion therapy must be individualized for the patient and to the surgical procedure. Partial exchange transfusions before major surgical procedures are usually advocated, which decrease blood viscosity, increase blood oxygen-carrying capacity, and decrease likelihood of sickling. The goal of such transfusions is generally to achieve a hematocrit of 35–40% with 40–50% normal hemoglobin (HbA).

Are there any special intraoperative considerations?

Conditions that might promote hemoglobin desaturation or low-flow states should be avoided. Every effort must be made to avoid hypothermia, hyperthermia, acidosis, and even mild degrees of hypoxemia, hypotension, or hypovolemia. Generous hydration and a relatively high (>50%) inspired oxygen tension are desirable. The principal compensatory mechanism for impaired tissue oxygen delivery in these patients is increased

cardiac output, which should be maintained intraoperatively. Goal-directed hemodynamic monitoring and fluid therapy utilizing arterial pulse wave analysis, esophageal Doppler, or transesophageal echocardiography, or central venous pressure or pulmonary artery pressure monitoring with mixed venous oxygen saturation is often useful. Mild alkalosis may help avoid sickling, but even moderate degrees of respiratory alkalosis may have an adverse effect on cerebral blood flow. Many clinicians also avoid the use of tourniquets.

Are there any special postoperative considerations?

Most perioperative deaths occur in the postoperative period, and the same management principles applied intraoperatively should be utilized in the postoperative period. Hypoxemia and pulmonary complications are major risk factors. Supplemental oxygen, optimal hemodynamic, fluid, and pain and symptom management, and pulmonary physiotherapy and early ambulation all help minimize the risk of these complications.

What is the significance of sickle cell anemia and thalassemia in the same patient?

The combination of HbS and thalassemia, most commonly sickle β-thalassemia, has a variable and unpredictable effect on disease severity. This combination is usually milder in black patients than in those of Mediterranean ancestry.

What is the pathophysiology of thalassemia?

Thalassemia is a hereditary defect in the production of one or more of the normal subunits of hemoglobin. Patients with thalassemia may be able to produce normal HbA but have reduced amounts of α- or β-chain production; the severity of this defect depends on the subunit affected and the degree to which hemoglobin production is affected. Symptoms range from absent to severe. Patients with α-thalassemia produce reduced amounts of α subunit, whereas patients with β-thalassemia produce reduced amounts of the β subunit. The formation of hemoglobins with abnormal subunit composition can alter the red cell membrane and lead to variable degrees of hemolysis as well as ineffective hematopoiesis. The latter can result in hypertrophy of the bone marrow and often an abnormal skeleton. *Maxillary hypertrophy* may make tracheal intubation difficult. Thalassemias are most common in patients of Southeast Asian, African, Mediterranean, and Indian ancestry.

What is hemoglobin C disease?

Substitution of lysine for glutamic acid at position 6 on the β subunit results in hemoglobin C (HbC). Approximately 0.05% of black Americans carry the gene for HbC. Patients homozygous for HbC generally have only a mild hemolytic anemia and splenomegaly and rarely develop significant complications. The tendency for HbC to crystallize in hypertonic environments is probably responsible for the hemolysis and characteristically produces *target cells* on the peripheral blood smear.

What is the significance of the genotype HbSC?

Nearly 0.1% of black Americans are simultaneously heterozygous for both HbS and HbC (HbSC). These patients generally have a mild to moderate hemolytic anemia. Some patients occasionally have painful crises, splenic infarcts, and hepatic dysfunction. Eye manifestations similar to those associated with HbSS disease are particularly prominent. Females with HbSC have a high rate of complications during the third trimester of pregnancy and delivery.

What is hemoglobin E?

Hemoglobin E is the result of a single substitution on the β chain and is the second most common hemoglobin variant worldwide. It is most often encountered in patients from Southeast Asia. Although oxygen-binding affinity is normal, the substitution impairs production of β chains (similar to β-thalassemia). Homozygous patients have marked microcytosis and prominent target cells, but are not usually anemic and lack any other manifestations.

What is the hematologic significance of glucose-6-phosphate dehydrogenase deficiency?

RBCs are normally well-protected against oxidizing agents. The sulfhydryl groups on

TABLE 51–8 Drugs to avoid in patients with G6PD[1] deficiency.

Drugs that may cause hemolysis
Sulfonamides
Antimalarial drugs
Nitrofurantoin
Nalidixic acid
Probenecid
Aminosalicylic acid
Phenacetin
Acetanilid
Ascorbic acid (in large doses)
Vitamin K
Methylene blue
Quinine[2]
Quinidine[3]
Chloramphenicol
Penicillamine
Dimercaprol
Other drugs
Prilocaine
Nitroprusside

[1]G6PD, glucose-6-phosphate dehydrogenase.

[2]May be safe in patients with A⁻ variant.

[3]Should be avoided because of potential to cause methemoglobinemia.

hemoglobin are protected by reduced glutathione. The latter is regenerated by NADPH (reduced nicotinamide adenine dinucleotide phosphate), which itself is regenerated by glucose metabolism in the hexose monophosphate shunt. Glucose-6-phosphate dehydrogenase (G6PD) is a critical enzyme in this pathway. A defect in this pathway results in an inadequate amount of reduced glutathione, which can potentially result in the oxidation and precipitation of hemoglobin in red cells (seen as *Heinz bodies*) and hemolysis.

Abnormalities in G6PD are relatively common, with over 400 variants described. Clinical manifestations are quite variable, depending on the functional significance of the enzyme abnormality. Up to 15% of black American males have the common, clinically significant, A⁻ variant. A second variant is common in individuals of eastern Mediterranean ancestry, and a third in individuals of Chinese ancestry. Because the locus for the enzyme is on the X chromosome, abnormalities are X-linked traits, with males being primarily affected. G6PD activity decreases as RBCs age; therefore aging red cells are most susceptible to oxidation. This decay is markedly accelerated in patients with the Mediterranean variant but only moderately so in patients with the A⁻ variant.

Most patients with G6PD deficiency are not anemic but can develop hemolysis following stresses such as viral and bacterial infections, or after administration of certain drugs (Table 51–8). Hemolytic episodes can be precipitated by metabolic acidosis (eg, diabetic ketoacidosis) and may present with hemoglobinuria and hypotension. Such episodes are generally self-limited because only the older population of RBCs is destroyed. Mediterranean variants may be associated with chronic hemolytic anemia of varying severity and may include the classic feature of marked sensitivity to fava beans.

Management of G6PD deficiency is primarily preventive, avoiding factors known to promote or exacerbate hemolysis. Measures aimed at preserving kidney function (see above) are indicated in patients who develop hemoglobinuria.

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