Hematologic System

Gail A. Bagwell

The hematologic system is probably one of the least understood body systems of the neonate. But in order to provide the utmost care to the neonate, a thorough and complete understanding of the hematologic system and its components is necessary. The knowledge of how the blood cells develop and function as well as how the hemostatic system functions is essential in the understanding the diseases of the newborn that affect the hematologic system. Without this knowledge the nurse will miss many of the subtle signs and symptoms that indicate that a problem has arisen. This chapter discusses the hematologic and hemostatic systems, as well as the most common hematologic diseases of the newborn period.

OVERVIEW OF THE HEMATOLOGIC SYSTEM

Hematopoiesis

The hematopoietic system is characterized by the presence of pluripotent stem cells that differentiate into the three types of circulating blood cells: red blood cells (RBCs), white blood cells (WBCs), and thrombocytes (platelets). The formation, production, and maintenance of blood cells is referred to as hematopoiesis. Hematopoiesis is a continuous process that involves cell maturation and destruction concurrent with new cell production. Gestational age and postnatal age influence maturation and govern individual cell components, the level of activity, and the site of production.

The liver becomes the main site for hematopoiesis beginning at approximately 5 to 6 weeks’ gestation. The production peaks at 4 to 5 months of age, then slowly regresses, with the bone marrow predominating from 22 weeks of gestation on. Also helping with hematopoiesis during the fetal period are extramedullary sites of the spleen, lymph nodes, thymus, and kidneys while the long bones are small.

Red Blood Cells

Erythropoiesis, the production of red blood cells, begins at approximately 3 to 4 weeks of gestation. The red blood cells (RBCs) are initially primitive megaloblasts, but when the liver becomes the primary site of hematopoiesis, a definitive line of RBCs is formed from the normoblasts, which progresses through several phases of refinement and accrue hemoglobin before reaching maturation. When the hemoglobin concentration of the normoblast reaches 34%, the nucleus is extruded and the cell becomes a reticulocyte. Approximately 1 to 2 days later, the reticulocyte becomes a mature RBC and is released into the bloodstream. The development of the RBC is identical in the bone marrow when it becomes the primary site of erythrocyte production.

The role of the red blood cell is to exchange oxygen and carbon dioxide between the lungs and tissues. Tissue oxygenation occurs by hemoglobin transport, whereas carbon dioxide removal is a reaction with carbonic anhydrase. Red blood cells also serve as a buffer to maintain acid-base balance.

The life span of fetal and newborn RBCs is much shorter than the adult RBC life span of 120 days. The term newborn’s erythrocyte can last 60 to 70 days; that of a preterm infant, 35 to 50 days. One theoretic reason for this is the diminished deformability of the neonatal erythrocyte. Because of its larger size and cylindrical shape, the neonatal erythrocyte is more prone to destruction in the narrow sinusoids of the spleen.

The mean RBC count in the term newborn is in the range of 5.1 million to 5.3 million per milliliter, with an elevated reticulocyte count of 3% to 7% during the first 24 to 48 hours of life (Robertson & Shilkofski, 2005). Mean RBC counts in the premature infant range from 4.6 million to 5.3 million per milliliter, with a greater number of circulating immature RBCs reflected in a higher reticulocyte count (3% to 10%). In both groups of infants, the reticulocyte count falls abruptly to about 1% and the erythropoietin level drops to low, often undetectable, levels by the first week of life.

Hemoglobin

At 10 weeks’ gestation, hemoglobin synthesis changes from the embryonic to the fetal form (hemoglobin F). The mechanism by which stem cells and progenitor cells perform this changeover remains unclear. Although low levels of a third form of hemoglobin, adult hemoglobin (hemoglobin A), are detectable at this time, hemoglobin F remains the predominant form during fetal development. At 30 weeks’ gestation, 90% to 100% of hemoglobin is the fetal form; the remainder is hemoglobin A. Between 30 and 32 weeks, the percentage of hemoglobin F starts to decline. At 40 weeks, 50% to 75% of RBCs contain fetal hemoglobin; at 6 months of age, 5% to 8%; and at 1 year of age, 1%.

Each type of hemoglobin has properties that make it valuable at the time of its synthesis. Each has a different affinity for oxygen that varies its uptake and release to the tissue (Figure 10-1). Fetal hemoglobin has a high affinity for oxygen, binding it more readily at the intervillous spaces in the placenta when the fetal partial pressure of oxygen (Po2) averages between 25 and 30 mm Hg. Adult hemoglobin has a decreased affinity for oxygen, which allows easier release of oxygen to the tissues when metabolic needs are high and the lungs are functional.

Erythropoietin

The factors that affect RBC production are still unclear, but erythropoietin appears to exert great control over erythro-
poiesis during late gestation. This circulating glycoprotein hormone, the gene of which is located on the seventh chromosome, is an obligate growth factor that stimulates stem cells to become committed progenitors of the erythrocyte (Figure 10-2). In adults the kidneys produce 90% to 95% of erythropoietin, but in the fetus the liver is considered the predominant site of production throughout most of gestation.

