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Critical Care Nursing of Infants and Children

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Hematologic Critical Care Problems

Debbie Brinker

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SUMMARY

Children in the pediatric intensive care unit (PICU) experience a variety of hematologic problems that vary in severity. This is partially because of the complex structure and function of blood and its components, which affect

every cell and organ system in the body. In addition, organs of the hematopoietic system, such as bone marrow, are prone to the adverse effects of sepsis, trauma, shock, and drugs used for critical illnesses. The majority of hematologic problems seen in critically ill children are acquired and often present as an acute episode.¹ The more common problems include disseminated intravascular coagulation (DIC), vascular access thrombi, anemias, hemolytic uremic syndrome (HUS), and blood dyscrasias.

This chapter focuses on assessment of hematologic function, supportive and therapeutic interventions (i.e., blood product administration and apheresis), and alterations in hematologic function, including disorders of coagulation and oxygen-carrying capacity. Disorders will be discussed as final common pathways of altered hematologic function with emphasis on pathophysiology and nursing care of the patient with DIC, sickle cell anemia (SCA), and HUS.

ESSENTIAL EMBRYOLOGY

During embryologic development, blood formation can be recognized as early as 3 weeks after conception. By the sixth week of gestation, hematopoiesis (the production of red cells, white cells, and platelets) moves from the yolk sac to the liver, which is the main site of blood formation during the middle portion of fetal life. Following the twentieth week of gestation, hematopoiesis then moves to the bone marrow; and following birth, it takes place almost entirely in the bone marrow.

ESSENTIAL ANATOMY AND PHYSIOLOGY

Hematopoietic Organs

Bone marrow is the chief site for hematopoiesis. There are two types of bone marrow: yellow marrow, which contains a large percentage of fat cells; and red marrow, which contains mostly blood cells. The infant and young child have a larger proportion of red marrow because of the high

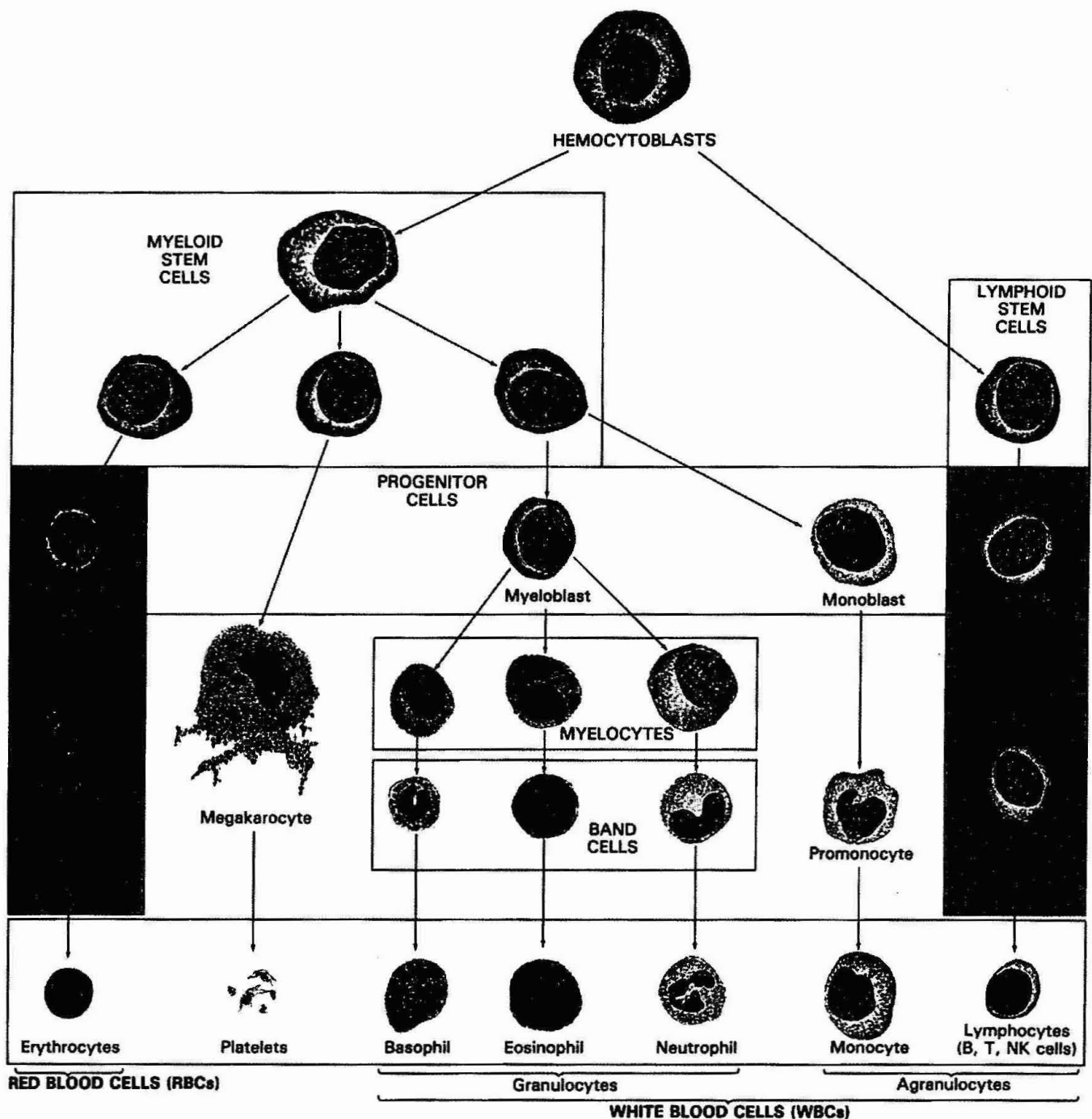


Fig. 24-1 The origins and differentiation of blood cells. (From Martini F, *Fundamentals of anatomy and physiology*, ed 3, Upper Saddle River, NJ, 1995, Prentice-Hall. Adapted by permission of Prentice-Hall, Upper Saddle River, NJ.)

requirements for red cell production. Early in life the red marrow is contained in the medullary cavities of the long bones. These cavities gradually fill with fat as the demands for red cell production decrease until the adult distribution of hematopoiesis (sternum, pelvis, vertebrae, cranium, ribs, and epiphyses of long bones) are reached at puberty. In

disease states associated with anemias, hematopoiesis can return to its former sites, including the long bones, skull, liver, spleen, and lymph nodes. It may also take place in the adrenal glands, cartilage, adipose tissues, and kidneys. Fig. 24-1 illustrates the formation and maturation of blood cells.

Blood Stem Cell

Human bone marrow contains a pluripotent hematopoietic stem cell precursor that is capable of differentiating into erythroid, granulocytic, monocytic, megakaryocytic, and certain lymphoid cell lines. This cell gives rise to the marrow stem cell, which produces the precursor for erythrocytes, granulocytes, monocytes, and platelets. Stem cells are present in small numbers in blood and bone marrow. Their turnover depends on the needs of the body. It has been suggested that the structure of the stem cell is similar to that of the lymphocyte.

Composition of Blood

Blood is composed of plasma in which are suspended certain proteins (such as albumin, globulin), clotting factors, and the blood cells. These include leukocytes (white blood cells [WBCs]), erythrocytes (red blood cells [RBCs]), and thrombocytes (platelets).

Leukocytes. The main function of the leukocytes are to fight infection; defend the body against foreign organisms through phagocytosis; and produce, transport, and distribute antibodies in the immune system. Leukocytes are discussed in detail in Chapter 15.

Erythrocytes. Erythrocytes (RBCs) are the most abundant component in the blood. They have biconcave discs without nuclei and are extremely flexible. This allows them to travel extremely fast and bend and twist as they pass through tiny capillaries. Their elongated shape in the capillaries allows for more surface area for the exchange of oxygen and carbon dioxide.

After birth, the rate of hemoglobin (Hgb) synthesis and production of RBCs decreases dramatically during the first few days of life. Over the next few weeks, as the conversion occurs from fetal to adult Hgb, and the threshold of decreased venous oxygen saturation is reached, a physiologic nadir is created at about 7 to 10 weeks. A signal in the form of increased erythropoietin production is sent to the marrow, and erythropoiesis is stimulated, eventually leading to an increase in Hgb, at about 3 to 4 months of age. Premature infants reach their nadir earlier than term infants and require a longer period of time to recover.²

The main function of erythrocytes is the transport of oxygen and carbon dioxide, which is accomplished through Hgb, the major component of RBCs. Oxygen binds with Hgb and then is released at tissue sites where gas exchange takes place.

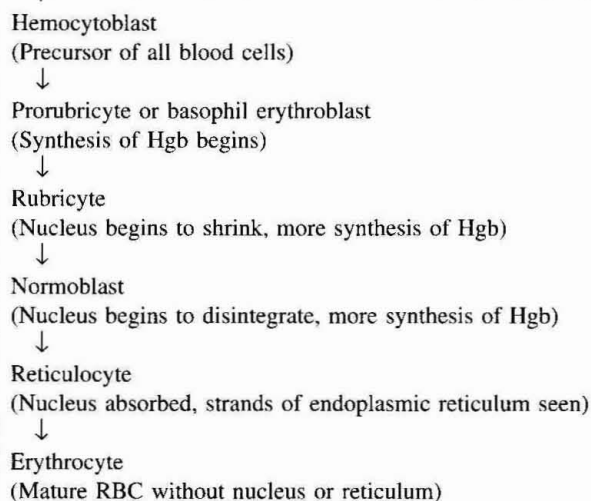
Fetal hemoglobin (Hb F) is present at birth and allows for more efficient binding of oxygen at lower surface tensions. Hb F constitutes 70% of the total Hgb at birth but declines rapidly. By 6 to 12 months of age, Hb F has been mostly replaced by adult Hgb, although levels of 1% to 2% of Hb F remain throughout life. Hb F shifts the oxyhemoglobin dissociation curve to the left so that oxygen bound to Hgb is not readily released to the tissues. This may compromise tissue oxygenation in newborns with diminished cardiovascular reserves.

RBCs are formed in the red bone marrow and progress through the stages of development outlined in Box 24-1.

Box 24-1



Development of Red Blood Cells



The mature erythrocyte is released into the circulation where the average lifespan is about 120 days. This time span represents the interval between the cell's release into the circulation from the bone marrow and its destruction. When the RBC ages, it is removed from the circulation by the spleen, liver, and red bone marrow. When the hematopoietic system is faced with a heavy demand for the production of RBCs, such as with hemorrhage, immature RBCs are released into the circulation. The number of immature cells and their degree of immaturity reflect the severity of stress placed on this body system. When the demand is great, the number of reticulocytes may increase by 30% to 50%. With an increased demand, the number of normoblasts may appear in large numbers. In severe anemias, the percentage of normoblasts may be as high as 5% to 20% of the circulating RBCs. Prorubricytes may also appear at this time. This information is also important in differentiating various types of anemias.

RBC production is also stimulated by decreased tissue oxygenation because RBC production depends not only on the actual number present in the circulation but also on their ability to carry oxygen and carbon dioxide. When tissue oxygenation is decreased, erythropoietin stimulates the stem cells in the bone marrow to produce mature RBCs. Erythropoietin is produced in the kidney and is released in response to hypoxia and anemia. Table 24-1 lists the normal RBC values at various ages.

Thrombocytes (Platelets). Platelet development takes place primarily in the bone marrow. Platelets are the smallest of the blood cell components. They are fragments of megakaryocytes. Megakaryocytes mature in the bone marrow and fragment, where each one releases approximately 5000 platelets into the blood. The lifespan of platelets is approximately 7 to 14 days. Approximately 10% to 15% of the circulating platelets are consumed in the daily repair of small vascular injuries.

**TABLE 24-1 Red Blood Cell Studies**

Test	Normal Values	Purpose	Clinical Significance
Red blood count (RBC)	Millions of cells/mm ³	Measures total number of circulating RBCs	Increased in polycythemia, severe diarrhea, dehydration, acute poisoning, during and immediately following hemorrhage Decreased in anemia, diseases of bone marrow function, hemolytic and pernicious anemia, subacute endocarditis
	1 wk		
	2 wk		
	1 mo		
	2 mo		
	3-6 mo		
	0.5-2 yr		
	2-6 yr		
	6-12 yr		
	12-18 yr		
Hematocrit (Hct)	M	Measures percentage of RBCs in a volume of blood	Increased in erythrocytosis, polycythemia, severe dehydration, shock—when hemoconcentration rises considerably Decreased in anemia, leukemia, acute massive blood loss, hemolytic reactions Unreliable immediately after transfusions, hemorrhage
	F		
	% of packed cells		
	3 days		
	2 mo		
	6-12 yr		
Hemoglobin (Hgb)	12-18 yr	Measures oxygen-carrying capacity of the blood	Increased in hemoconcentration of the blood, CHF Decreased in anemia; severe hemorrhage, hemolytic reactions Unreliable immediately after transfusions, hemorrhage
	M		
	F		
	g/dl		
	1-3 days		
	2 mo		
Erythrocyte sedimentation rate (ESR)	6-12 yr	Measures the rate at which RBCs settle out of unclotted blood in 1 hr Based on the fact that inflammatory and necrotic processes result in aggregation of RBCs, which makes them heavier and more likely to settle	Increased values found in infections, inflammatory diseases, carcinomas, cell or tissue destruction, toxemia, nephritis, pneumonia, severe anemia Decreased values found in polycythemia vera, sickle cell anemia, CHF
	12-18 yr		
	M		
	F		
	13.0-16.0		
	12.0-16.0		

Reticulocyte count	Infants	2%-5% of total RBCs	Measures the number of immature RBCs (reticulocytes) compared with total RBCs	Increased in hemolytic anemia, sickle cell disease, leukemia, 3-4 days following hemorrhage, after splenectomy, following treatment of anemia
	Children	0.5-4.0% of total RBCs	Indicates an increase in RBC production and/or a decrease in RBC destruction	Decreased levels indicate that the bone marrow is not producing enough erythrocytes and is seen in iron-deficiency anemia, aplastic anemia, chronic infection, radiation therapy
Mean corpuscular volume (MCV)		μm^3	Measures the volume occupied by a single RBC and indicates size of the cell:	Decreased in anemia, thalassemia
	1-3 days	95-121		Increased in liver diseases, deficiency of folate or vitamin B ₁₂
	0.5-2 yr	70-86	Normocytic—of normal size	
	6-12 yr	77-95	Microcytic—smaller than normal	
	12-18 yr		Macrocytic—larger than normal	
	M	78-98		
	F	78-102		
Mean corpuscular hemoglobin concentration (MCHC)	% Hgb/cell or g Hgb/dl RBC		Measure of the concentration of hemoglobin in an average cell	Most valuable in evaluating therapy for anemia because the two most accurate hematologic determinations (Hgb and Hct) are used in this test
	1-3 days	30-36		Increased MCHC usually indicates spherocytosis
	1-2 wk	29-37		Decreased MCHC indicates that a unit volume of packed RBCs contains less hemoglobin than normal
	1-2 mo	29-37		May be seen in iron-deficiency anemia, thalassemia
	3 mo-2 yr	30-36		
Mean corpuscular hemoglobin (MCH)	2-18 yr	31-37		
		%/cell	Measure of the average weight of hemoglobin in the RBC	Increased MCH associated with macrocytic anemia
	1-3 days	31-37		Decreased value associated with iron-deficiency anemia
	1 wk-1 mo	28-40	Less accurate than MCHC because uses RBC count in the calculation and that count may be inaccurate	
	2 mo	26-34		
	3-6 mo	25-35		
	0.5-2 yr	23-31		
	2-6 yr	24-30		
	6-12 yr	25-33		
	12-18 yr	25-35		

From Fischbach F: *A manual of laboratory diagnostic tests*, Philadelphia, 1980, JB Lippincott; Foster RL, Hunsberger MM, Anderson JJ: *Family-centered nursing care of children*, Philadelphia, 1989, WB Saunders.

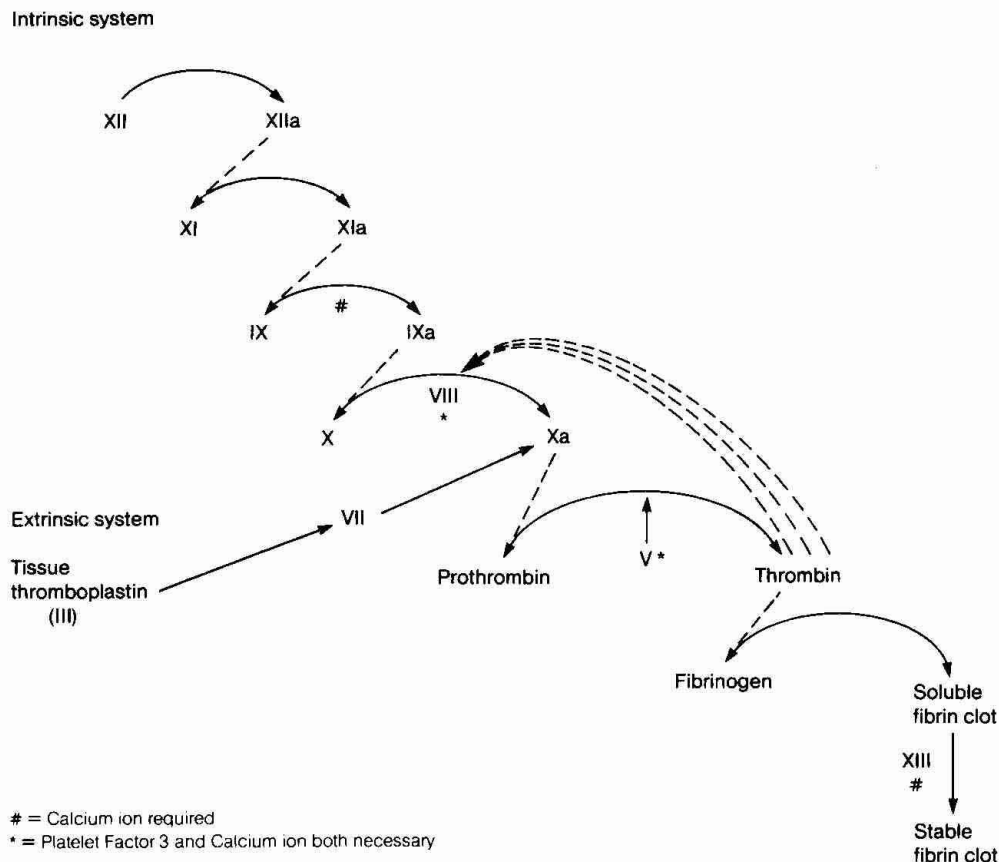


Fig. 24-2 The coagulation sequence. (From Hudak C, Gallo B, Lohr T, eds: *Critical care nursing*, Philadelphia, 1973, JB Lippincott.)

The rate of platelet production and the level of circulating platelets are thought to be controlled by thrombopoietin or thrombopoiesis-stimulating factor. The level of circulating catecholamines also has an effect on platelet levels. The administration of epinephrine can immediately produce a 20% to 50% increase in the platelet count. This response is likely to be the result of mobilization from the splenic pool. Hypoxia also increases the number of circulating platelets.

Platelets play a primary role in the process of hemostasis. Hemostasis is achieved by vascular spasm, formation of a platelet plug, formation of a blood clot, and formation of connective tissue, which permanently repairs the damaged vessel. Vascular spasm reduces blood flow through a damaged blood vessel to prevent further blood loss. When platelets come in contact with the damaged blood vessel, they adhere to the walls of the vessel at the site of damage. Other platelets in the area are activated, and aggregation occurs when these cells adhere to the first. Thus platelets group together to repair the damaged vessel.

Coagulation is a complex process involving an intricate series of reactions that include a number of different factors present in the blood or the tissues. These substances influence the mechanisms of clotting by promoting clotting with procoagulants (clotting factors) or inhibiting clotting with anticoagulants. Some are also involved in the removal of a clot once it is formed. Each clotting factor acts as an

enzyme, which, when activated, proceeds in a stepwise fashion to the next reaction. This is referred to as the *clotting cascade*, or more appropriately as a *clotting continuum*, because feedback is involved to activate and/or inhibit the coagulation process (Fig. 24-2).

The first step of coagulation is the formation of prothrombin activator. This step is the most complex because it involves a group of clotting factors involved in the extrinsic and intrinsic pathways. The extrinsic pathway is activated by trauma to the vascular walls and surrounding tissues. Factor III must be released from the endothelial cells and other tissues before activation can begin. When chemicals released into the tissues at time of injury (tissue factor) contact factor VII, sequential activation of factors X, V, II, and I take place. These factors then convert factor X to activated factor X.

When factor XII and platelets come in contact with collagen in the damaged wall of a vessel, the intrinsic pathway is activated. Factors XI, IX, VIII, X, II, and I are then activated, followed by the activation of factor X.

With the help of factor V, activated factor X forms prothrombin activator. Once this is formed, with the assistance of calcium ions, prothrombin is activated. Prothrombin is converted to thrombin with assistance of factor V. In the presence of thrombin and calcium ions, fibrinogen is converted into fibrin. The fibrin threads form a

**TABLE 24-2 Clotting Factors**

Factor	Synonym
I	Fibrinogen
II	Prothrombin
III	Tissue thromboplastin
IV	Calcium
V	Proaccelerin
VII	Proconvertin
VIII	Antihemophilic factor A
IX	Christmas factor
X	Stuart-Prower factor
XI	Plasma thromboplastin antecedent
XII	Hageman factor
XIII	Fibrin stabilizing factor

From Eskenazi AE, Gordon JB, Bernstein ML: Hematologic disorders in the pediatric intensive care unit. In Rogers MC, ed: *Textbook of pediatric intensive care*, ed 3, Baltimore, 1996, Williams & Wilkins.

network over the damaged area of the vessel, which traps blood cells, platelets, and plasma. A blood clot is formed and prevents further leakage through the damaged vessel. Within minutes of formation, clot retraction pulls together the sides of the damaged vessel.

Once formed, the clot may be the basis for new connective tissue or it undergoes the processes of lysis and dissolution. After a few hours, fibroblasts invade the clot, and within 7 to 10 days, fibrous connective tissue is formed. Plasminogen and plasminogen activator, which are trapped within the clot with platelets and RBCs, ultimately produce plasmin, which lyses the clot.

The extrinsic pathway is activated when factor III gains access to the bloodstream; the intrinsic pathway is activated when blood comes in contact with an abnormal surface. Regardless of the initiating mechanism, the end is the same. Large amounts of thrombin are produced, which is then followed by the transformation of fibrinogen to fibrin. Table 24-2 lists the factors involved in the clotting mechanism.

ASSESSMENT AND DIAGNOSIS OF HEMATOLOGIC DISORDERS

On admission, infants and children may present with primary diagnoses of bleeding and/or coagulation disorders, or have coincidental findings discovered per history, physical examination, or laboratory results.

Clinical History

An admitting history includes questions regarding bleeding disorders (e.g., patient or family history of hemophilia or von Willebrand's disease), and whether a child bleeds or bruises easily. It is important for a parent/historian to distinguish "normal childhood bruising" over extremity bones and bony prominences versus soft-tissue bruising with no apparent cause.

Other important issues include symptoms from decreased or dysfunctional RBCs or WBCs. A history for anemia (decreased RBCs) includes fatigue, listlessness, decrease in activity or energy level, syncope, and pallor. An infectious history (e.g., frequent sinus infections, joint infections, and lacerations that do not heal) may be indicative of decreased (or dysfunctional) WBCs. Immunosuppressive conditions or therapies such as chemotherapy or antirejection drugs posttransplant are important to evaluate in terms of WBC and infection risk.

Assessment and Physical Examination

Physical examination of the child with a hematologic disorder begins with observation of the child's general appearance. The child may appear pale because of anemia. Jaundice may be present if the child has a potential clotting problem from hepatic dysfunction. Signs of clotting include petechiae, purpura (small, red/purple areas that may be flat in abnormal bleeding states such as DIC, or raised [palpable] areas in cutaneous vasculitis disorders such as Henoch-Schönlein purpura [HSP]), and ecchymosis.

Cardiovascular symptoms may manifest as massive bleeding secondary to trauma with hemodynamic instability and prolonged bleeding. Oozing from venipuncture, intravenous, or arterial puncture sites may also be present.

Pulmonary symptoms may include frank bleeding from endotracheal tube or prolonged nose bleeds. Signs of respiratory distress such as tachypnea and dyspnea (especially on exertion) correlated with a decreased Hgb value may also be present. Neurologic symptoms of hematologic dysfunction include signs of cerebral vascular accident (CVA) or a central nervous system (CNS) hemorrhage as evidenced by a change in the level of consciousness. The child may demonstrate unilateral changes in reflexes (including pupils), circulation, sensation, or movement (CSM).

The major gastrointestinal (GI) manifestation of hematologic dysfunction is frank or occult bleeding in GI contents. The presence of blood in the urine also may signal a bleeding disorder.

Monitoring Hematologic Function

Multiple laboratory tests are used to monitor hematologic function. The most common tests include the complete blood count (CBC) and coagulation studies. It is important to interpret the CBC based on age comparison normals because growth and developmental changes occur in the hematologic system. A summary of RBC studies is reviewed in Table 24-1 and coagulation studies are described in Table 24-3.

Bone marrow aspiration is a common procedure performed to assess hematologic status. The bone marrow is typically obtained from the posterior iliac crest. This diagnostic procedure allows for assessment of marrow cellularity, quantitative and qualitative changes in hematologic precursors (i.e., cytopenias), and evaluation for disorders such as acute leukemia (discussed in Chapter 25), and aplastic anemia.

**TABLE 24-3 Coagulation Studies**

Test	Normal Values*	Purpose	Clinical Significance
Platelet count	150,000-400,000/mm ³	Measures total number of circulating platelets	Abnormally decreased in ITP; pernicious, aplastic, and hemolytic anemia; drugs, especially chemotherapeutic agents; bone marrow malignancies Abnormally increased after splenectomy and in certain cancers; may predispose to thrombotic episodes
Prothrombin time (PT) or INR (international normalized ratio)	11-15 sec <1.2	Indirectly measures the ability of the blood to clot and directly measures a defect in phase II clotting mechanisms (prothrombin, fibrinogen, factors V, VII, X)	Prolonged in prothrombin deficiency; vitamin K deficiency; deficiencies of fibrinogen; factors V, VII, X; anticoagulant therapy; severe liver disease; DIC
Activated partial thromboplastin time (APTT)	20-35 sec	Same as for PTT but more sensitive and faster to perform	Same as PTT
Fibrinogen	>150 mg/dl	Measures fibrinogen level	Decreased in liver disease, DIC
D-Dimer	<0.5 µg/ml	Measure of degradation of cross-linked fibrin	Increased in DIC
Thrombin time (TT); thrombin clotting time	9-13 sec	Measures fibrinogen to fibrin formation; detects stage III of fibrinogen abnormalities	Prolonged with low fibrinogen levels; anticoagulant therapy; liver disease; DIC

From Fischbach F: *A manual of laboratory diagnostic tests*, Philadelphia, 1980, J.B. Lippincott; Foster RL, Hunsberger MM, Anderson JJ: *Family-centered nursing care of children*, Philadelphia, 1989, W.B. Saunders; Jackson BS, Jones MB: Hematologic anatomy and physiology. In Kinney MR, Packa DR, Dunbar SB, eds: *AACN's clinical reference for critical-care nursing*, ed 2, New York, 1988, McGraw-Hill.

*Normal laboratory values vary by laboratory and are age dependent.

SUPPORT OF HEMATOLOGIC FUNCTION

There are a variety of interventions that are used to treat hematologic dysfunction. These include blood product transfusion therapy, pharmacologic interventions (i.e., anticoagulants and immune globulins), and mechanical interventions (i.e., apheresis).

Blood Product Transfusions

Critically ill pediatric patients may require blood product administration for a variety of reasons. Knowledge of special donor designation, modifications of the blood products including special processing procedures, and the potential risks of transfusions is essential for the provision of care. Table 24-4 presents blood products commonly used in the PICU, indications for these blood products, dosage, and nursing implications.

Special Donor Designation. Blood administration requires an understanding regarding donor-directed (designated) blood and human leukocyte antigen (HLA)-matched blood products. With the concern regarding safety of blood, most blood centers offer the ability for family and friends to donate blood for a specific patient. Although this is not possible for the emergent needs of a critically ill patient, parents may request information from the blood bank regarding donor-direction for postadmission transfusion needs. Directed donations, however, have not offered a

safety advantage over ordinary banked blood derived from anonymous volunteer donors.³ There is a concern regarding the potential for increased clerical errors resulting from the additional steps in the donation process, as well as inaccurate history disclosure. Directed donation from parents to neonates is not recommended because of maternal alloantibodies and maternal antibodies in the infant's circulation.³

Another special donor situation occurs when HLA-matched platelets are required. Patients, especially after multiple platelet transfusions, may develop antibodies to antigens on platelets, and require HLA cross-matching to minimize chance of reaction to the donor platelets in order to receive an adequate rise in platelet count.

Patients who require ongoing (lifelong) transfusions (e.g., sickle cell disease [SCD]) may develop multiple alloantibodies to donor blood antigens, which make cross-matching difficult. This may cause a delay in availability of blood products for these individual patients.

Knowledge regarding special donor requirements for individual patients is important. It is vital to document the number of products available for immediate transfusion and to send patient blood samples when required for cross-matching to prevent a delay in product availability.

Modifications of Blood Products. Various methods are available to modify blood products before administration to minimize the risks of transfusions for patients with



TABLE 24-4 Blood Products Commonly Used in the PICU

Blood Product	Indication	Dosage	Must be ABO Compatible	Requires Compatibility Testing	Rate of Administration	Available Modifications	Special Considerations
Whole Blood	Symptomatic deficit of oxygen-carrying capacity plus hypovolemic shock Massive blood loss Exchange transfusions	20 ml/kg initially, followed by volume necessary to stabilize child's condition	Yes (must be ABO identical, Rh ⁺ may receive Rh ⁻)	Yes	As fast as tolerated	Warmed Irradiated Leukocyte-depleted CMV neg, frozen, deglycerolyzed	Rarely used, usually for massive acute blood loss Platelets, WBCs, and clotting factors within stored whole blood are not functional
Packed Red Blood Cells (PRBC)	Anemia/symptomatic deficit of oxygen-carrying capacity ± hypovolemia	10-20 ml/kg	Yes	Yes	2-4 hr (not greater than 6 hr)	Washed Warmed Irradiated Leukocyte-depleted CMV neg, frozen Deglycerolyzed	Multiple transfusions may result in dilution of coagulation factors Wait 4-6 hr after transfusion to check hematocrit
Platelets	Thrombocytopenia (usually platelet count <20,000 or <50,000 with active bleeding) Abnormal platelet function	1-2 units/10 kg	Yes (preferred)	No	As fast as tolerated, but usually not faster than 1 ml/kg/min	Irradiated Leukocyte-depleted CMV neg Volume-reduced Single donor HLA matched	Do not use microaggregate filters High risk of alloimmunization with repeated transfusions Transfusion not indicated in platelet-destruction conditions, except with hemorrhage
Fresh Frozen Plasma	Deficit of plasma coagulation factors (prolonged PT, PTT)	Clotting deficiency: 10-15 ml/kg Acute hemorrhage: 15-30 ml/kg	Yes	No	Depends on patient tolerance. Not faster than 1 ml/kg/min, not slower than 4 hr	Irradiated	Should not be used for hypovolemia/hypoproteinemia unless coagulation values are prolonged Must be used within 6 hr of thawing
Cryoprecipitate	Hemophilia A Hypofibrinogenemia Factor XIII deficiency Von Willebrand disease	1 unit/5 kg	Yes	No	As fast as tolerated, usually not faster than 1 ml/kg/min	Irradiated	Must be used within 6 hr of thawing
Albumin	Hypovolemia	5%: 10-20 ml/kg 25%: 2-4 ml/kg	No	No	5%: As fast as tolerated 25%: 20-60 min	NA	No infectious risk Risk of circulatory overload secondary to increased osmotic pressure, especially with 25% albumin Use within 6 hr of entering container

special needs. Modifications include leukodepletion and irradiation of blood products.