The major stimulus for erythropoietin release is diminished tissue oxygenation. In the absence of erythropoietin, hypoxia has no effect on the production of RBCs. However, if erythropoietin production is intact, hypoxia stimulates a rapid increase in erythropoietin levels, which remain elevated until hypoxia no longer exists. Although the liver is less responsive to hypoxia than the kidneys, production of erythropoietin in the fetus and newborn increases within minutes to hours after a precipitating event such as hypoxia. Erythropoietin acts by directly stimulating the RBC precursors, accelerating their passage through the various maturational stages. Although erythropoietin levels increase rapidly, no change in the number of erythrocytes is noted for approximately 5 days after a hypoxic stress. When erythropoietin stimulates production of excess RBCs, the red blood cells are released into the circulation before they have reached maturity (i.e., as reticulocytes); this is reflected in an elevated reticulocyte count.

Factors besides hypoxia that increase erythropoietin production in the newborn are maternal hypoxemia, smallness for gestational age, and poor placental function. Erythropoietin levels are also increased by testosterone, estrogen, thyroid hormone, prostaglandins, and lipoproteins. Cord blood levels normally are elevated compared with adult values but drop dramatically to almost undetectable levels in the newborn. The healthy newborn, therefore, produces few RBCs in the first few weeks of life because the hypoxic stimuli of low fetal PO_2 levels are no longer present. Erythropoietin levels do not increase in the term infant until 8 to 10 weeks of age, when tissue hypoxia caused by anemia is sensed by the kidneys.

The characteristics of the neonatal erythrocyte predispose both preterm and term infants to problems associated with hemolysis and immature hepatic response to erythrocyte destruction, as well as to the effects of shortened erythrocyte life span (as is seen in physiologic neonatal anemia and anemia of the premature infant). In addition to maturational influences, preexisting maternal diseases and intrauterine abnormalities can impair RBC function and production, resulting in increased oxygen and nutritional requirements for the growing fetus.

The affinity for oxygen (i.e., the ability of the hemoglobin molecule to bind and hold the oxygen molecule) is markedly different between fetal and adult hemoglobin. Fetal hemoglobin has a greater affinity for oxygen. It is able to bind to oxygen more readily at the intervillous spaces of the placenta, a property that is useful in the low partial pressure of oxygen (PO_2) environment of the fetus. Adult hemoglobin has a diminished affinity for oxygen, which allows easier release of oxygen to the tissue when metabolic needs are higher than those that arise in the fetus. From Sacks L, Delivoria-Papadopoulos M (1984). Hemoglobin-oxygen interactions. *Seminars in perinatology* 8:168-183.

![Figure 10-1](image1.png)

**FIGURE 10-1**
The affinity for oxygen (i.e., the ability of the hemoglobin molecule to bind and hold the oxygen molecule) is markedly different between fetal and adult hemoglobin. Fetal hemoglobin has a greater affinity for oxygen. It is able to bind to oxygen more readily at the intervillous spaces of the placenta, a property that is useful in the low partial pressure of oxygen (PO_2) environment of the fetus. Adult hemoglobin has a diminished affinity for oxygen, which allows easier release of oxygen to the tissue when metabolic needs are higher than those that arise in the fetus. From Sacks L, Delivoria-Papadopoulos M (1984). Hemoglobin-oxygen interactions. *Seminars in perinatology* 8:168-183.

![Figure 10-2](image2.png)

**FIGURE 10-2**
Hematopoietic stem cells stimulated to become erythrocytes initially develop into multipotent colony-forming cells (Multi-CFC). A portion of the Multi-CFC become erythroid progenitor cells, the early and late erythroid burst-forming units (BFU-E), which eventually differentiate into erythroid colony-forming units (CFU-E). These progenitor cells progress to form the normoblast, the erythrocyte precursor. Multiple divisions and alterations of the normoblast lead to the development of the reticulocyte. When the reticulocyte extrudes its nucleus, it normally moves out of the predominant production sites (i.e., the liver or bone marrow) and into the blood. Modified from Luchtman-Jones L et al (2006). The blood and hematopoietic system. In Fanaroff A et al, editors. *Neonatal-perinatal medicine: diseases of the fetus and infant*, ed 8. Philadelphia: Mosby.
**TABLE 10-1** Age-Specific Normal Blood Cell Values in Fetal Samples (26 to 30 Weeks’ Gestation) and Neonatal Samples (28 to 44 Weeks’ Gestation)