To reduce the risk of nonhemolytic febrile reactions, leukocyte-depleted blood products may be transfused, especially to patients receiving frequent transfusions. Leukocyte-depleted blood products are ordered primarily when it has been demonstrated or suspected that the patient has previously experienced a febrile transfusion reaction. Other indications for leukocyte-depleted blood products are to prevent alloimmunization in recipients of frequent platelet transfusions, to prevent cytomegalovirus (CMV) infection when CMV-negative blood products are not available, and in prospective renal allograft recipients. Leukocyte depletion is usually achieved by prestorage or bedside filtration—a process that removes 70% to 99% of WBCs. Leukocytes can also be removed by washing RBCs or by freezing and deglycerolyzing RBCs.³⁻⁵

Leukocytes present in the transfused blood component can react against an immunosuppressed patient, causing transfusion-associated graft-versus-host disease (TA-GVHD). Irradiation destroys the leukocytes' ability to engraft in the patient. Patients susceptible to TA-GVHD include transplant recipients, severely immunocompromised patients, and those with lymphoma or acute leukemia. The incidence of TA-GVHD is not known, but many oncology units and some neonatal centers routinely use irradiated blood.⁶ It is generally recommended that patients at risk for TA-GVHD in the PICU receive irradiated blood products. Irradiated blood products pose no danger to healthcare personnel.⁷ Filtration of blood products at the bedside includes use of a 170- to 260-micron filter, which is standard in blood administration and platelet recipient sets. These filtered tubing sets should hang no longer than 4 hours. Each set can be used for up to four units if total time is less than 4 hours. WBC filters (Pall filters) may also be used if leukofiltration is indicated and has not been accomplished prestorage at the blood bank.

Most transfusions can be administered without the use of a blood warmer. However, transfusions of more than one unit of blood every 10 minutes, and exchange transfusions in neonates, mandate the use of a blood warmer to prevent severe hypothermia, dysrhythmias, and cardiac arrest. Patients who are hypothermic before the transfusion, and those who have cold agglutinin disease, also require warmed blood products. When blood must be warmed, it is heated via an inline system. Because RBCs heated above 37° C. may hemolyze, only temperature-controlled devices designed specifically to warm blood should be used.⁷

Potential Complications. The most important potential complication associated with blood product administration is transfusion reaction. Transfusion reactions are generally classified as hemolytic or nonhemolytic reactions. Each reaction has some characteristic signs and symptoms, but the type of reaction may be difficult to ascertain initially. Table 24-5 summarizes reactions, signs and symptoms, and treatments.

Acute Hemolytic Reactions. Acute hemolytic reactions are potentially the most serious of transfusion reac-

tions. A hemolytic reaction occurs when the blood product recipient has antibodies to some antigen on the transfused RBCs. The most common etiology of this antibody-antigen reaction is ABO incompatibility. The most frequent source of hemolytic reactions is mismatched blood, usually as a result of clerical error.^{4,5} Hemolytic reactions may be either immediate (fever, hematuria, etc.) or delayed. Delayed reactions may occur 3 to 5 days after the transfusion, with development of anemia and hematuria. Delayed reactions from low antigen titers undetected during cross-matching cause a slow build-up of antibody response; thus the delayed symptoms occur.

Nonhemolytic Reactions. Nonhemolytic reactions are generally classified into febrile and allergic reactions. Febrile reactions, which are characterized by fever and possibly shaking chills, are the result of an immune response to infused WBCs or plasma proteins. Febrile reactions usually occur in frequently transfused patients and are rarely serious. However, because fever can be the initial manifestation of a life-threatening hemolytic reaction, the transfusion should be discontinued if the patient's temperature rises 1° C or more above baseline. Antipyretics may be administered to control the fever. Providing frequently transfused patients with leukocyte-depleted blood products can prevent febrile reactions.³

The other common type of nonhemolytic reaction is an allergic reaction. Most allergic reactions are mild, characterized by local erythema, pruritus, and urticaria. The transfusion is stopped temporarily, and an antihistamine preparation is administered. If the symptoms are mild and resolving, the transfusion may be restarted slowly. Patients who have had an allergic reaction to a transfusion may be pretreated with an antihistamine drug before subsequent transfusions.

Rarely, an anaphylactic reaction occurs. Features that distinguish an anaphylactic reaction are bronchospasm, hypotension, and absence of fever. These reactions, which are typically apparent after administration of only a few milliliters of the transfused blood product, occur almost exclusively in IgA-deficient recipients. Collaborative interventions include the administration of epinephrine, fluids, and corticosteroids.³

Alloimmunization. Alloimmunization is another potential complication of receiving blood products, especially in patients who receive multiple transfusions. Such patients develop antibodies against antigens that they intrinsically lack, but that are present on the surface of the cells that have been transfused. Subsequent transfusions are affected; these newly formed antibodies may destroy future transfused cells that possess the targeted antigens. When platelets are transfused to a patient alloimmunized against platelets, there is no therapeutic effect; the patient is considered refractory to platelet therapy. Single-donor or HLA-matched platelets may offset the effects of alloimmunization. When RBCs are transfused to a patient alloimmunized against red cell antigens, hemolysis of the donor's cells may result. Appropriate cross-matching should prevent a serious hemolytic reaction. Using leukocyte-depleted blood components reduces the risk of alloimmunization.^{3,5}

TABLE 24-5 Transfusion Reactions to Blood or Blood Products

Reaction	Cause	Signs and Symptoms	Treatment
Anaphylaxis (occurs with infusion of only a few ml of product)	Most often caused by antigen-antibody complexes involving antibodies to IgA	Bronchospasm Cough Respiratory distress Hypotension*	Discontinue transfusion Keep vein open with NS (completely new tubing set) Notify physician Administer epinephrine, steroids Provide respiratory support Use deglycerolized (washed) red cells in future transfusions
Acute hemolytic trans- fusion reaction	Transfusion of ABO- incompatible blood resulting in hemoly- sis of red cells	Fever, chills* Hypotension* Hemoglobinemia Hemoglobinuria Lumbar pain (classic sign) Shock Dyspnea Diaphoresis Anxiety (sense of impending doom) Chest pain Restlessness DIC	Stop transfusion Keep vein open with NS (completely new tubing set) Notify physician Treat shock and/or respiratory distress Produce osmotic diuresis to prevent acute tubular necrosis Treat DIC
Nonhemolytic	Recipients reacting to poorly defined trans- fused antigens or recipients' antibodies reacting to transfused leukocytes and/or plasma proteins	Fever (mild to severe)* Chills Headaches Palpitations Hives Local erythema Itching	Stop transfusion Keep vein open with NS (completely new tubing set) Notify physician Relieve symptoms (antipyretics, antihis- tamines) If reaction mild such as urticaria and/or slight fever and chills, may consider continuing transfusion after antihista- mine. May also consider premedication and/or leukocyte-poor products for future transfusions.

*Consider bacterial contamination of product.

Circulatory Overload. Circulatory overload is a potential complication of blood product administration, which occurs when the transfusion volume exceeds circulatory system capacity. Critically ill pediatric patients are at increased risk of circulatory overload because of their relatively small baseline blood volume and potentially compromised cardiovascular, pulmonary, and renal systems. This complication can usually be prevented by adjusting the transfusion volume and flow rate based on the patient's size and clinical status. The blood bank can divide packed cells into smaller aliquots and can provide "volume-reduced" platelets to fluid-sensitive patients. Increased respiratory support and diuretics may be necessary to treat circulatory overload.

Citrate Toxicity. Citrate is a substance that is present in the anticoagulant preservative solution added to most blood products. In the body, citrate binds with serum calcium, potentially causing hypocalcemia. The patients

most at risk for symptomatic citrate toxicity are those who receive very rapid transfusions, those who receive multiple transfusions over a relatively short period of time, and patients with existing hepatic or renal dysfunction because citrate is metabolized in the liver and excreted by the kidneys.⁸

The serum calcium level of patients at risk for citrate toxicity is checked before and during transfusions. When toxicity in the presence of hypocalcemia is anticipated, intravenous calcium chloride or calcium gluconate may be administered prophylactically.

Transmission of Infectious Diseases. Transmission of infectious diseases is a potential complication of blood product administration. Although fear of acquiring HIV, which causes AIDS, is generally the dominant concern of transfusion recipients and their families, the chances of contracting other infectious diseases, such as hepatitis or CMV poses a more significant health risk.

Approximately 2.5% of adult AIDS cases reported to the Centers for Disease Control and Prevention (CDC) have been related to transfusions. However, pediatric AIDS cases have a much higher proportion of posttransfusion etiology. The vast majority of patients with transfusion-acquired AIDS were infected before 1985. Since 1985, all blood-collecting facilities have used the HIV antibody test to screen donated blood, which has significantly decreased the risk of HIV transmission. The current risk of acquiring HIV from a blood transfusion is unknown, but it is estimated to be 1 in 420,000. There is evidence that the risk is declining by 30% per year.³

The exact incidence of posttransfusion hepatitis is unknown. Hepatitis A virus (HAV) is usually transmitted by the fecal-oral route. At one time, it was believed that posttransfusion HAV infection was virtually nonexistent. More recently, there have been reports in the literature that document HAV transmission by transfusion. For example, several nursery-wide outbreaks of posttransfusion HAV infection among newborns have been reported. Fortunately, none of these studies has demonstrated significant morbidity from HAV.⁹

In contrast, hepatitis B virus (HBV) has long been known to produce posttransfusion infection, which can cause significant morbidity and mortality. Despite the fact that all blood is screened for hepatitis B surface antigen (HBsAg), several prospective studies have documented that up to 1.7% of transfusion recipients develop HBV infection. Possible explanations for this phenomenon include the presence of infectious donors who are in the incubation phase, before HBsAg testing would be positive, and infectious donors with a serum level below the limits of detectability with current assays.⁹

Non-A non-B hepatitis (NANBH) is the most common posttransfusion hepatitis, accounting for about 60% of all cases. Hepatitis C virus (HCV) has been confirmed to be the cause of most, if not all, cases of NANBH. In adults, the sequelae of NANBH are chronic active hepatitis in 40% to 50% of cases, and cirrhosis in 20%. Children who acquire HBV or HCV during infancy usually have a persistent viremia and chronic, mild liver disease, although cases of childhood cirrhosis and hepatocellular carcinoma have been reported. Adolescents may have a sustained neuroinflammatory activity that progresses into a more severe liver disease.¹⁰

Since May 1990, all units of blood and blood products have been tested for HCV antibody. Before routine testing, the risk of transfusion-associated HCV infection was estimated to be as high as 1 in 100. The estimate for transmitting HCV is 1 in 80,000.¹¹

CMV transmission is another potential infectious risk of blood transfusions. Approximately 50% of the population are potential transmitters of CMV. Fortunately, in the majority of patients, CMV infection does not cause a clinical illness.

However, two populations at risk for serious complications from CMV infection are neonates and immunocompromised patients. In infants born to mothers without detectable CMV antibodies, acquired CMV infections

can lead to atypical lymphocytosis, hepatosplenomegaly, pneumonia, or death. In immunosuppressed children, such as patients with oncologic disease and transplant recipients, CMV infection can cause life-threatening pneumonitis or hepatitis. Patients at risk for clinical CMV disease should receive blood that has been screened for antibodies to CMV.⁸

Coagulopathy. Coagulopathy can occur during massive transfusion, which is defined as the replacement of more than one blood volume.¹² During a rapid blood loss, the body cannot replace more than a small fraction of coagulation factors and platelets. Stored blood has also lost platelets and coagulation factors, such as factor VIII, which have become less active. When multiple transfusions are given over a short period of time, it is generally recommended that for every three units of packed RBCs administered, the child also receive one unit of fresh frozen plasma (FFP) and one unit of platelets.¹³ Coagulation studies may be done to determine specific component replacement.

Pharmacologic Therapy

Growth Factors. The development and usage of engineered growth factors has dramatically changed the support provided for RBC, WBC, and platelet stimulation. Erythropoietin is a natural hormone produced by the kidneys to stimulate RBC production. The genetically engineered product (i.e., Procrit or Epo) is used for anemia secondary to chronic renal failure, chemotherapy-induced anemia, and for anemic Jehovah's Witness patients who will not accept blood product transfusions. The product is administered intravenously or subcutaneously.

WBC stimulation is promoted with granulocyte colony stimulating factor (G-CSF, i.e., Neupogen) or granulocyte macrocyte-colony stimulating factor (GM-CSF, i.e., Leukine). Its primary indication is prevention of chemotherapy-induced neutropenia. It also is administered for other causes of neutropenia, such as drug-induced neutropenia or sepsis. It may be administered intravenously or subcutaneously.

Other stimulating factors include platelet-stimulating factor (e.g., Neumega), which may be administered for postchemotherapy thrombocytopenia.

Immune Globulin Therapy. Indications for intravenous immune globulin (IVIg) administration in PICU patients include primary and secondary immunodeficiency states, immune thrombocytopenic purpura (ITP), and Kawasaki disease. Dosage and rate of administration of IVIg depends on the product used. Current standard dosage for ITP is 1 g/kg/day until therapeutic effect is noted (daily infusion, up to 5 days). Research regarding giving lower doses (e.g., 400 mg/kg/day) has proved efficacious for patients with ITP.¹⁴

Administration of IVIg requires an understanding of the starting rate of each product and recommended titration of the infusion rate to decrease the possibility of a severe allergic reaction. Patients are assessed and monitored closely for the spectrum of allergic reactions—mild to anaphylaxis. Many reactions are rate dependent and subside if the rate is slowed. If a patient has demonstrated a reaction,

but has a continued need for IVIG therapy, premedication with diphenhydramine (Benadryl) and acetaminophen (Tylenol) may prevent an allergic response.

Anticoagulants. Anticoagulants administered in the PICU include heparin, low-molecular weight heparin (LMWH) (e.g., Enoxaparin), warfarin (e.g., Coumadin), tissue plasminogen activator (t-PA), or streptokinase (SK). Table 24-6 summarizes these medications, including indications, dosages, laboratory tests, and implications for nursing care. Specific information regarding heparin-induced thrombocytopenia (HIT) and care of patients with vascular access thrombi is discussed later in this chapter.

General nursing care for patients on anticoagulants includes careful monitoring of platelet count and coagulation studies, avoiding intramuscular injections and platelet-interfering drugs (i.e., ASA and NSAIDs), observation for frank and occult bleeding, and applying pressure (extended time) for all venipunctures and line insertion sites.

Mechanical Intervention

Apheresis. The term *apheresis* is derived from the Greek word for *removal*. Apheresis is a therapeutic process used to selectively extract abnormal blood components from the circulation. It is also used to harvest peripheral blood stem cells for storage and future transplantation, and for single-donor platelet concentrate collection.

All apheresis procedures have certain basic principles in common. Blood is withdrawn from the patient, pumped through a cell separator that removes the desired component by centrifugal force, and then returned to the patient. Each procedure is labeled according to the major component removed. Thus removal of leukocytes is termed *leukapheresis*, red cell removal is *erythropheresis*, and so forth. *Plasmapheresis*, which is also called *intensive plasma exchange*, refers to the removal of plasma.¹⁵

As with many advanced technologies, apheresis has been used more extensively in adults than in children. However,

TABLE 24-6 Anticoagulants

Medication	Indication	Dosage	Laboratory Testing	Nursing Implications
Heparin	Prevention and/or treatment of DVT, pulmonary embolus, and venous or arterial thrombi	IV 0.75 mg/kg loading dose IV over 10 min. Initial maintenance dose <1 yr of age: 28 u/kg/hr >1 yr of age: 20 u/kg/hr Adjust heparin to maintain APTT at 60-85 sec	APTT 4 hr after loading dose; every 4 hr until therapeutic level then qid CBC, platelet count, and PT qd	If platelet count <150,000 or bleeding occurs, contact physician; may be secondary to HIT
Low Molecular Weight Heparin (LMWH)	Same as for heparin Patients in whom venous access for administration and monitoring for standard heparin is difficult	Treatment dose for enoxaparin (Lovenox) <2 mo: 1.5 mg/kg/dose q12h 2 mo: 1.0 mg/kg/dose q12h (Usual maximum dose is 2 mg/kg q12h)	CBC, PT, APTT at baseline Platelet count Anti-factor levels should be drawn 4-6 hr after SC dose qd × 2 days Weekly if therapeutic level is reached	For platelet count <150,000 or bleeding occurs contact physician
Warfarin (Coumadin)	Same as for heparin When patient has stable APTT and can be changed to oral dosing Patient who has mechanical valves	Oral Day 1: Loading dose 0.2 mg/kg (0.1 mg/kg following Fontan or liver dysfunction) Day 2-4 loading doses based on INR response (Dosage is age dependent and is adjusted based on INR [usual dose is 2.0-3.0 mg])	Protime/INR Measure daily for first 2-3 days, then weekly after therapeutic level reached. Consider monthly checks if patient is stable and on long-term therapy	Patient remains on heparin with warfarin until INR is stable Patients may require dosage adjustments because of dietary or drug interactions with warfarin

APTT, Activated partial thromboplastin time; CBC, complete blood count; DVT, deep vein thrombosis; INR, international normalized ratio; IV, intravenous; PT, prothrombin time; SC, subcutaneous.

pediatric apheresis use has increased substantially since the early 1980s, with documented safety and efficacy for a variety of conditions. Apheresis has been successfully performed on very young and critically ill patients, but the smaller and sicker the patient, the greater the risks involved.¹⁵⁻¹⁸

Indications. The indications for apheresis in the PICU patient are specific to the type of procedure. Plasmapheresis is indicated for the following conditions.

1. *HUS or thrombotic thrombocytopenic purpura (TTP).* Removal of circulating endotoxin and/or replacement of normal platelet aggregating factors. Outcome has variable success rate in HUS but has documented efficacy in TTP.^{19,20}
2. *End-stage liver disease (immediately before transplant).* Removal of coagulant-poor plasma and replacement with coagulant-rich plasma and cryoprecipitate, keeping the patient euvolemic.
3. *Autoimmune (including hemolytic disorders), hyperacute GVHD posttransplant, Guillain-Barré syndrome, and acute hemolytic transfusion reaction.* Removal of deleterious antibodies and immune complexes.

Erythropheresis is utilized for SCD patients in acute crisis (especially acute chest syndrome) to remove sickled RBCs and replace with normal RBCs. Leukopheresis is primarily used for patients admitted with leukemia, with WBCs fewer than 150,000/mm³, at high risk for acute tumor lysis syndrome, before administration of chemotherapy. The procedure removes excessive leukocytes while leaving RBCs and plasma.

Procedure. The preparation and implementation of the apheresis procedure is typically the responsibility of the apheresis team (usually a hematologist and a specially trained apheresis nurse).

Vascular Access. The first, and often the most challenging, technical aspect to be considered in pediatric apheresis is the establishment of vascular access. A double-lumen catheter is necessary to simultaneously remove and return blood to prevent hypovolemia. Another line should be available for maintenance fluid and medication administration.

Priming and Anticoagulation. Priming of the apheresis tubing for pediatric patients is usually accomplished with albumin or packed RBCs (PRBCs) because the amount of extracorporeal blood necessary to fill the apheresis equipment may represent a significant proportion of the patient's blood volume (i.e., greater than 10%) and priming with saline would dilute the patient's hematocrit (Hct). Pediatric patients can become hypovolemic if the tubing is not primed with a solution to replace the blood being drawn off at the onset of the procedure.¹⁵⁻¹⁷

Anticoagulation with heparin and acid-citrate dextrose (ACD) is required to prevent thrombus formation in the tubing. It is crucial for nurses to monitor for side effects (i.e., bleeding from heparin [decreased perfusion; hypotension]) and hypocalcemia from ACD/citrate toxicity.

Complications. There are a number of potential complications associated with apheresis procedures in the PICU, including hypovolemia, circulatory overload, hypocalcemia,

hypothermia, and bleeding. Patients are monitored carefully for changes in condition to permit timely and appropriate intervention. The apheresis team is responsible to manage the apheresis procedure itself, whereas the critical care team is responsible for patient assessment and monitoring.

Hypovolemia can occur if an excessive amount of the child's blood is in the extracorporeal circuit, or from depletion of albumin, causing a shift of fluid out of the intravascular space. It is standard to have less than 15% of the child's circulating blood volume in the circuit at any given time.²¹ The PICU nurse carefully monitors vital signs and assesses perfusion for signs of shock. The rate of blood removed may be slowed, albumin administered, and/or fluids infused to correct hypovolemia.

The child who receives a large volume of albumin or fluids in excess of amount infused may be at risk for circulatory overload. Assessment for signs of fluid excess includes increased central venous pressure (CVP), gallop rhythm, crackles from pulmonary edema, and/or increased postpheresis weight. The net fluid balance is calculated postpheresis. Fluids during the procedure may be adjusted or diuretics may be administered for symptomatic fluid overload.

Children are at risk for hypocalcemia resulting from loss of calcium in pheresed plasma and from citrate in the anticoagulant, which inactivates calcium. Ionized calcium is monitored during the procedure. Total calcium is inaccurate because of fluctuating albumin. Calcium gluconate or chloride is administered for clinical and/or laboratory signs of hypocalcemia.

Hypothermia may result from the blood being circulated in the extracorporeal circuit outside the body, exposed to room temperature. This may exacerbate the temperature instability of the critically ill child, especially those with sepsis or neurologic compromise. Temperature is monitored every 15 to 30 minutes and patients are assessed for other signs of hypothermia such as bradycardia and shivering. Caution is necessary when "cold" blood from the circuit is infused into a right atrial line, which can cause severe ventricular arrhythmias. Treatment includes increasing the ambient room temperature, applying warmed blankets, and potentially warming the circuit blood before returning it to the patient.

A number of factors put the pediatric apheresis patient at risk for bleeding complications, including preexisting coagulopathy, systemic anticoagulation, depletion of fibrinogen and platelets owing to the apheresis process, and the presence of a large intravascular line.

Prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen level, platelet count, Hct, and activated clotting time (ACT) are measured before and after apheresis. These values help to determine the type and amount of anticoagulant used during the procedure. The apheresis nurse generally measures the ACT at the bedside at regular intervals, and the citrate and/or heparin doses are titrated accordingly. Normal ACT is 90 seconds; the desired ACT during apheresis is usually 150 to 180 seconds.¹⁵⁻¹⁷

The child is monitored for clinical signs of bleeding during and after the procedure. Platelets or other clotting

factor transfusions may be necessary to replace those depleted during apheresis. In rare instances, protamine sulfate may be administered to reverse the anticoagulant effects of heparin. All hematologic values are rechecked 24 hours after the apheresis procedure.

DISORDERS OF COAGULATION

Immune Thrombocytopenic Purpura

Etiology/Incidence. ITP is characterized by destruction of antibody-sensitized platelets by the reticuloendothelial system (RES), particularly the spleen. The child has normal laboratory results, except for moderate to severe thrombocytopenia ($<50,000/\mu\text{l}$).

ITP is acute in 80% of all pediatric cases, usually following a viral illness. About 60% of children recover within 4 to 6 weeks, and more than 90% recover within 3 to 6 months.¹⁴ The true incidence is unknown, mostly because the disease is transient. Children in the PICU may present with primary ITP or secondary ITP from diseases such as systemic lupus erythematosus (SLE) or HIV.

Pathogenesis. In most cases, ITP is mediated by antiplatelet antibodies, resulting in an increased rate of platelet destruction. The antibodies are also formed against donor platelets. The spleen plays a major role in platelet destruction; however, splenectomy is reserved for emergency treatment (e.g., uncontrollable hemorrhage in the PICU patient).

Although serious bleeding is rare despite severe thrombocytopenia ($<30,000/\mu\text{l}$), critically ill infants and children typically present with hemorrhagic symptoms, purpura, and signs of platelet bleeding (i.e., petechiae). Hemorrhagic blisters may be seen on the mucous membranes and lips. Epistaxis is common. Infrequently, patients will have GI or genitourinary (GU) bleeding. Intracranial hemorrhage is the most feared complication, which occurs in 0.5% to 1.0% of children, often at diagnosis.²² Most children will have a normal bleeding time and minimal symptomatology from ITP alone when their platelet counts are greater than $30,000/\mu\text{l}$.

The natural history of ITP is more benign in children than in adults. Treatment centers around conservative management until the condition improves sufficiently on its own. Treatment for symptomatic patients (and those with platelet counts less than $30,000/\mu\text{l}$) consists of steroids and immunoglobulins to suppress the immune response and prevent platelet destruction. Splenectomy, although usually definitive therapy for ITP, is avoided because more cases of death from postsplenectomy sepsis have been reported than from hemorrhage in children with chronic disease.²²

Hypervigilance is required in the assessment of children with ITP, especially those with platelet counts lower than $30,000/\mu\text{l}$. Assessment includes observing for signs of oozing and hemorrhage, as well as occult bleeding. Neurologic status, including level of consciousness and changes in motor, sensation, and pupillary checks is monitored for signs of intracranial hemorrhage. Pulmonary secretions, GI content, and urine are observed and/or tested for occult or

frank blood. If the patient has a distended abdomen, girth measurements may be trended, and the patient evaluated for GI bleeding. The skin and mucous membranes are assessed frequently for signs of new bleeding. Invasive line and venipuncture sites are observed for oozing and hemorrhage. Bleeding is controlled, with additional pressure and dressings provided for external bleeding sites. Epistaxis control measures are at the bedside. Protocols are institution specific, but may include Neo-synephrine nose drops and nasal packing material. In addition, ongoing monitoring is required for the patient's coagulation and CBC results, type and screen/cross-matching status, and availability of blood products for the patient who has an emergent need.

Critical Care Management. ITP treatment includes administration of steroids, IVIg or IV anti-D (i.e., Rhogam, for Rh⁺ patients, or Winrho) to suppress the antibody response to platelets. Emergent treatment for hemorrhage includes transfusion of platelets because the patient may receive a transient rise before antibody destruction of the donor platelets. Transfusion of platelets is followed by steroid and immunoglobulin administration to enhance the platelet effect. Splenectomy is reserved for the emergently bleeding patient or the patient who is at high risk for bleeding and who is refractory after 24 to 48 hours of supportive management (steroids and immunoglobulins).²²

High-dose steroid administration, (methylprednisolone 30 mg/kg/day, or Prednisone 1 to 2 g/kg/day), in divided doses and IVIg 1 g/kg/day are standard therapy for patients who are at high risk for bleeding. For patients who are Rh positive, intravenous Anti-D (Winrho), may be administered at an initial infusion dose of 25 to 50 $\mu\text{g/kg}$. Infusions of immunoglobulins may be repeated on subsequent days, following platelet counts closely. IV Anti-D has demonstrated a 48- to 72-hour delay before the platelet count increases, but has also demonstrated fewer reactions than IVIg.²³

Patients are observed closely for signs of potential infection because the patient will be immunosuppressed on steroid therapy. Guidelines for the administration of IVIg are followed with close monitoring for the occurrence of allergic reactions.

Plasmapheresis may be considered in addition to steroid and immunoglobulin therapy to provide an acute effect. Plasmapheresis alone would be insufficient because the time required to have an effect on the platelet count rise would take about 2 to 5 days.²²

Androgen therapy (i.e., danazol) and monoclonal antibodies have been used to decrease platelet antibody production. Currently, these agents are not standard therapy for the critically ill child with ITP.^{22,23}

Disseminated Intravascular Coagulation

Etiology/Incidence. DIC is not a distinct disease, but rather an abnormal coagulation syndrome which occurs secondary to another disease process.^{19,24} It is characterized by excessive use of coagulation factors that exceeds the ability to replenish these factors and results in the rapid production of thrombin and activated factor X or excessive

bleeding as a result of failure of clot formation. The onset of DIC is usually preceded by massive activation of the hemostatic processes. The leading cause is infection. Many bacterial processes invoke activating factors that initiate the intrinsic coagulation system. Endothelial and tissue damage also enhance intrinsic stimulation as well as activate the extrinsic coagulation pathway.

DIC may also occur secondary to shock, burns, malignancies, fat emboli, hemolytic transfusion reactions, or immune disease. Other precipitating factors are hypoxia, acidosis, and hypotension. DIC has actually been reported to complicate more than 100 clinical disorders.²⁵

Pathogenesis. In DIC, there is acceleration of normal coagulation, but the end result is bleeding. Excessive production of thrombin and plasmin degrades fibrinogen to fibrin, leading to further activation of the coagulation system, deposition of fibrin in the microvasculature, activation of the fibrinolytic system, and platelet activation. Consumption of clotting factors and platelets occurs and, as the process continues, fibrin split products (FSPs) are produced. If FSPs are not cleared from the circulation by the RES, anticoagulation will be enhanced. Normally the RES removes fibrin, activated clotting factors, endotoxins, and FSPs from the circulation. Dysfunction of the RES owing to shock or liver disease impairs removal of these substances, leading to hypercoagulability and DIC. With an increase in circulating FSPs, there is decreased platelet function and adherence, inhibition of thrombin, activation of complement, and further endothelial damage. The development of microvascular thrombi and bleeding leads to cellular ischemia (Fig. 24-3).

The clinical presentation of DIC varies dramatically from one patient to another. Onset may be sudden or gradual. It may be difficult to differentiate clinical signs from those of the underlying disease state. DIC may be suspected only because of its known association with certain pathologic states. Bleeding is the most obvious clinical sign of DIC. In children, abnormal bleeding is often identified from ecchymoses or petechiae or in oozing from intravenous and venipuncture sites.¹⁹

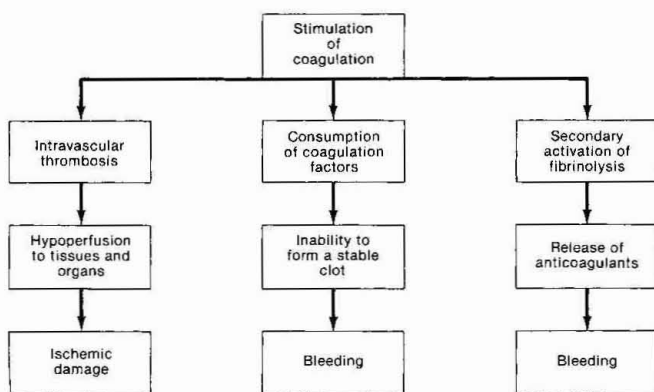


Fig. 24-3 The pathophysiology of DIC. (From Dressler DK: Patients with coagulopathies. In Clochesy JM et al, eds: *Critical care nursing*, Philadelphia, 1992, WB Saunders.)

In its most extreme case, the child with DIC shows pallor and circulatory failure, which is manifested by tachycardia and hypotension. Purpura and overt bleeding that may involve the pulmonary, cerebral, and intraventricular systems may be seen. In addition, thrombosis of the central and peripheral veins may lead to gangrene and tissue necrosis.

Abnormal serum coagulation values are an early indication of DIC. Typical findings include anemia with RBC fragmentation, thrombocytopenia, and prolonged PT, PTT, and thrombin time. An increase in FSPs is the cardinal sign of DIC. The greatest degree of diagnostic specificity is the measurement of the D-dimer FSP fragment, which is a breakdown product of cross-linked fibrin in either plasma or serum.^{26,27} Fibrinogen levels are usually decreased but may be normal in some cases. Factors V and VIII are normal or may be extremely elevated. The presence of fragmented blood cells or schistocytes may be seen and indicates fibrin deposition in small vessels and a thrombolytic occurrence.