<table>
<thead>
<tr>
<th>Age</th>
<th>Hb (g%)</th>
<th>HCT (%)</th>
<th>MCV (fl)</th>
<th>MCHC (g/% RBC)</th>
<th>Reticulocytes</th>
<th>WBCs (×10³/mm³)</th>
<th>Platelets (×10³/mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>26 to 30 weeks’ gestation&lt;sup&gt;a&lt;/sup&gt;</td>
<td>13.4</td>
<td>41.5</td>
<td>118.2</td>
<td>37.9</td>
<td>—</td>
<td>4.4</td>
<td>254</td>
</tr>
<tr>
<td>(11)</td>
<td>(34.9)</td>
<td>(106.7)</td>
<td>(30.6)</td>
<td>(5-10)</td>
<td>—</td>
<td>(2.7)</td>
<td>(180 to 271)</td>
</tr>
<tr>
<td>28 weeks</td>
<td>14.5</td>
<td>45</td>
<td>120</td>
<td>31.0</td>
<td>(5-10)</td>
<td>—</td>
<td>275</td>
</tr>
<tr>
<td>32 weeks</td>
<td>15.0</td>
<td>47</td>
<td>118</td>
<td>32.0</td>
<td>(3-10)</td>
<td>—</td>
<td>290</td>
</tr>
<tr>
<td>Term&lt;sup&gt;b&lt;/sup&gt; (cord)</td>
<td>16.5 (13.5)</td>
<td>51 (42)</td>
<td>108 (98)</td>
<td>33.0 (30.0)</td>
<td>(3-7)</td>
<td>18.1 (9 to 30)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>290</td>
</tr>
<tr>
<td>1 to 3 days</td>
<td>18.5 (14.5)</td>
<td>56 (45)</td>
<td>108 (95)</td>
<td>33.0 (29.0)</td>
<td>(1.8 to 4.6)</td>
<td>18.9 (9.4 to 34)</td>
<td>192</td>
</tr>
<tr>
<td>2 weeks</td>
<td>16.6 (13.4)</td>
<td>53 (41)</td>
<td>105 (88)</td>
<td>31.4 (28.1)</td>
<td>—</td>
<td>11.4 (5 to 20)</td>
<td>262</td>
</tr>
<tr>
<td>1 month</td>
<td>13.9 (10.7)</td>
<td>44 (33)</td>
<td>101 (91)</td>
<td>31.8 (28.1)</td>
<td>(0.1 to 1.7)</td>
<td>108 (4 to 19.5)</td>
<td></td>
</tr>
</tbody>
</table>


<sup>a</sup> Data are mean (number in parenthesis is –2 standard deviations [SD]).

<sup>b</sup>Data are mean (number in parenthesis is –2 SD).

<sup>d</sup> In infants younger than 1 month, capillary Hb exceeds venous Hb: at 1 hour old, the difference is 3.6 g; at 5 days, 2.2 g; at 3 weeks, 1.1 g.

<sup>c</sup> Mean (95% confidence limits).
Blood Group Type

The RBCs have antigens located on the surface of the cell membranes that can cause antigen-antibody reactions. Blood is classified by group and types based on the antigens that are found on the RBC. The four major blood types are A, B, O, and AB. The most common blood types in the population are O at 47% and A at 41% (Guyton & Hall, 2006a). Antibodies to the antigens of different blood types occur naturally in the plasma (Table 10-2). For example, type A blood has A antigens on the cell surface but has circulating anti-B antibodies in the plasma. Type B blood has just the opposite, B antigens on the cell surface and anti-A antibodies in the plasma. Type AB blood has A and B antigens on the cell surface and neither antibody in the plasma, and type O blood has neither antigen on the cell surface and both anti-A and anti-B antibodies in the plasma. Antigens usually are polypeptides and complex proteins; antibodies are immunoglobulins (mostly IgG and IgM).

The other type of antigen is Rh antigens. Chromosome 1 stores the genetic material governing Rh antigens, but the number of genes involved in their synthesis has not been fully determined (Porter et al, 2003). There are three presumed Rh gene loci with the capability of producing five recognized antigens in the Rh complex: C, D, E, c, and e. The d antigen is considered an absence of antigen D because it cannot be isolated at present. Each individual has a paired set of these factors, having inherited a single set of C or c, D or d, and E or e from each parent. A predilection exists toward three particular combinations, two Rh positive (CDe and cDe) and one Rh negative (cde). Of these six factors, the two involved in Rh determination are D and d. The D antigen is most prevalent; its presence on the RBC indicates an Rh-positive cell, whereas its absence indicates an Rh-negative cell. Because of single-set inheritance from each parent, the potential exists for three different combinations of paired antigens: one pair being both D (Rh positive, homozygous), another pair being both d (Rh positive, homozygous), and the third pair being a combination of d and D (Rh positive, heterozygous). The end product is the production or absence of Rh antigen positioned on the surface of the RBC. The Rh antigen can be detected as early as 38 days’ gestation on the fetal RBC and attains complete development during fetal life. This antigen is necessary for normal function of the RBC membrane and, unlike A and B antigens, which can be found in other tissues, it is confined exclusively to the RBC. Antibodies never occur naturally in the Rh system; exposure to the antigen is necessary to produce antibodies.

HEMOSTATIC SYSTEM

The components involved in blood coagulation and fibrinolysis (dissolution of a formed clot) are produced in the liver, vascular wall and tissue during early fetal life. Many of the clotting factors (procoagulants) and anticoagulants (inhibitors) can be identified during the 8th to 12th weeks of gestation. However, procoagulants, anticoagulants, and the substances responsible for dissolution of a clot, fibrinolitics, do not increase in number and function or reach adult levels simultaneously (Tables 10-3, 10-4, and 10-5). Some components increase with increasing gestational age, whereas others achieve normal adult levels several weeks to months before the fetus reaches term. Still other components do not achieve normal adult levels until several weeks to months after birth. Although the function of coagulation factors and anticoagulants in the fetus is not identical to that in an older child or adult, initial vascular response to injury by release of tissue thromboplastin is functional in the fetus as early as 8 weeks.