Many patients in the PICU are at risk to develop DIC. Thorough nursing assessment is essential in the prompt recognition and subsequent management of patients with DIC. The skin, mucous membranes, and all drainage or secretions are observed for obvious or occult bleeding.

Vital sign changes that may be indicative of bleeding and hypovolemia are tachycardia, tachypnea, and hypotension. It is important to remember that hypotension is a late sign in the child. Changes in mental status, such as irritability, restlessness, and lethargy, are signs of decreased cerebral perfusion related to hypovolemia and may present in the child with bleeding related to DIC.

Critical Care Management. Critical care management of patients with DIC is supportive, aimed at stabilization of cardiac status and restoration of fluid and electrolyte balance. Specific treatment of the underlying disorder includes correction of shock, acidosis, and electrolyte imbalance, and antibiotic therapy for bacterial infections. Replacement of coagulation factors is often necessary. PRBCs may be administered for active bleeding. In addition, if the child is actively bleeding and has a low platelet count ($<20,000/\mu\text{l}$), platelets are administered to increase the platelet count to $60,000/\mu\text{l}$. If the platelet count is higher than $50,000/\mu\text{l}$ and the child is still bleeding, FFP 10 to 15 ml/kg body weight is administered to replace consumed clotting components. Cryoprecipitate is administered for fibrinogen levels below 75 g/dl to elevate fibrinogen levels. Table 24-4 presents specific implications associated with the use of these blood products.

Nursing care for the child receiving these blood products consists of monitoring for reactions to blood products, signs of fluid imbalance, and vital signs, including central venous pressure. Intake and output volumes are also strictly measured.

Controlling and preventing further bleeding is of paramount importance in caring for the critically ill child with DIC. Vital signs and laboratory studies are monitored frequently for changes that indicate bleeding. All output, including urine, stool, and nasogastric drainage, is tested for the presence of blood. All invasive sites are closely observed for oozing or active bleeding. Intramuscular injections and

rectal procedures are avoided because of the increased risk for bleeding.

Heparin therapy for DIC is controversial because its efficacy has not been proven.²⁸ The rationale for administering heparin is the enhancement of antithrombin (AT) III activity, a major inhibitor of thrombin. With thrombin activity inhibited, degradation of fibrinogen to fibrin is impeded and further development of microvascular thrombi is slowed or halted. The concern about heparin therapy is the potential risk of further bleeding. When heparin is administered, the child receives an initial intravenous loading dose of 25 to 50 units/kg, followed by a continuous intravenous infusion of 5 to 10 units/kg/hour. Supportive therapy with platelet, FFP, and cryoprecipitate transfusions is continued.

The most valuable test for evaluating the effectiveness of heparin is the fibrinogen level. Even with a severe decrease in fibrinogen, the level should rise to a normal or near-normal level within 24 to 48 hours of effective heparin therapy.^{19,29}

Assessing the child closely for the exacerbation of bleeding related to heparin is critical because this is the indication for discontinuation of heparin therapy. The child is also reevaluated regarding the need for further replacement of platelets and coagulation factors. Protamine sulfate may be administered to counteract the effects of heparin (1 mg for every 100 units of heparin). However, this is only rarely necessary owing to the short half-life of heparin.

The duration of heparin therapy for DIC may vary from 12 to 24 hours in conditions when the underlying disease may be treated effectively. Other conditions, such as leukemia, may require therapy for as long as 2 to 3 weeks.

Partial exchange transfusions with heparinized fresh blood or reconstituted FFP and PRBCs may be necessary if fluid overload becomes a persistent problem and the child continues to require large volumes of blood or clotting factors. Removal of selected mediators also may break the vicious, self-perpetuating cycle of DIC. Nursing responsibilities related to apheresis have been discussed previously.

Heparin-Induced Thrombocytopenia

Etiology/Incidence. HIT is typically characterized by a 50% or greater decrease in platelet count after 5 or more days of unfractionated (standard) heparin therapy. If a patient has been exposed to heparin in the recent past (less than 100 days), the presentation is often rapid, within the first 24 hours of reexposure. The platelet count nadir is usually around 50,000 μ l; however, in some postoperative patients, mean platelet counts may remain above 300,000 μ l.³⁰ The platelet nadir is not related to the risk of thromboemboli.

HIT is an uncommon complication of heparin therapy that can cause significant morbidity and mortality in the PICU patient. The incidence of HIT is about 5% in adult patients receiving unfractionated heparin, and unknown in pediatric patients. Twenty percent of patients with HIT can have paradoxically thrombotic complications, which can be devastating, including loss of limb or death.

HIT usually occurs in patients 5 to 15 days after beginning heparin therapy, but can occur earlier in patients with prior exposure to heparin. An unexplained drop in platelet count in a patient receiving heparin should raise the suspicion of HIT.

Pathogenesis. HIT is caused by an antibody-antigen reaction on the surface of platelets with unfractionated heparin. The mechanism by which HIT predisposes to thromboemboli is by the production of platelet-derived microparticles that are released in the circulation and activate the coagulation system. HIT is an intensely prothrombotic condition.

The pediatric patient suspected of having HIT needs to be assessed closely for signs of clotting (increased bruising, thrombus formation), or bleeding if the platelet count is extremely low. Blood samples from patients are tested for induction of platelet aggregation by heparin or serum evaluation for specific antibodies.

Critical Care Management. Any source of heparin, including LMWH (though it rarely causes HIT), is discontinued. This includes arterial and central line flush solutions. If there is no evidence of thrombosis and no indication for continuation of anticoagulants, discontinuation of heparin will result in the platelet count returning to normal.

If a thrombus is present and a need for continuation of anticoagulant therapy exists, medications such as danaparoid (Orgaran) and Ancrod may be administered because they have minimal cross-reactivity with heparin-induced antibody. Minimal data regarding drug selection exists for the pediatric population.

Vascular Access Thrombi

Etiology/Incidence. The small size of a central venous catheter lumen predisposes the infant and small child to the development of thrombi that can occlude the catheter. Central line occlusion can be caused by chemical-related thrombi, which develop from precipitates formed when incompatible solutions mix, and blood-related thrombi, which are caused by inadequate flow rate or flushing of the lumen, with subsequent platelet aggregation and thrombus formation.

Pathogenesis. Central venous catheters are thrombogenic because they are foreign to the body, they damage vessel walls and disrupt blood flow, and some infusions injure the vessels. Central venous catheter thrombotic complications include clots at the tips that impair infusion or withdrawal of blood, fibrin sleeves that are not adherent to vessel walls but may occlude lines, and deep venous thrombi that adhere to vessel walls with partial or complete obstruction.³⁰

The most common presentation is the child with a central catheter from which blood cannot be withdrawn or into which fluids cannot be infused. The obstruction may be present in one or all lumens. Diagnostic work-up after failure to obtain line patency with antithrombotic instillation should include a venogram or Doppler ultrasound.

Emergent signs of superior vena cava syndrome may also be present if a large vessel thrombus occludes venous


TABLE 24-7 Vascular Access Occlusion Therapy

Drug	Local Instillation Amount	Guidelines
Alteplase (rTPA) (2 mg/ml)	2 ml to each lumen (or volume required to fill lumen)	Dwell \times 1 hr Aspirate and flush with NS Repeat \times 1 if needed
Streptokinase (3000 IU/ml)	3000 IU/ml to fill lumen (1.8-2.5 ml per each lumen)	Dwell \times 1 hr Aspirate and flush with NS and attempt to aspi- rate blood Consider adminis- tering antihista- mine and acetaminophen to decrease potential for allergic reaction

drainage from the upper body. Immediate diagnostic tests include a venogram, and possibly a \dot{V}/\dot{Q} scan.

Critical Care Management. Prevention of central venous catheter occlusion requires adequate flushing, especially between incompatible medications, and adequate infusion rates to keep lumens patent. Early detection of line problems, including slow blood return, mandates an increase in flushing frequency for heparin-locked ports, or early instillation of an antithrombotic agent.

Despite all efforts to maintain catheter patency, thrombi may develop. If the line is blocked without evidence of clinical compromise, an attempt is made to "dissolve" the clot, using SK, which has a high allergic reaction potential, or t-PA. Table 24-7 provides instillation guidelines for these agents. Small local occlusive thrombus (<1 cm) are treated with local low-dose thrombolytic infusion therapy for 24 to 72 hours, or more rapidly if immediate central line patency is required.

If the catheter is still not patent after local instillation, or if it has occluded a second time, further work-up is indicated. If a large vessel thrombus is suspected, a venogram or Doppler ultrasound evaluation is performed.³¹

Close monitoring of coagulation studies (PT, APTT, and fibrinogen) every 8 hours is performed after initiation of therapy. Assessment for signs of bleeding (frank and occult) and signs of movement of the thrombus (increased respiratory distress, or ECG changes secondary to pulmonary embolus) is essential.

If pulmonary embolus is suspected (or documented by \dot{V}/\dot{Q} scan), the central line is either left in place or removed, depending on patient status, and heparin therapy (followed by 3 months of Coumadin), or LMWH is indicated.³³

ANEMIAS

Anemia is defined as a deficiency in RBCs, Hgb, total volume, or any combination of the three, with the primary problem of insufficient oxygen transported on Hgb to meet cellular demand.^{1,32} Patients with anemia may present to the PICU as an emergency or with an acute exacerbation of a chronic anemia. Overall, the main problems seen in children with anemia of any etiology are ineffective gas exchange, altered tissue perfusion, and altered fluid volume. Nursing care is directed toward assessment and management of these problems.

Anemia results from an excessive loss or destruction of blood, an inadequate production of Hgb and RBCs resulting from bone marrow failure or a deficiency state, or a combination of both.³⁴ The pathophysiologic process producing signs and symptoms of anemia primarily relates to the decreased oxygen-carrying capacity of the RBCs, resulting in inadequate oxygen to meet tissue demands. When a patient has excessive blood loss, pathophysiologic changes occur due to hypovolemia, with inadequate cardiac output for tissue perfusion.

The anemias seen in children are reviewed in Box 24-2 and discussed briefly in this section. SCA is discussed in more detail because children with this disease present to the PICU more frequently than do children with other types of chronic anemia.

Anemia Related to Blood Loss

Etiology/Incidence. Acute or chronic blood loss may produce anemia. With acute blood loss, the anemia is present after the loss of blood volume is replaced with extracellular fluid (ECF). Chronic blood loss produces anemia when the body has expended its iron reserve.

Pathogenesis. The clinical presentation of a child with anemia related to blood loss varies greatly. Those with chronic anemia often adapt to a low Hct and Hgb without compromise. On the other hand, a previously healthy child who has a sudden and dramatic reduction in Hct and Hgb may present as an acutely ill child in respiratory distress/failure and shock and require aggressive intervention. Clinical manifestations of acute hemorrhage include signs of shock (i.e., decreased level of consciousness, pallor, cool extremities, poor peripheral pulses, prolonged capillary refill, with a normal or low blood pressure, and possibly respiratory distress symptoms resulting from inadequate oxygenation). Bleeding may be obvious, with external hemorrhage, or hidden with internal bleeding until perfusion and oxygenation are severely compromised.

Laboratory tests to evaluate this type of anemia include a CBC with RBC indices, platelet count, PT, PTT, serum fibrinogen level, and FSP. During and shortly after an episode of bleeding, the platelet count and serum fibrinogen level may transiently decrease. The Hct and Hgb remain relatively stable in the acutely bleeding child because 24 to 72 hours are necessary for the Hct and Hgb levels to equilibrate and accurately reflect the total amount of blood loss.

Box 24-2

Classification of Anemias of Childhood

- A. Abnormal RBC production
 - 1. Disorder of proliferation/differentiation
 - a. Aplastic anemia
 - b. Pure red cell aplasia
 - c. Erythropoietin deficiency
 - 2. Disorder of DNA synthesis
 - a. Vitamin B₁₂ deficiency
 - b. Folate deficiency
 - 3. Disorder of Hgb synthesis
 - a. Iron deficiency
 - b. Thalassemia
- B. Increased RBC destruction
 - 1. Intrinsic RBC abnormalities
 - a. Membrane defects
 - Hereditary spherocytosis
 - Liver disease
 - b. Abnormal red cell metabolism
 - Glucose-6 phosphate dehydrogenase deficiency
 - Pyruvate kinase deficiency
 - 2. Extrinsic abnormalities
 - a. Mechanical destruction
 - Microangiopathic hemolytic anemia
 - Traumatic hemolysis (cardiac valve prosthesis)
 - b. Infection
 - Bacterial
 - Viral
 - Parasitic
 - c. Antibody-mediated
 - Alloimmune hemolytic disease of the newborn
 - Drug reaction
 - Autoantibody-mediated destruction of erythrocytes
 - d. Hypersplenism
- C. Blood loss
 - 1. Traumatic or gastrointestinal hemorrhage
 - 2. Surgical

From Nugent DJ, Tarantino MD: Hematology-oncology problems in the intensive care unit. In Fuhrman BP, Zimmerman JJ, eds: *Pediatric critical care*, St Louis, 1992, Mosby.

Hemolytic Anemia

Etiology/Incidence. The average lifespan of a RBC is 100 to 120 days. About 1% of RBCs are removed from the circulation each day and the same percentage is replaced by new red cells (reticulocytes) released from the bone marrow. Hemolytic anemia results when RBC destruction is abnormally high and the bone marrow compensatory mechanism cannot keep pace with the loss of RBCs. Hemolysis of RBCs may be caused by a variety of etiologies, as described in Box 24-2. Causes of hemolysis can be attributed to factors extrinsic to RBCs, such as in microangiopathic hemolytic anemias (e.g., HUS and TTP), infections, and autoantibodies (e.g., SLE). Intrinsic RBC defects may also cause hemolysis, including hemoglobinopathies such as glucose-6 phosphate dehydrogenase (G6PD), thalassemia, and spherocytosis.

Pathogenesis. The child may have presenting symptoms, which vary from typical symptoms of mild anemia to life-threatening complications from acute loss of oxygen-carrying capacity and compromised tissue perfusion as previously discussed.

Because hemolysis of RBCs is the cause of this anemia, diagnosis is based on the fact that RBCs are undergoing premature disruption. A decreased (or often unmeasurable) haptoglobin, elevated lactate dehydrogenase (LDH), an elevated reticulocyte count, and elevated serum levels of unconjugated bilirubin are seen. Erythroid hyperplasia and a decrease in the granulocyte to erythrocyte level are revealed in examination of the bone marrow.

Critical Care Management. If the child is experiencing critical signs of diminished oxygenation and/or tissue perfusion, PRBCs are administered. Blood products are not ordered based on a specific number, but based on clinical need for the patient with critical organ perfusion problems. If the child is experiencing an autoimmune hemolytic reaction owing to an underlying disorder such as lupus or lymphoma, a cross-match may be unreliable. There is an increased risk of severe transfusion reaction secondary to underlying alloantibodies that are not able to be detected. When required, transfusions should be given cautiously because the transfused RBCs are also subject to destruction. However, if the anemia is causing hemodynamic instability, the child is transfused with type-specific blood in a sufficient amount to stabilize the cardiovascular system, in spite of incompatibility. Close assessment for fluid overload is required because the child's ECF volume may be expanded as a result of compensatory mechanisms to meet oxygen and perfusion demands.

Aplastic Anemia

Etiology/Incidence. Aplastic anemia refers to a pronounced reduction in the number of RBCs, WBCs, and platelets resulting from hypoplasia or aplasia of the bone marrow in the absence of malignant disease. This type of anemia may be congenital or acquired, resulting from medications, infections, chemical exposure, or radiation.

There are many specific etiologies for aplastic anemia, which include infections (e.g., Epstein-Barr virus and

Critical Care Management. Treatment for acute blood loss is aimed at restoring intravascular volume, initially with crystalloid solutions, followed by blood. The indication for RBC transfusion in the hemorrhaging patient is impaired oxygen delivery to end organs.¹ Patients primarily receive PRBCs as the component of choice. These may be given concurrently with FFP if plasma coagulation factors are also needed.

Chronic anemia is generally well tolerated, and transfusion is not usually necessary unless the Hgb falls below 6 to 7 g/dl. Because extracellular volume (ECV) is increased in the child with chronic anemia, caution is taken if the patient is transfused because volume overload is a potential risk. The child is assessed carefully for congestive heart failure and pulmonary edema during transfusion therapy.

hepatitis), drugs (e.g., chloramphenicol), and idiopathic causes. The majority of cases are idiopathic.¹

Pathogenesis. Children show the classic signs of a low blood count. Anemia, pallor, and fatigue may be present because of a decreased RBC count; increased susceptibility to infections from a low WBC count; and ecchymosis, petechiae, and epistaxis resulting from a low platelet count. Bone marrow biopsy reveals a marked reduction in all cells. Children with severe aplastic anemia may present to the PICU with signs of decreased oxygenation resulting from a reduction in the oxygen-carrying capacity of the blood, cardiac failure, overwhelming infection, or massive bleeding.

Critical Care Management. The treatment priority for the child with life-threatening complications of aplastic anemia is cardiopulmonary stabilization. RBC transfusions are administered and platelet transfusions are indicated for the child with signs of severe bleeding (e.g., GI bleeding). All blood products are irradiated and filtered before transfusion because of the risk of posttransfusion GVHD related to sensitization of the recipient to HLA antigens in the donated blood. Infections are treated with broad-spectrum antibiotics or antifungal agents, if a fungal infection is present.

Treatment specific to aplastic anemia includes androgen therapy, immunosuppressive therapy, and bone marrow transplantation. Bone marrow transplantation is the treatment of choice if a compatible donor is available. Chapter 25 provides information on the care of the child receiving a bone marrow transplant.

Sickle Cell Disease

Etiology/Incidence. SCD refers to a group of hemoglobinopathies distinguished by the development of sickled cells in response to deoxygenation. SCA is the most common cause of SCD. SCA is an autosomal recessive disorder in which the child produces sickle hemoglobin (Hb S) rather than Hb A. The child with sickle cell trait has inherited a sickle gene (Hb S) from one parent and a normal hemoglobin gene (Hb A) from the other parent. This child is always a carrier of SCA, although the trait does not progress to anemia.

When the child inherits two Hb S genes, SCA results. The red cells of SCA contain up to 80% to 100% of Hb S. This is a potentially fatal disease that occurs predominantly in the black race.

Pathogenesis. Sickling of the RBC describes the change of a normal round RBC to a sickle-shaped one. The sickling process begins with the substitution of valine for glutamic acid on the beta chain of the hemoglobin molecule. This process produces Hb S, which is less soluble than the normal cell when deoxygenated. The decreased solubility causes Hb S to become more viscous and change to the sickle shape.

Once RBCs sickle, they are more fragile and easily destroyed. They cannot flow easily through the capillary beds and tend to become clumped, causing obstruction and impediment to blood flow. Tissue hypoxia develops, which

promotes further sickling. As the hypoxia worsens, infarctions and necrosis can develop (Fig. 24-4).

There are several factors that cause Hb S to sickle (Box 24-3). Hypoxia is a major determinant. Characteristics of blood flow can also increase the tendency toward sickling. Under normal circumstances, the cardiac output of the child with SCD is elevated. This compensatory mechanism ensures that the transit time of blood between the capillary and the lung is rapid so that sickling cannot occur. However, any pathophysiologic process that affects pressure (such as hypotension or pulmonary hypertension) or increases resistance (such as vasoconstriction or increased Hct) promotes sickling.

The clinical presentation of children with SCD varies greatly. The symptoms seen are usually the result of (1) hemolysis of the cells and the compensatory mechanisms invoked by the subsequent anemia, and (2) thrombi in the small vessels of various organs resulting from the sickling. General symptoms seen in the child with SCD include weakness, pallor, fatigue, tissue hypoxia, and jaundice, as the result of RBC hemolysis. The heart may become enlarged because of the higher cardiac output demanded by the chronic anemia. Thrombi from the sickled cells may cause progressive damage to multiple organs, including the eyes, liver, and lungs.

Box 24-3

Factors That May Promote Sickling

1. Pressure-related
 - a. Hypotension
 - b. Pulmonary hypertension
2. Resistance-related
 - a. Vasoconstriction
 - b. Increased Hct (>35%)
3. Desaturation-related
 - a. Hypoxemia
 - b. Acidosis

From Eskenazi AE, Gordon JB, Bernstein ML: Hematologic disorders in the pediatric intensive care unit. In Rogers MC, ed: *Textbook of pediatric intensive care*, ed 3, Baltimore, 1996, Williams & Wilkins.

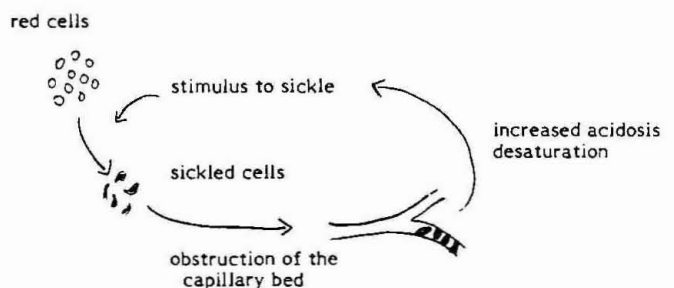


Fig. 24-4 The “vicious cycle” of progressive sickling causing intravascular occlusion. (From Eskenazi AE, Gordon JB, Bernstein ML: Hematologic disorders in the pediatric intensive care unit. In Rogers MC, ed: *Textbook of pediatric intensive care*, ed 3, Baltimore, 1996, Williams & Wilkins.)

Diagnosis of SCD and sickle cell trait are made through a variety of tests. The most commonly used is a hemoglobin electrophoresis. This assay separates the various types of hemoglobin and quantifies the percentages of various hemoglobins present. There are less sensitive tests that determine the presence or absence of Hb S; however, positive results require further screening with hemoglobin electrophoresis. Diagnosis may be made prenatally by using fetal blood obtained in placental aspiration or photoscope.

Critical Care Management. A PICU admission often signals a life-threatening episode with a high risk of morbidity and mortality for children with SCD. Outcome is often dependent on which organs are affected, the type of virus and/or bacteria causing the infection, if one is present, and the degree of progressive damage that has already occurred because of the disease. Nursing care is critical in managing the effects of the SCD crises.

The child with SCD may have signs of respiratory distress for a number of reasons. Pneumonia and pulmonary infarctions occur more often in this patient population. Splenic sequestration may also cause respiratory distress because the engorged spleen pushes up on the diaphragm. Hypoxemia causes increased sickling and, in turn, causes a vicious cycle of deoxygenation related to anemia and vaso-occlusive crisis.³⁵

Assessment of breath sounds on a regular basis is imperative. The patient is observed for signs of respiratory distress, and the lungs are auscultated to detect decreased breath sounds along with abnormal sounds. Monitoring arterial blood gases on a regular schedule and continuous monitoring of oxygen saturation is essential. Oxygen by face mask or nasal cannula may be the only respiratory support that is needed. However, if the blood gases do not demonstrate improved oxygenation and the child's respiratory status continues to deteriorate, intubation and ventilatory support are necessary. Daily chest films are routinely performed to monitor progression or resolution of pulmonary complications.

Vaso-occlusive crises can vary in location, duration, and intensity. During a sickling event, vaso-occlusion prevents oxygen and nutrients from reaching the tissues. Pain is often the cardinal sign of a vaso-occlusive event. The pain has been described as being tremendously variable and unpredictable in onset, location, character, intensity, and duration.³⁶ Pain is the most common reason for emergency department visits and hospital admissions.³⁷ On admission to the PICU, the child's pain and level of analgesia is assessed. Pain assessment requires that the health care team, including the patient and family, be able to quickly differentiate between pain from vaso-occlusive crisis and pain from other complications of SCD.³⁶ Pain intensity is quantified by a chosen pain scale and documented on a flowsheet to monitor progression of the pain over time.

Drug therapy is the treatment of choice for pain associated with SCD. Ibuprofen or acetaminophen is used to initially manage mild to moderate pain. Codeine may be added if these are not effective. Severe pain may be treated with immediate-release or sustained-release morphine, oxycodone, hydromorphone, or methadone, given either orally

or intravenously around the clock.³⁵ Another recommended regimen for pain management is intravenous morphine sulfate given every 1 to 2 hours around the clock.³⁸ A continuous narcotic infusion may be considered because bolus injections may not provide satisfactory analgesia because of the short plasma half-life of the narcotic. Patient-controlled analgesia (PCA) is an accepted method of pain management for children who are able to and want to manage their own pain relief. Two methods of PCA were compared in children with SCD. Children who received high-dose PCA with a low basal infusion required less morphine, had shorter lengths of stay, and had lower pain scores on day 2 of hospitalization when compared with children who received low-dose PCA with high basal infusions.³⁸

Additional medications have been used to treat pain associated with a vaso-occlusive crisis. Intravenous methylprednisolone given in high doses has been shown to decrease the duration of severe pain.^{39,40} A parenteral antiinflammatory drug (ketorolac) has been used for crisis pain and has the advantage of avoiding the risks associated with narcotics. However, one study did not demonstrate a synergistic analgesic effect for ketorolac; a lower morphine dose was not able to be used.⁴¹ A case report presented the development of ketorolac-induced irreversible renal failure.⁴² Further study is needed to evaluate the effectiveness of additional medications.

Hypovolemia is often seen in children with SCD in the PICU. Fluid replacement depends on the clinical condition and the results of the serum electrolytes, Hct, and coagulation studies. Children with splenic sequestration require crystalloid and RBCs immediately to restore circulating blood volume. Children in aplastic crisis require PRBCs because of their decreased Hct level. Crystalloids may be the only fluid replacement in vaso-occlusive crisis, depending on the degree of sickling and whether or not there is ischemia or infarction of the affected organ.

Patients with SCD tolerate a low Hct level extremely well, and transfusions should be initiated only when absolutely necessary. The Red Blood Cell Administration Practice Guideline Development Task Force of the College of American Pathologists recommends that RBC transfusions are indicated only to prevent recurrent refractory vaso-occlusive complications, stroke, or during certain illnesses (Box 24-4).⁴³ The potential for significant complications related to multiple transfusions include infection, iron overload, and alloimmunization. Iron overload results from the addition of 200 to 250 mg of iron added to the body's iron stores with each transfusion. This results in increased serum ferritin levels. If serum ferritin levels are greater than 2500 to 3500 mg/ml and the child still requires transfusions, chelation therapy is given.⁴⁴ Chelation therapy removes iron from body tissue and allows it to be excreted from the body. Deferoxamine is administered as a continuous subcutaneous infusion over 5 to 6 hours several times per week.³⁵

Hydroxyurea has been used as an alternative to blood transfusions as a means to prevent recurrent stroke. Hydroxyurea reduces the frequency of vaso-occlusive crisis,

Box 24-4

Partial Exchange Transfusion in the PICU

1. Preparation
 - a. Decision to transfuse
 - b. Insertion of venous and arterial catheters (or two large-bore venous catheters, if possible)
 - c. Blood sent to laboratory for:
 - i. Complete blood count
 - ii. Quantitative sickle cell preparation (this appears to correlate well with the quantity of Hb S noted at electrophoresis)
 - iii. Electrolytes and calcium determination
 - iv. Cross-match with PRBCs (sickle negative)
2. Procedure
 - a. Volume of packed cells ($2 \times \text{Hct} \times 0.7 \times \text{wt [kg]}$)
 - b. Rate
 - i. Adjust intravenous line so transfusion occurs over 4 to 6 hr (more difficult if over 1000 ml are to be exchanged)
 - ii. Withdraw blood at 10- to 15-min intervals from arterial line or large-bore venous catheter
 - iii. Balance maintained within 5% of blood volume (blood volume, 80 ml/kg)
 - c. Monitoring
 - i. Heart rate and blood pressure (continuously)
 - ii. Hematocrit (every 2 hr, and at last hour)
 - iii. Electrolytes, calcium (at last hour)
 - d. Endpoint
 - i. Hematocrit 33% to 37% (add FFP to remainder of PRBCs if Hct is $>35\%$)
 - ii. % Hb S is $<40\%$ (initial screening by quantitative sickle cell preparation, followed by chromatography or electrophoresis)

From Eskenazi AE, Gordon JB, Bernstein ML: Hematologic disorders in the pediatric intensive care unit. In Rogers MC, ed: *Textbook of pediatric intensive care*, ed 3, Baltimore, 1996, Williams & Wilkins.

though the mechanism is unclear. It has been shown that there is an increase in the proportion of fetal Hgb cells within 8 to 12 weeks of beginning treatment.^{45,46}

The nurse monitors for reactions to blood products and for signs of fluid imbalance. Children with SCD may require frequent transfusions during an acute episode, which increases the risk of volume overload. It is critical to closely monitor the patient for signs of fluid overload. The use of short-acting diuretics before or after the transfusion may help to prevent this complication. Other nursing responsibilities include monitoring vital signs and laboratory values and maintaining an accurate record of intake and output.

Exchange or partial exchange transfusions are often used for acute complications of SCA. The advantage of an exchange or partial exchange transfusion over a simple transfusion is that there is less risk for volume overload and a more rapid reduction in the percentage of cells containing Hb S. Preoperative exchange transfusions may be performed for children with SCD requiring surgery to reduce the risk of postoperative vaso-occlusive complications. Apheresis may also be used in the treatment of acute complications of SCD.

Prophylactic transfusions, done on a regular basis (every 3 to 6 weeks), are showing signs of promise in reducing complications associated with SCD.⁴⁷ Nursing responsibilities related to these procedures have been discussed in the previous section.

SCD is considered a multiorgan disease because of the risk of ischemia or infarction of many organs caused by sickling of RBCs and vaso-occlusion. The organs most commonly affected are the spleen, kidneys, and bone marrow; however, involvement of the lungs and the brain can also occur. Children with frequent episodes of intravascular sickling are at risk for progressive organ dysfunction because of decreased tissue perfusion, ischemia, and necrosis. All organs can be affected during an acute episode, as well as chronically. A complete and ongoing assessment of all organ systems during an intensive care admission is imperative.

A newer method of treating SCD is bone marrow transplantation. Transplantation changes the electrophoresis pattern in the child's Hgb toward the donor's pattern.³⁵ It is considered a curative therapy. Patients can experience GVHD and some have died from this complication.

Complications of Sickle Cell Disease. The most common clinical manifestations of SCD are vaso-occlusive crises, sequestration crises, and aplastic crises. These may lead to life-threatening complications such as acute chest syndrome, stroke, acute anemia, and sepsis, which require admission to the PICU.

Vaso-occlusive Crises. The most common reason for admission to the PICU is vaso-occlusive crisis with ischemia or infarction of the occluded organ. Vaso-occlusive crisis is an acute, painful episode that is the result of intravascular sickling, occlusion of small vessels, and tissue ischemia and infarction. The onset is acute and may be precipitated by infection, hypoxia, fever, acidosis, dehydration, change in climate, and psychologic factors. However, a predetermining factor is often not identified. The joints and the extremities are most often affected.

Therapy for the child with vaso-occlusive crisis is aimed at removing the precipitating cause, treating complications, and preventing further crises. Treatment is supportive and includes hydration, antibiotics, and pain management, as discussed above. Oxygen is provided if the child is hypoxemic in order to prevent further sickling and possibly promote conversion of sickled RBCs to normal shape.

Acute Chest Syndrome. Acute chest syndrome is the development of a new pulmonary infiltrate in combination with fever or respiratory symptoms in a patient with SCD.⁴⁸ It is the result of sickling of RBCs in the pulmonary vasculature, which may cause intrapulmonary shunting and abnormalities in gas exchange. These patients are also at high risk for pulmonary infarctions from recurrent sickling and pneumonia.