Hemostasis consists of a delicate and dynamic balance between factors that prevent exsanguination and those that keep the blood in a fluid form. The balanced interrelationship among four distinct components ensures orderly hemostasis and fibrinolysis when vascular integrity is destroyed or interrupted. The four constituents are vascular spasm, platelets and their activating substances, coagulation or plasma factors, and the fibrinolytic pathway.

Initial Steps in Hemostasis

Vascular Spasm

Initial hemostasis in a ruptured blood vessel consists of vascular spasm, which is a consequence of multiple mediator interactions, nervous reflexes, and localized muscle spasm. Although nervous reflexes are a response to pain, most of the vascular spasm is due to muscle contraction in the vessel wall secondary to direct injury. This vascular response to injury is present in an 8-week fetus and at term is the equivalent of adult norms in regard to capillary fragility and bleeding time. This component is gestational age dependent, as is evident in the increased capillary fragility shown by the preterm infant.

Platelet Plug Formation

The second mechanism of hemostasis after vascular injury is the formation of the platelet plug. Platelets coming into contact with an injured vascular wall adhere to the wall and form a platelet plug. This hemostatic plug is the primary means of closing small vascular holes at the capillary and small-vessel level. The platelets’ ability to adhere on contact to a denuded vascular wall requires a glycoprotein, von Willebrand factor, which is synthesized by vascular endothelial cells and megakaryocytes. von Willebrand factor complexes with Factor VIII (antithrombophilic factor) and both circulate jointly. Platelets also have the ability to aggregate (stick to other platelets), forming large clumps. Aggregation is made possible by the platelet’s ability to modify its shape and to secrete many biochemical substances (platelet release reaction) that enhance cohesion. When platelets and associated glycoproteins are activated by excess release of these biochemical substances during times of stress, fibrinogen receptors appear on the
<table>
<thead>
<tr>
<th>Test/Factor</th>
<th>19 to 27 Weeks Mean ± SD</th>
<th>28 to 31 Weeks Mean (Boundary)</th>
<th>30 to 36 Weeks, Day 1 Mean (Boundary)</th>
<th>30 to 36 Weeks, Day 5 Mean (Boundary)</th>
<th>Full Term, Day 1 Mean (Boundary)</th>
<th>Full Term, Day 5 Mean (Boundary)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TEST</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prothrombin time (PT) (seconds)</td>
<td>—</td>
<td>15.4 (14.6 to 16.9)</td>
<td>13 (10.6 to 16.2)</td>
<td>12.5 (10 to 15.3)</td>
<td>13 (10.1 to 15.9)</td>
<td>12.4 (10 to 15.3)</td>
</tr>
<tr>
<td>Activated partial thromboplastin time (APTT) (seconds)</td>
<td>—</td>
<td>108 (80 to 168)</td>
<td>53.6 (27.5 to 79.4)</td>
<td>50.5 (26.9 to 74.1)</td>
<td>42.9 (31.3 to 54.5)</td>
<td>42.6 (25.4 to 59.8)</td>
</tr>
<tr>
<td>Thrombin clotting time (TCT) (seconds)</td>
<td>—</td>
<td>—</td>
<td>24.8 (19.2 to 30.4)</td>
<td>24.1 (18.8 to 29.4)</td>
<td>23.5 (19 to 28.3)</td>
<td>23.1 (18 to 29.2)</td>
</tr>
<tr>
<td><strong>FACTOR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>1 ± 0.4</td>
<td>2.56 (1.6 to 5.5)</td>
<td>2.43 (1.5 to 3.73)</td>
<td>2.8 (1.6 to 4.18)</td>
<td>2.83 (1.67 to 3.99)</td>
<td>3.12 (1.62 to 4.62)</td>
</tr>
<tr>
<td>Factor II (units/ml)</td>
<td>0.12 ± 0.02</td>
<td>0.31 (0.19 to 0.54)</td>
<td>0.45 (0.2 to 0.77)</td>
<td>0.57 (0.29 to 0.85)</td>
<td>0.48 (0.26 to 0.7)</td>
<td>0.63 (0.33 to 0.93)</td>
</tr>
<tr>
<td>Factor V (units/ml)</td>
<td>0.41 ± 0.1</td>
<td>0.65 (0.43 to 0.8)</td>
<td>0.88 (0.41 to 1.44)</td>
<td>1 (0.46 to 1.54)</td>
<td>0.72 (0.34 to 1.08)</td>
<td>0.95 (0.45 to 1.45)</td>
</tr>
<tr>
<td>Factor VII (units/ml)</td>
<td>0.28 ± 0.04</td>
<td>0.37 (0.24 to 0.76)</td>
<td>0.67 (0.21 to 1.15)</td>
<td>0.84 (0.3 to 1.38)</td>
<td>0.66 (0.28 to 1.04)</td>
<td>0.89 (0.35 to 1.43)</td>
</tr>
<tr>
<td>Factor VIII (units/ml)</td>
<td>0.39 ± 0.14</td>
<td>0.79 (0.37 to 1.26)</td>
<td>1.11 (0.5 to 2.13)</td>
<td>1.15 (0.53 to 2.05)</td>
<td>1 (0.5 to 1.78)</td>
<td>0.88 (0.5 to 1.54)</td>
</tr>
<tr>
<td>von Willebrand factor (vWF) (units/ml)</td>
<td>0.64 ± 0.13</td>
<td>1.41 (0.83 to 2.23)</td>
<td>1.36 (0.78 to 2.1)</td>
<td>1.33 (0.72 to 2.19)</td>
<td>1.53 (0.5 to 2.87)</td>
<td>1.4 (0.5 to 2.54)</td>
</tr>
<tr>
<td>Factor IX (units/ml)</td>
<td>0.1 ± 0.01</td>
<td>0.18 (0.17 to 0.2)</td>
<td>0.35 (0.19 to 0.65)</td>
<td>0.42 (0.14 to 0.74)</td>
<td>0.53 (0.15 to 0.91)</td>
<td>0.53 (0.15 to 0.91)</td>
</tr>
<tr>
<td>Factor X (units/ml)</td>
<td>0.21 ± 0.03</td>
<td>0.36 (0.25 to 0.64)</td>
<td>0.41 (0.11 to 0.71)</td>
<td>0.51 (0.19 to 0.83)</td>
<td>0.4 (0.12 to 0.68)</td>
<td>0.49 (0.19 to 0.79)</td>
</tr>
<tr>
<td>Factor XI (units/ml)</td>
<td>—</td>
<td>0.23 (0.11 to 0.33)</td>
<td>0.3 (0.08 to 0.52)</td>
<td>0.41 (0.13 to 0.69)</td>
<td>0.38 (0.1 to 0.66)</td>
<td>0.55 (0.23 to 0.87)</td>
</tr>
<tr>
<td>Factor XII (units/ml)</td>
<td>0.22 ± 0.03</td>
<td>0.25 (0.05 to 0.35)</td>
<td>0.38 (0.1 to 0.66)</td>
<td>0.39 (0.09 to 0.69)</td>
<td>0.53 (0.13 to 0.93)</td>
<td>0.47 (0.11 to 0.83)</td>
</tr>
<tr>
<td>Prekallikrein (PK) (units/ml)</td>
<td>—</td>
<td>0.26 (0.15 to 0.32)</td>
<td>0.33 (0.09 to 0.57)</td>
<td>0.45 (0.26 to 0.75)</td>
<td>0.37 (0.18 to 0.69)</td>
<td>0.48 (0.2 to 0.76)</td>
</tr>
<tr>
<td>High-molecular-weight kininogen (HMWK) (units/ml)</td>
<td>—</td>
<td>0.52 (0.19 to 0.52)</td>
<td>0.49 (0.09 to 0.89)</td>
<td>0.62 (0.24 to 1)</td>
<td>0.54 (0.06 to 1.02)</td>
<td>0.74 (0.16 to 1.32)</td>
</tr>
<tr>
<td>Factor XIIIa (units/ml)</td>
<td>—</td>
<td>—</td>
<td>0.7 (0.32 to 1.08)</td>
<td>1 (0.57 to 1.45)</td>
<td>0.79 (0.27 to 1.31)</td>
<td>0.94 (0.44 to 1.44)</td>
</tr>
<tr>
<td>Factor XIIIb (units/ml)</td>
<td>—</td>
<td>—</td>
<td>0.81 (0.35 to 1.27)</td>
<td>1.1 (0.68 to 1.58)</td>
<td>0.76 (0.3 to 1.22)</td>
<td>1.06 (0.32 to 1.8)</td>
</tr>
<tr>
<td>Plasminogen (units/ml)</td>
<td>—</td>
<td>—</td>
<td>1.7 (1.12 to 2.48)</td>
<td>1.91 (1.21 to 2.61)</td>
<td>1.95 (0.35 to 44)</td>
<td>2.17 ± 0.38 (50)</td>
</tr>
</tbody>
</table>