Signs and symptoms include pleuritic chest pain, hypoxia, tachypnea, retractions, and nasal flaring. The radiographic picture is consistent with pulmonary infiltrates. This may progress to a complete "whiteout" of lung fields and respiratory failure. Fever and an increased WBC count may be seen with both infection and infarction.

Box 24-5



Indications for Red Blood Cell Transfusion in Sickle Cell Disease

Acute Simple Transfusion

Symptomatic Anemias Resulting From Blood Loss

Complicated pain crisis not relieved by other medical therapy
 Aplastic crisis
 Splenic sequestration
 Accelerated hemolysis (such as caused by delayed hemolytic transfusion reaction, warm autoimmune hemolytic anemia, or sickle crisis)
 Preoperative preparation for most surgeries

Chronic Simple Transfusion

Prevention of recurrent occlusive stroke (<30% Hb S)
 Selected sickle cell disease pregnancies (such as recurrent fetal loss, multiple gestations)
 Possible role in recurrent chest syndrome and skin ulcers

Partial RBC Exchange Transfusions

Acute or impending stroke, including transient ischemic attack
 Fat embolism syndrome
 Unresponsive acute priapism
 Acute, rapidly progressive chest syndromes
 Preoperative preparation for some major surgeries and eye surgery

Simon TL, AuBuchon J, Cooper ES et al: Practice parameters for the use of red blood cell transfusions, *Arch Pathol Lab Med* 122:130-138, 1999.

Therapy for acute chest syndrome follows the general principles of therapy for vaso-occlusive crises. Pain relief is critical to allow effective pulmonary toilet and coughing. Antibiotics are recommended in any febrile child with acute chest syndrome because untreated bacterial infections can be devastating for children with SCD. Oxygen is necessary for the hypoxemic child to promote normal oxygenation and prevent further sickling. Partial exchange transfusion may be necessary even in the child with mild symptoms to halt progression of the disorder (Box 24-5). Recurrent acute chest syndrome is a criteria for bone marrow transplantation.⁴⁸

Cerebrovascular Accident. CVA is most often the result of thrombosis in the major cerebral arteries in younger children and hemorrhage in older children. CVA affects about 5% of children with SCD.⁴⁹

The diagnosis of CVA is made on the basis of clinical signs. Unfortunately, warning signs of an impending CVA are rare. Some children may complain of headache or dizziness, but often the first signs are apparent only with the CVA itself. These signs may be hemiplegia, aphasia, speech difficulties, visual disturbances, seizures, or coma.

Upon admission of a child with neurologic signs suggesting CVA, assessment includes a history and a detailed neurologic examination. A CT or MRI is done to rule out a lesion such as subdural hematoma if the history (such as recent head trauma) suggests this. The CT is done

without contrast materials because they may precipitate sickling by drying out the RBCs. If there are no signs of increased intracranial pressure, a lumbar puncture may be done to rule out an infectious process. Angiography is postponed until the child's condition is stable and the Hb S has been decreased to below 10% by exchange transfusion.

The most critical intervention for the child presenting with a CVA is a partial exchange transfusion to prevent progression of the CVA. Other therapy is supportive. If the child has experienced a large infarction, close monitoring for intracranial hypertension is necessary. Anticoagulant therapy is contraindicated. Bone marrow transplantation may benefit the child who experiences recurrent strokes.⁵⁰

Splenic Sequestration. Splenic sequestration is a life-threatening complication of SCD and one of the leading causes of death in children with this disease. There is massive engorgement of the splenic sinuses with blood and a significant amount of the RBC mass becomes trapped in the spleen. The result is an abrupt fall in hemoglobin levels, which may result in death from circulatory failure. The etiology of this complication is unknown and the severity of the crisis ranges from mild splenic enlargement with minimal decrease in hemoglobin level to substantial splenomegaly, life-threatening anemia, and shock.

Splenic sequestration is normally seen in infants and children younger than 6 years of age because these children have not yet undergone autosplenectomy. Autosplenectomy is a process by which repeated episodes of infarction reduce the spleen to fibrotic tissue with deposits of iron. By age 5 years, most patients with SCA have become permanently asplenic because of this process.⁵¹

Children with splenic sequestration have acute, severe left upper quadrant pain, vomiting, acute onset of anemia, a rapidly distending abdomen, and signs of hypovolemia. On physical examination, there is severe hypotension, cardiac enlargement, and splenomegaly. The Hct is often half the patient's normal value, and there is usually a rapid reticulocytosis with increased immature RBCs and moderate to severe thrombocytopenia.

Therapy for this crisis is the immediate transfusion of PRBCs to restore intravascular volume and oxygen-carrying capacity. Once the cardiovascular status stabilizes, the child usually improves rapidly. The spleen shrinks within a few days, and the thrombocytopenia resolves. Splenic sequestration may recur, usually within 4 months of the initial episode. Emergency splenectomy for an acute crisis is not indicated so long as prompt attention to crisis is provided.

Aplastic Crisis. Aplastic crisis is a condition that results from a primary erythropoietic failure often associated with a parvovirus infection. The cessation of bone marrow function causes the Hct to decrease dramatically. If the anemia is severe and the child is symptomatic or if general condition is compromised, an intensive care admission may be necessary.

The child with aplastic crisis usually appears listless and pale. Hemoglobin values are decreased and the reticulocyte count is less than 1%.

Most aplastic episodes are mild and require no treatment. Recovery is usually spontaneous with an elevated nucleated

RBC count, followed by reticulocytosis in 1 or 2 days. PRBCs may be administered to maintain a hemoglobin of 8 g/dl or more if the anemia is severe.

Sepsis. Infection is the most common cause of death in children with SCD. These children are immunocompromised because of decreased splenic function with the loss of its filtering capabilities and diminished antibody function. Infections in children with altered splenic function are usually caused by organisms such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*.⁵² Children with SCD seem to be at particular risk for septic shock caused by *S. pneumoniae*.

In children with SCD, a temperature higher than 38.5° C, band count greater than 1000/mm³, or a high erythrocyte sedimentation rate (ESR) are treated with antibiotic therapy regardless of whether they appear septic. Children who appear septic are treated with antibiotics regardless of their temperature.

Other Crises. The child admitted to the PICU with SCD may experience a variety of other crises. As with acute chest syndrome and CVA, any crisis may be precipitated by infection, dehydration, fatigue, and hypoxia.

Bony crises may involve the marrow or the cortex of the bone itself. The small bones of the hands and feet are commonly affected in infants and toddlers, giving rise to dactylitis or hand-foot syndrome. In all bony crises, pain, fever, and leukocytosis are present. With bone cortex involvement, pain, redness, and swelling over the affected area are seen.

Abdominal crises are often the result of occlusion of the mesenteric vessels or vessels of some of the viscera, such as the spleen or the kidney. These crises are characterized by acute abdominal pain, fever, malaise, anorexia, nausea, and an increased WBC count. These symptoms are often indistinguishable from an acute "surgical abdomen," and a thorough history and surgical evaluation are required. Patients with "crisis pain" usually remain in stable condition or improve slightly with supportive measures such as hydration and analgesics. Patients with an acute surgical abdomen do not improve with these measures, and instead become more acutely ill.

Therapy for other crises is supportive. Adequate hydration must be maintained. Antibiotic therapy is indicated if there is redness and swelling over a bone. Pain management is crucial with all crises. For the child with an abdominal crisis, pain management prevents atelectasis that occurs because of splinting of the abdomen.

MIXED DISORDERS

Hemolytic Uremic Syndrome

Etiology. HUS is a clinical syndrome characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. HUS is the most common cause of acquired renal failure in children. Although the primary systemic effects are hematologic and renal, there is potential for multisystem involvement, primarily of the GI and neurologic systems.

HUS does not appear to have a single etiology but is a syndrome of diverse causes. Numerous agents and predisposing factors have been associated with HUS, including infectious organisms, medications, and hereditary traits, but causality has not been definitively established.

Etiologic investigations of HUS have focused on infectious agents, specifically verotoxin-producing organisms such as *Escherichia coli*. One particular strain of *E. coli* (*E. coli* 0157:H7) has been identified as the most common pathogen associated with HUS; 80% to 90% of stools cultured from children with HUS are positive for *E. coli* 0157:H7. The most common source of contamination has been undercooked beef, although enterohemorrhagic strains of *E. coli* have also been found in unpasteurized juices and dairy products.⁵³⁻⁵⁵

Other infectious organisms that have been less commonly associated with HUS are *Shigella dysenteriae*, *Salmonella typhi*, *Camphylobacter jejuni*, *S. pneumoniae*, *Yersinia pseudotuberculosis*, and *coxsackie virus*.^{53,55} HUS patients who have positive cultures for one of these enteropathogens (including *E. coli*) at the onset of their illness are "typical" HUS patients.

"Atypical" HUS etiologies may also include a familial form of HUS caused by a genetic deficiency of prostacyclin-stimulating hormone. Other potential precipitating factors include medications (e.g., cyclosporin A, mitomycin, chemotherapeutic agents, oral contraceptives), and conditions such as pregnancy, malignancy, lupus erythematosus, and malignant hypertension.^{53,55} It is unclear which of these may cause HUS, which are chance simultaneous occurrences, or which are related to some third unidentified causal factor.

Incidence. HUS most commonly affects children between the ages of 6 months and 4 years. Approximately 80% of the cases of HUS occur in children under the age of 5 years.^{56,57} The majority of reported cases of HUS (75% to 80%) occur between the months of April and September.^{56,57} No explanation for the age distribution or seasonal variation of HUS has been established.

The incidence of HUS in North America has been reported as two to four cases per 100,000 children younger than the age of 5 years.⁵⁷ Some studies have documented an increasing incidence of HUS since the early 1980s. The increased occurrence of HUS has coincided with an increased appearance of verotoxin-producing strains of *E. coli* as pathogens in humans.

Pathogenesis. The major underlying mechanism of injury in HUS is vascular endothelial damage. In the postenteropathic (typical) form of HUS, the verotoxin, or shiga-like toxin (SLT) released by *E. coli* or other organisms initiates the endothelial damage.⁵³ The kidneys are the primary site of endothelial disruption, but thrombotic microangiopathy may be found in all organs.

Typically, damaged endothelial cells within the vasculature of the renal glomerulus swell and become separated from the basement membrane, creating a widened subendothelial space. Fibrin, platelets, and lipids are deposited in the subendothelial space, which when combined with the swollen endothelial cells, produce thick-

ened glomerular capillary walls and thus reduced capillary lumen size. Small arterioles become thrombosed as a result of local intravascular coagulation activation. Thus the renal vasculature becomes obstructed by endothelial swelling and/or thrombi, resulting in a reduced filtering surface and renal ischemia. Consequently, the glomerular filtration rate is significantly diminished, and acute renal failure develops.⁵⁸ Histopathologic studies of renal tissue in children with HUS have demonstrated glomerular thrombotic microangiopathy and cortical necrosis.⁵⁸

Thrombocytopenia in HUS is the result of both aggregation and destruction of platelets within the damaged microvasculature. Normally, an anticlumping substance released from the endothelium (prostacyclin) keeps platelet aggregation in check. However, there is evidence that in HUS, inappropriate platelet aggregation is facilitated by diminished prostacyclin activity. "Familial" HUS may be seen in patients who have a hereditary prostacyclin deficiency. The mechanism of prostacyclin inhibition in other forms of HUS is unknown. More recently, studies have demonstrated an increase in large von Willebrand factor multimers in the HUS patient, which may be responsible for systemic platelet aggregation and adherence. The result is that significant numbers of platelets are "trapped" in multiple microvascular thrombi or are injured and removed from the circulation by the spleen.⁵⁹ The pathogenesis of the hemolytic anemia of HUS is also related to renal endothelial disruption. Erythrocytes are mechanically damaged as they pass through the swollen and occluded arterioles. The spleen and liver remove these fragmented RBCs from the circulation, causing a progressive and severe anemia. An increase in von Willebrand factor multimers have also been implicated in causing hemolysis because they promote adhesion of young erythrocytes to endothelial cells.^{59,60} The body attempts to compensate by accelerating RBC production, as evidenced by reticulocyte counts, which are often increased 2% to 20%.⁵³

Although the kidneys are the primary location of pathologic changes in HUS, extrarenal involvement occurs in a significant proportion of patients. The GI system is actually the first site of physiologic derangement in most cases of "typical" HUS. Hemorrhagic colitis, frequently caused by *E. coli*, precedes the onset of HUS in up to 90% of patients. The mechanism of bowel injury is similar to the renal pathophysiologic process: endothelial disruption and thrombosis of the microvasculature, leading to ischemic/necrotic tissue damage. GI complications of HUS include perforation, obstruction, stricture, or intussusception of the bowel.⁵³ It has recently been recognized that in up to 20% of HUS patients, the pancreas suffers comparable hemorrhagic and necrotic damage. These microangiopathic changes are hypothesized to be endotoxin mediated. Similar hemorrhagic, thrombotic, and necrotic lesions have been documented in the CNS, lungs, adrenal glands, and hearts of some patients with HUS.^{53,58}

HUS is not limited to renal, hematologic, and GI involvement. Approximately 30% of patients with HUS experience neurologic dysfunction because of involvement of the microvasculature of the brain and the direct neuro-

logic effects of the toxins, similar to TTP, where the brain is the primary affected organ. Neurologic sequelae may include hemiparesis, cortical blindness, and a persistent state of altered consciousness.⁵³

In the majority of HUS patients, the syndrome is preceded by a prodromal illness. Approximately 90% of children diagnosed with HUS have experienced gastroenteritis with some combination of diarrhea (usually bloody), vomiting, and/or abdominal pain at the onset of their illness. Less commonly, the diagnosis of HUS may be preceded by an upper respiratory infection or by no specific signs of illness at all. The average interval between onset of diarrhea and diagnosis of HUS is 1 week. Patients with nondiarrheal, "atypical" HUS are less likely to present with a prodromal illness condition and commonly have a more aggressive course.⁵³ Approximately one third of HUS patients are febrile in the prodromal period.⁶¹

Initial physical assessment of the child with HUS generally reveals a pale, lethargic, and/or irritable child, with evidence of abdominal pain or tenderness. Inspection of the skin may reveal hemorrhagic manifestations, such as bruising, petechiae, or purpura. Admission vital signs are usually within normal limits for age, although some children may have tachycardia and/or tachypnea if anemia is severe at presentation. Tachypnea may also reflect an attempt to compensate for metabolic acidosis resulting from renal failure. Hypertension may be present, but usually it develops later in the course of the disease.

Up to 10% of children with HUS present with seizure activity. The etiology of seizures at presentation is usually hyponatremia, but seizures may be the result of early CNS microangiopathy.⁵⁷

Oliguria or anuria is present in more than 60% of children who develop HUS.⁵⁶ Urine is usually grossly hematuric. Laboratory analysis confirms acute renal failure, with rapidly increasing blood urea nitrogen (BUN) and creatinine levels. It is not unusual for a child with HUS to have a BUN level higher than 100 mg/dl and a creatinine level higher than 4 mg/dl within the first 2 days of diagnosis. Urinalysis reveals proteinuria and the presence of urinary casts. Serum electrolyte values may be initially normal, or consistent with acute renal failure (decreased sodium and calcium, increased potassium and phosphorus).⁵³

Hematologic analysis helps to confirm the diagnosis of HUS. Microangiopathic hemolytic anemia is present, with a Hct typically less than 25%. Microscopic examination of the peripheral blood film reveals typical schistocytes (fragmented red cells). Thrombocytopenia (platelet count less than 100,000/ μ l) is present, but other coagulation values (PT, PTT) are typically within normal limits, differentiating this disorder from DIC. Commonly, the CBC also reveals leukocytosis upon presentation.⁵³

If stool cultures are sent, the most common organism identified is *E. coli* 0157:H7. Other potential enteropathogens are listed within the discussion of HUS etiologies. Cultures from other sites are generally negative at presentation.