surface of the platelet. These receptors enhance the platelets’ ability to bind fibrinogen, which in turn cross-links the platelets, allowing them to aggregate. This provides a tight mesh of clot around an injured vessel that controls bleeding (Figure 10-3). After 32 weeks’ gestation, average platelet counts are comparable to those of term infants and adults, but the ability of platelets to aggregate is relatively diminished.

Coagulation

When bleeding cannot be controlled with merely a platelet plug, circulating plasma coagulation factors are triggered to form a network of fibrin that turns the existing plug into a hemostatic seal, which in turn completes hemostasis. Fibrin threads, necessary for clot formation, can develop within 15 to 20 seconds in the presence of normal coagulation factors. Within 3 to 6 minutes after vascular rupture, the entire opening is occluded by clot; within 30 to 60 minutes, the clot begins to retract, pulling the injured vascular portions together and further sealing the vascular end. This coagulation reaction involves several plasma proteins and three distinct phases. The first phase involves the formation of prothrombin activator, followed by the activation of prothrombin to thrombin (formation of thrombin), and then concludes with the conversion of soluble fibrinogen to fibrin (fibrin clot formation) (Guyton & Hall, 2006).

### Phase I: Formation of Prothrombin Activator

According to the earliest theories on coagulation (cascade theory), prothrombin activator can be generated by two separate pathways, the intrinsic and extrinsic pathways. The intrinsic pathway is triggered by trauma or damage that occurs inside the vessel or to the blood itself and the extrinsic pathway is triggered by the production of tissue thromboplastin that is generated by vessel wall damage. This bimodal pathway can be interrupted or negated by a deficiency in platelets or any of the plasma coagulation factors or by the presence of inhibitors (anticoagulants) in the plasma. Selective activation of one of these pathways depends on the site and severity of injury.

Activation of the intrinsic pathway is slower because it lacks the major stimulus of the extrinsic pathway, tissue thromboplastin generated by vessel wall damage. The intrinsic pathway relies on blood trauma or injury within the vessel to

<table>
<thead>
<tr>
<th>TABLE 10-4</th>
<th>Normal Blood Levels of Coagulation Inhibitors in Newborns (30 Weeks’ Gestation to Term)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulation Inhibitors</td>
<td>30 to 36 Weeks’ Gestation</td>
</tr>
<tr>
<td>Antithrombin III (ATIII) (units/ml)</td>
<td>0.38 (0.14 to 0.62)</td>
</tr>
<tr>
<td>Alpha2-macroglobulin (α2-M) (units/ml)</td>
<td>1.1 (0.56 to 1.82)</td>
</tr>
<tr>
<td>C1 esterase inhibitor (C1E-NH) (units/ml)</td>
<td>0.65 (0.31 to 0.99)</td>
</tr>
<tr>
<td>Alpha2-antitrypsin (α2-AT) (units/ml)</td>
<td>0.9 (0.36 to 1.44)</td>
</tr>
<tr>
<td>Heparin cofactor II (HCII) (units/ml)</td>
<td>0.32 (0.1 to 0.6)</td>
</tr>
<tr>
<td>Protein C (units/ml)</td>
<td>0.28 (0.12 to 0.44)</td>
</tr>
<tr>
<td>Protein S (units/ml)</td>
<td>0.26 (0.14 to 0.38)</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>TABLE 10-5</th>
<th>Normal Blood Levels of Fibrinolytic Components in Premature and Term Newborns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinolytic Component</td>
<td>Premature Infants</td>
</tr>
<tr>
<td></td>
<td>Day 1 Mean (Boundary)</td>
</tr>
<tr>
<td>Plasminogen (units/ml)</td>
<td>1.7 (1.12 to 2.48)</td>
</tr>
<tr>
<td>Tissue plasminogen activator (TPA) (ng/ml)</td>
<td>8.48 (3 to 16.7)</td>
</tr>
<tr>
<td>Alpha2-antiplasmin (α2-AP) (units/ml)</td>
<td>0.78 (0.4 to 1.16)</td>
</tr>
<tr>
<td>Plasminogen activator inhibitor (PAI) (units/ml)</td>
<td>5.4 (0 to 12.2)</td>
</tr>
</tbody>
</table>

alter platelets and plasma proteins and to convert dormant factors (zymogens), naturally found in circulating blood, into active proteolytic enzymes (Figure 10-4). Each activated enzyme subsequently reacts with the succeeding factor, changing it into its activated form. The steps of intrinsic activation of coagulation are as follows:

1. An activator (blood trauma, injury within the vessel, or contact with collagen) activates Factor XII, converting it to Factor XIIa, while simultaneously damaging platelets, which causes a release of platelet phospholipids.

2. Factor XIIa, in conjunction with prekallikrein and high-molecular-weight kininogen, activates Factor XI, converting it to Factor XIa.

3. Factor XIa activates Factor IX, converting it to Factor IXa.

4. Factor IXa, platelet phospholipid, and Factor VIII combine to activate Factor X, converting it to Factor Xa.

5. Factor Xa combines with Factor V and platelet phospholipids to form prothrombin activator (prothrombinase), which releases thrombin from prothrombin. Calcium is required for this and the preceding two steps.

The extrinsic pathway can generate thrombin in a matter of seconds when injury occurs outside the vascular space (Figure 10-5). Tissue thromboplastin (tissue factor), composed of glycoproteins and phospholipids, is produced when tissue is injured. When plasma comes in contact with this substance, the initial intrinsic phases are bypassed and the following responses occur:

![Diagram of intrinsic pathway](image)
X activator of the third and final phase of coagulation.

When prothrombin forms the potent coagulant complex (Factors VII, IX, and X) along with the other factors that form the prothrombin is synthesized by the liver under the influence of vitamin K, unstable plasma protein prothrombin. Prothrombin (Factor II) clotting cascade by further influencing the breakdown of the activator from either of the two pathways continues the identical, with both proceeding to phase II.

Phase II: Formation of Thrombin

Prothrombin activator from either of the two pathways continues the clotting cascade by further influencing the breakdown of the unstable plasma protein prothrombin. Prothrombin (Factor II) is synthesized by the liver under the influence of vitamin K, along with the other factors that form the prothrombin complex (Factors VII, IX, and X). When acted on by prothrombin activator, prothrombin forms the potent coagulant thrombin. The newly formed thrombin stimulates completion of the third and final phase of coagulation.

Phase III: Fibrin Clot Formation

Fibrin stabilizing factor (Factor XIII) further strengthens the tight bond of this developing fibrin mesh. Fibrin stabilizing factor is naturally found in the plasma and is also secreted by entrapped platelets. The forming fibrin clot begins to contract and retract with the help of platelets that have actin-myosin action, the same action by which a muscle works. Extension of the clot into the surrounding circulating blood promotes further thrombosis. Thrombin from the clot has the ability to cleave prothrombin into more thrombin and enhances the production of prothrombin activator, thus acting as a potent biofeedback system for perpetuation of the clotting cascade.