Diagnostic work-up of the patient with HUS is generally limited to laboratory analysis. Occasionally, abdominal pain and colitis lead to an exploratory laparotomy before the diagnosis of HUS is made, especially if the rest of the clinical picture is not consistent with "typical" HUS.⁵³

Critical Care Management. Management of the child with HUS is primarily focused on rapid recognition, supportive care, and treatment of complications, which include acute renal failure, anemia, CNS dysfunction, and GI symptoms. Goals of management focus on restoration and maintenance of: (1) fluid and electrolyte balance, (2) renal function, (3) optimal cardiovascular function and blood pressure, (4) adequate RBC volume and functional platelets, (5) neurologic function, and (6) GI function and nutritional support.

Initially, the child with HUS may present with dehydration resulting from GI losses (diarrhea, vomiting) and decreased oral intake. As the disease progresses, GI losses generally diminish, and the child is at risk for fluid overload from acute renal failure. Treatment consists of strict intake and output with intravenous fluid adjustment, renal replacement therapy, and management of hypertension.

Initial fluid replacement with intravenous solutions is administered cautiously, with careful monitoring of serum electrolytes and an ongoing assessment for fluid overload. Subsequently, the patient with HUS is monitored closely for signs of hypervolemia, including peripheral edema, tachycardia, hypertension, pulmonary edema, and increased weight. In the oliguric or anuric patient, fluid intake is restricted to insensible losses (approximately 30% maintenance) plus urine output replacement.

Nursing responsibilities include assessing for signs of pulmonary edema, such as rales, hypoxemia, frothy sputum, tachypnea, and increased heart size and infiltrates, which are seen on chest radiographs. Serum electrolyte values are monitored closely (every 6 to 8 hours), along with assessment for complications of electrolyte imbalances (e.g., hyperkalemia, hyponatremia). Careful monitoring and treatment of hyponatremia with fluid restriction and dialysis are critical to electrolyte balance.

The majority of critically ill patients with HUS require dialysis during the acute phase of their illness. The decision to dialyze a patient is not based on absolute criteria, but on an overall assessment of the individual patient's status. Indications for dialysis include one or more of the following: anuria for longer than 24 hours, hypertension, pulmonary edema, hyperkalemia, and severe azotemia. Some clinicians initiate dialysis prophylactically for BUN concentrations greater than 100 to 150 mg/dL.⁵⁶

Patients with HUS may receive peritoneal dialysis (PD) or hemodialysis (HD), or continuous veno-venous hemofiltration with dialysis (CVVHD). The advantages of PD are that fluid is removed gradually, so that hemodynamic stability is ensured, and that PD does not require vascular access. However, there are a number of disadvantages to PD as compared with HD or CVVHD for the HUS patient. The high glucose solutions used in PD may cause

hyperglycemia, especially if the patient has pancreatic insufficiency caused by HUS. Probably the biggest disadvantage to PD in this population is the risk of precipitating or exacerbating the abdominal complications associated with HUS.

The main advantage of HD, aside from avoiding involvement of the GI tract, is that it provides more precise correction of fluid imbalance, electrolyte values, and acidosis. One disadvantage is that patients who are hemodialyzed must be systemically heparinized for each procedure, which may transiently increase their risk of bleeding.

CVVHD has been used with good results as a primary renal replacement therapy for HUS patients with severe GI inflammation and bleeding.⁶² Primary advantages are that the GI tract is avoided, CVVHD can be accomplished in younger patients because of small filter sizes, and hemodynamic stability can be optimally maintained in comparison to HD.

Optimization of cardiovascular function may include antihypertensive medications, vasoactive therapy with inotropes and vasodilators, as well as treatment of severe anemia, bleeding, and fluid overload as previously discussed. Management of hypertension in the patient with HUS is a collaborative responsibility. In addition to fluid overload, hypertension is exacerbated by excessive renin release by the kidneys caused by decreased renal perfusion. Antihypertensives are required to control blood pressure in up to 40% of critically ill patients with HUS.⁵³

The primary risk factor for bleeding in patients with HUS is thrombocytopenia. However, in addition to a decrease in the absolute number of platelets, there is evidence that the HUS patient's circulating platelets are hyporesponsive to aggregating agents, implying an additional platelet function abnormality.⁵⁹ It has been established that the platelets of uremic patients in general do not function properly; however, it is unclear whether there is an additional mechanism compounding this "malfunctioning" in HUS patients.

The child with HUS requires close monitoring for signs of bleeding, such as bruising, petechiae, oozing from invasive line sites, epistaxis, or upper and/or lower GI bleeding. Procedures that may promote bleeding, such as intramuscular injections and rectal instrumentation, are avoided. In addition, the child is assessed for signs of occult bleeding, such as increased abdominal girth, increased pulse and respiratory rate, diminished peripheral perfusion, a change in neurologic status, or hypotension (a late sign of hypovolemia).⁵³

Blood component replacement is generally not aggressive in patients with HUS because there is evidence that transfused platelets and RBCs suffer the same damage in the microvasculature as the child's intrinsic blood components and may exacerbate the risk of thrombus formation. Consequently, RBCs are generally transfused only when the Hct falls below 15% to 20%, or sooner if the Hct is falling rapidly or if the patient is symptomatically anemic.⁵⁶ Most HUS patients receive at least one blood transfusion during the acute phase of their illness. Platelets are usually not

administered until the platelet count is below 10,000 to 20,000/ μ l, or if there is active bleeding.

All blood products are administered slowly and timed to coincide with dialysis when possible, to minimize the risks of circulatory overload. All patients are monitored for signs of a transfusion reaction.

There are a number of potential risk factors for neurologic dysfunction in the HUS patient. There is evidence that the microangiopathic process that obstructs perfusion in the renal vasculature can develop in the cerebral vasculature. Thus there is a risk of microthrombi or even large thrombus formation in the cerebral arterioles, potentially leading to infarction. In addition, thrombocytopenia coupled with hypertension puts the patient with HUS at significant risk for an intracranial hemorrhage.

Seizures, affecting about 10% of children with HUS, are treated with short-acting anticonvulsants, (i.e., benzodiazepines), followed by fosphenytoin or phenobarbital for sustained seizure control.⁵⁶

Vigilance by the nurse is required to monitor for changes that may indicate neurologic damage. This can be challenging because patients are typically lethargic and/or irritable upon admission because of uremia, anemia, and/or a postictal state. Signs of focal infarction or hemorrhage include hemiparesis, seizures, change in motor strength, cranial nerve deficits, and a change in level of consciousness. Signs of increased intracranial pressure include decreased responsiveness to stimuli, pupillary changes, change in respiratory pattern, (late) decreased pulse, and increased blood pressure with widened pulse pressure. A brain CT or MRI may be required to identify infarctions, edema, or hemorrhage so that neurologic recovery can be optimized.

If there is clinical or radiologic evidence of neurologic deterioration, therapeutic modalities aimed at the removal of circulating endotoxin and the normalization of platelet-aggregating factors may be instituted. Fresh plasma infusion and plasmapheresis are the two most commonly employed therapies. Because plasmapheresis is so successful in treating TTP, which has similar pathophysiology to HUS, it may improve neurologic outcome. Case reports have shown efficacy, but studies have not demonstrated clinical significance in outcome.^{59,60}

Collaborative interventions to optimize neurologic functioning include control of seizures with anticonvulsants and electrolyte balance. Standard interventions to reduce or prevent rises in intracranial pressure are instituted if the patient with HUS demonstrates cerebral edema on CT or MRI. The only modification for the anuric patient is that osmotic diuretics are not used because they draw fluid into the intravascular space, which can not be excreted, thereby exacerbating hypervolemia.

The patient with HUS is at risk for GI complications resulting from vascular endothelial damage, thrombi, and necrosis of bowel tissue. Careful monitoring of the patient is the cornerstone of managing GI complications. The child is assessed for abdominal tenderness, cramping, and distension, especially as compared with baseline status upon

admission. Abdominal girth is measured and recorded each shift, and all gastric output is tested for the presence of blood. Ranitidine is administered to prevent gastric ulceration.

If a paralytic ileus or an acute abdominal process develops, the patient with HUS is kept on a nothing-by-mouth (NPO) status and a nasogastric tube is inserted to decompress the stomach. Approximately half the children with HUS require parenteral nutrition during the acute phase of their illness. The GI tract may require serial evaluation with kidney, ureter, and bladder (KUB) x-ray and/or abdominal ultrasound examination. Signs of an acute bowel infarction, perforation, obstruction, or necrosis include tachycardia, hypotension, acidosis, vomiting, and abdominal distension. Surgical intervention may be necessary.⁵⁶

Nutritional support with total parenteral nutrition (TPN) is instituted early to stop catabolism present on admission, especially with the patient with diarrhea and vomiting. Once diarrhea and GI inflammation has resolved, enteral nutrition (nasoduodenal or jejunal) is instituted with formula requirements calculated in light of renal compromise.^{53,56}

Pancreatitis, with both endocrine and exocrine involvement, has been recognized as a potential complication of HUS, presumably resulting from the same mechanisms that injure renal, GI, and cerebral tissue.⁵⁶ It may be difficult to evaluate the patient with HUS for pancreatitis because the clinical signs, abdominal pain and vomiting, may be present because of another etiology. Patients with these signs are made NPO regardless of whether a definitive diagnosis is made. Serum amylase and lipase levels are followed, but because these enzymes are partially excreted by the renal route, levels greater than four times normal are necessary to diagnose pancreatitis in patients with renal failure.⁵⁶ Abdominal ultrasound examinations may be performed; enlargement and sonolucence of the pancreas is consistent with pancreatitis.

The nurse assesses the patient with HUS for hyperglycemia resulting from pancreatic insufficiency, which may necessitate exogenous insulin administration. The anuric patient cannot be monitored for glycosuria; therefore serum glucose is measured every 4 to 8 hours. Serum glucose is maintained at 100 to 200 mg/dl with insulin administration carefully titrated by the nurse.

Antibiotic therapy for HUS and hemorrhagic colitis caused by *E. coli* 0157:H7 is controversial, with conflicting study results as to benefit, or even showing adverse effects.^{56,58} Other therapies studied at various times include heparin, thrombolytic agents, prostacyclin infusion, gamma globulin, and vitamin E. None of these therapies has consistently proved effective for HUS, but some are still used in cases of severe disease, especially with cerebrovascular involvement.

The mortality rate from HUS is approximately 5%.^{57,63} Of children with a one-time occurrence of HUS, 60% to 80% recover completely. Another 10% to 30% are left with long-term sequelae, which include hypertension, chronic renal failure, and neurologic complications such as hemipa-

resis, seizures, blindness, and cognitive deficits. Currently, less than 5% of all patients studied progressed to end-stage renal disease and renal transplantation, but recent long-term studies show evidence that in some post-HUS patients, renal function declines after apparent recovery.^{53,57}

Extensive analysis has been done to identify patients at high risk for a poor outcome from HUS. Poor outcome is generally defined as chronic renal failure, neurologic sequelae, or death. Some investigators differentiate between typical (or classic) and atypical HUS when discussing prognosis. The typical form, which has a better prognosis, affects young children (usually younger than 3 years old), has a prodrome of bloody diarrhea, occurs during the summer, and is nonrecurrent. Hereditary and other atypical forms of HUS have a poorer prognosis in terms of morbidity and mortality.⁵⁶

Other factors that have been statistically correlated with a poor outcome are high neutrophil count upon admission (which may reflect the degree of endotoxin exposure), short diarrhea prodrome before admission (which may reflect a higher infectious dose of circulating toxin), higher Hgb count upon admission (more invasive disease may prompt admission before hemolysis has occurred), seizures upon admission, bowel necrosis during the acute phase, and longer duration of anuria during the acute phase.⁵⁷ Although it is still difficult to predict the long-term outcome for an individual patient, even limited prognostic information may be useful in guiding therapies and in counseling parents of patients with HUS in the intensive care unit.

Thrombotic Thrombocytopenic Purpura

Etiology/Incidence. TTP has traditionally been considered an “adult” counterpart to HUS, very similar in pathophysiology, but with the CNS being the primary affected organ in TTP.

TTP has been reported rarely in children, with 16 case reports in a 1998 MEDLINE search.⁶⁴ The disorder can present in infancy or childhood, and relapses can occur at varying intervals. Etiology is similar to HUS, with a viral prodrome before presenting symptoms. Case reports of TTP secondary to HIV infection have been reported.⁶⁵

Pathogenesis. The basic process in both HUS and TTP is the deposition of fibrin in the microcirculation with subsequent microangiopathic hemolysis and thrombocytopenia. The pathophysiology is unclear; however, the most consistent hematologic feature is platelet aggregation with the presence of unusually large von Willebrand factor multimers.^{59,65}

Thrombocytopenia is the major complication in TTP, followed by hemolysis. Pathophysiologic changes in the brain and microvasculature of other organs cause the presenting signs and symptoms.

Children most commonly (about 50%) present with neurologic symptoms, ranging from dizziness, weakness, lethargy to obtundation, and hemiparesis.⁶⁵ Other symptoms

include fever and bleeding (epistaxis and/or bruising). Hematuria, oliguria (or anuria), and bloody diarrhea are seen less often. Laboratory values are similar to HUS, with a low Hct and low platelet count.

Despite excellent assessment and critical care management, the outcome for TTP in children is discouraging, with 38% mortality in the 16 reported cases. Microthrombi were demonstrable in all major organs at autopsy. No pretreatment characteristics were identified as prognostic indicators of relapse.⁶⁵

The critically ill child usually presents with profound neurologic impairment, along with hemorrhage and, often, renal impairment. Assessment and nursing care include neurologic system observation for changes in level of consciousness and/or signs of hemorrhage, respiratory assessment for adequate oxygenation and ventilation, close observation for signs of renal failure with strict intake and output and urine testing, and hypervigilant assessment for signs of frank and occult bleeding. CBC and coagulation studies are monitored frequently and interpreted with the clinical assessment to determine the need for blood product administration.

Critical Care Management. The mainstay of treatment for TTP is plasmapheresis and excellent supportive care. Plasmapheresis has been shown to be much more beneficial in treating patients with TTP, as opposed to treating HUS.¹⁹ Treatment with blood products, including PRBCs, platelets, and fresh frozen plasma are the mainstay of supportive therapy.^{61,65} Recognizing the consumptive nature of the pathophysiology of TTP, in the presence of active hemolysis, transfused RBCs are hemolyzed in the same manner as native RBCs. Transfused platelets may also be destroyed and cause more microthrombi. Other therapies that have been used with varying success include corticosteroids, high-dose IVIg, vincristine, antiplatelet agents, and splenectomy.¹⁹

IVIg and antiplatelet agents and steroids are also administered with the goal of halting the peripheral platelet aggregation. Remission has been demonstrated with the prophylactic use of FFP without plasmapheresis.⁶⁵ Children with renal impairment who need dialysis are treated in the same manner as those with HUS—with peritoneal dialysis, HD, or CVVHD being the therapeutic modalities.

Care of the TTP patient requires the same level of nursing expertise that is required for any child with multisystem failure. The child with TTP is usually very critical, with profound neurologic, renal, and other system dysfunction or failure. Nurses require skills in caring for the patient undergoing pheresis and/or dialysis therapies as discussed in previous sections. Line placement for dialysis/pheresis is difficult in terms of access and bleeding status of the patient. Hemodynamic monitoring of the patient with impaired cardiovascular function may be required, especially for the unstable child during dialysis/pheresis procedures. Cardiovascular support with titration of vasoactive infusions to optimize cardiac output may be needed. Intubation and mechanical ventilation is often

required for airway protection and to provide optimal oxygenation and ventilation in the neurologically impaired child.

SUMMARY

Critically ill children may experience a wide range of hematologic problems related to a variety of causes. Anemia and thrombocytopenia also may be part of the pathologic process that brings children to the PICU. Children's

response to medical and nursing interventions depends on their preexisting state, the severity of their illness, and length of time before treatment is initiated.

Caring for these children requires a collaborative approach. It is imperative that the nurse caring for these children be vigilant for subtle but significant signs that occur because of the complexity of the patient's needs and the potential for rapid changes in the patient's condition. Expert nursing management is essential to maximize the potential for a positive outcome.

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