Anticoagulants. Throughout the entire coagulation pathway, the action of the activated enzymes is modulated at each stage by multiple and specific inhibitors (anticoagulants). Consequently, coagulation is a process of balance between coagulation factors and naturally occurring inhibitors. Some of these anticoagulants are endothelial surface factors that prevent coagulation until the vessel's endothelial wall is damaged. One such factor is the smoothness of the wall, which prevents any adherence and subsequent activation; another is the monomolecular layer of protein covering the wall, which repels plasma clotting factors and platelets.

Two inhibitors, alpha1-antitrypsin and C1 esterase inhibitor, interfere with the coagulation factors involved in the initial activation of the intrinsic pathway, as does Factor Va despite its role in cleaving prothrombin into thrombin. Factor Va rapidly binds with a tissue factor pathway inhibitor (TFPI) found in the plasma. This complex, TFPI–Factor Va, joins with the tissue factor–Factor VIIa complex to form a quaternary complex that inhibits further activation of Factor X by tissue factor (Edstrom et al, 2000).

Thrombin also acts as its own inhibitor by stimulating activation of protein C, which inactivates Factors V and VIII in the presence of another vitamin K–dependent inhibitor, protein S. A deficiency of these two proteins has been implicated in cases of neonatal thrombosis.

Other inhibitors of thrombin formation are (1) fibrin threads created during clot formation, which absorb thrombin, thus removing it from circulation and eliminating its potential for further coagulation; (2) thrombomodulin, found on the endothelial surfaces of the body and in the plasma complexes with thrombin, which eliminates thrombin’s ability to cleave fibrinogen; (3) alpha2-macroglobulin, which inhibits proteases, including thrombin; (4) antithrombin III, which combines with thrombin, blocking the conversion of fibrinogen into fibrin; and (5) heparin cofactor II, which removes several activated procoagulants. Both antithrombin III and heparin are produced in the precapillary connective tissue of the lungs and liver.

Fibrinolysis. Once a clot develops, it can be invaded by fibroblasts that lay down connective tissue throughout the clot or it can be dissolved. The process of dissolution occurs by activation of naturally occurring factors that lyse the clot. Fibrinolysis is activated simultaneously with stimulation of the coagulation system, with powerful but inactivated anticoagulants built right into the clot (Figure 10-6). One of these anticoagulants, plasminogen, is manufactured by the liver, kidneys, and eosinophils. Under the influence of thrombin, activated Factor XII, tissue plasminogen activator (t-PA; located on the vascular endothelium) and urokinase plasminogen activator (u-PA; found in the urine), plasminogen is converted into plasmin, a proteolytic enzyme that

1. Tissue thromboplastin or tissue factor (Factor III) activates Factor VII to Factor VIIa. These two factors form a complex with glycoprotein in the presence of ionized calcium (tissue factor–Factor VIIa complex) that activates Factor X, converting it to Factor Xa. In the presence of calcium, Factor Xa forms complexes with phospholipids and Factor V to form prothrombin activator.

2. From this point on, the intrinsic and extrinsic pathways are identical, with both proceeding to phase II.

FIGURE 10-5

breaks down fibrin into fibrin split products. Plasmin not only digests the fibrin chains but also deactivates fibrinogen; Factors V, VII, and XII; and prothrombin. Plasmin can be inactivated by its inhibitor, alpha2-antiplasmin; tissue plasminogen activator can be inactivated by its inhibitor, plasminogen activator inhibitor-1.

In summary, both term and preterm newborns have the ability to create a balance between transitory deficiencies in the amount and function of a variety of clotting factors, platelets, and anticoagulant factors. The homeostasis between clotting factors and anticoagulants places the newborn in a mildly hypercoagulable state at birth. Compared with older children and adults, therefore, the newborn has no greater tendency to bleed but does have several differences in regard to coagulation components and reserves, including (1) gestational age-dependent variations in the concentrations of coagulation factors, anticoagulants, and fibrinolytics; (2) a faster turnover rate of components; (3) a slower rate of synthesis of components; and (4) limited ability to supply necessary components during times of increased need.

**ASSESSMENT OF HEMATOLOGIC FUNCTION**

Because infants respond to a variety of problems in a similar manner, many clinical findings (e.g., hypoglycemia, hyponatremia, hypercalcemia, hypothermia, apnea, bradycardia, cyanosis, lethargy, poor feeding) warrant at least a complete blood count (CBC) to determine if a hematologic reason exists for these symptoms. With active bleeding, platelet counts, clotting studies, fibrinogen levels, and measurements of products of fibrinolysis (e.g., d-dimer, fibrin split products, or fibrin degradation products) can shed light on the type of blood dyscrasia present and can direct the caregiver to the appropriate therapeutic response. These studies also provide a way to monitor and evaluate treatments. However, laboratory data are most helpful when they are used in conjunction with astute observation and physical assessment skills.

Several physical findings can help determine the well-being and homeostasis of the hematologic system (Box 10-1). Cutaneous abnormalities such as hematomas, abrasions, petechiae, and bleeding should alert the nurse to the possibility of a hematologic abnormality. Hepatosplenomegaly also can indicate abnormal breakdown of RBCs. Hepatosplenomegaly concurrent with hyperbilirubinemia and hemolysis can signal alloimmune problems (e.g., Rh and ABO incompatibilities) or acquired, congenital, or postnatal infection (e.g., cytomegalovirus infection, toxoplasmosis, herpes simplex infection, or hepatitis).

**COMMON HEMATOLOGIC DISORDERS**

**Blood Group Incompatibilities**

Blood group incompatibilities were first recognized in the 1940s with the discovery of the Rh grouping and the first test for detection of antibody-coated RBCs, devised by Coombs in 1946. Before the introduction of Rh immune globulin (RhIG, RhIG, or RhoGAM) in 1964 and its release for general use in 1968, Rh incompatibility accounted for one third of all blood group incompatibilities. With the use of RhIG, the frequency of Rh incompatibility has dropped significantly, and ABO has become the main blood group incompatibility, with sensitization occurring in 3% of all infants. Both incompatibilities involve maternal antibody response to fetal antigen, leading to RBC destruction by hemolysis. Rh antibody response is elicited on exposure to antigen and does not exist spontaneously, whereas anti-A and anti-B antibodies occur naturally. These entities also differ in the severity of the effect on the fetus and newborn and in the method of treatment.

Other minor blood groupings (e.g., Kell, C, E, Duffy, and Kidd) may also be involved in incompatibilities that result in hyperbilirubinemia, but Rh and ABO incompatibilities are the most common, accounting for 98% of all cases. There are 400 known RBC antigens that can induce antibody production. Some of these antibodies are induced after transfusion therapy with incompatible blood; others occur in response to the transfer of incompatible fetal blood cells into the maternal circulation during pregnancy. The Rh system alone has 40 discrete antigens, but only five (C, D, E, c, and e) are important.
ABO Incompatibility

Antigens or agglutinogens present on the RBC surface of each blood type, react with antibodies or agglutinins found in the plasma of opposing blood types. Of the 30 common antigens involved in antigen-antibody reactions, the ABO antigens are one of two groups most likely to be a problem, the other being the Rh group (Guyton & Hall, 2006a). As discussed earlier in this chapter, the four major blood types are A, B, O, and AB, with the antibodies to the antigens of different blood types occurring naturally in the plasma (Table 10-6).

With antigen and antibody in harmony, no RBC destruction occurs, but when a conflicting antibody is introduced into the circulation, RBC destruction may occur. RBCs have multiple binding sites to which opposing antibodies can attach. An antibody is capable of simultaneously attaching to several RBCs, thus creating a clump of cells. This clumping of cells, known as agglutination, can cause occlusion of small vessels and impair local circulation and tissue oxygenation. Fetal RBCs coated with antibodies attract phagocytes and macrophages that eventually destroy these agglutinated RBCs, usually through hemolysis by the reticuloendothelial cells in the spleen. Hemolysis can occur without preliminary agglutination, but it is a more delayed process because the body must first activate its complement system. High antibody titers (hemolysins) are required to stimulate this system, which causes the release of proteolytic enzymes that rupture the cell membrane.

In a transfusion reaction, when opposing blood types are mixed, the donor's RBCs are agglutinated, and the recipient's blood cells tend to be protected. The plasma portion of donor blood that contains antibodies becomes diluted by the recipient's blood volume, thus reducing donor antibody titers in the recipient's circulation. However, recipient antibody titers are adequate to destroy the donor RBCs by agglutination and hemolysis or by hemolysis alone. This is the situation in ABO incompatibility. In such cases, the maternal blood type usually is O, containing anti-A and anti-B antibodies in the serum, whereas the fetus or newborn is type A or B. Although incompatibility can occur between A and B types, it is not seen as frequently as AO or BO because of the globulin composition of the antibodies. In the O-type mother, the antibodies are usually IgG and can cross the placenta, whereas the antibodies of the type A or B mother frequently are IgM, which are too large to cross the placenta.

When transplacental hemorrhage (TPH) occurs between an ABO-incompatible mother and fetus, fetal blood entering the maternal circulation undergoes agglutination and hemolysis by maternal antibodies. This rapid response prevents the development of antibodies to other antigens present on fetal RBCs, because a time lapse is required for activation of the immune system. Consequently, fetal RBCs that are Rh positive in addition to being type A or type B are destroyed by naturally occurring anti-A or anti-B antibodies before any maternal antibodies to Rh factor (anti-D) can be produced.

<table>
<thead>
<tr>
<th>TABLE 10-6 Comparison of Features Seen in Rh and ABO Incompatibility</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BLOOD GROUP SETUP</strong></td>
</tr>
<tr>
<td>Mother</td>
</tr>
<tr>
<td>Infant</td>
</tr>
<tr>
<td><strong>TYPE OF ANTIBODY</strong></td>
</tr>
<tr>
<td><strong>CLINICAL ASPECTS</strong></td>
</tr>
<tr>
<td>Occurrence in firstborn</td>
</tr>
<tr>
<td>Predictable severity in subsequent pregnancies</td>
</tr>
<tr>
<td>Stillbirth or hydrops</td>
</tr>
<tr>
<td>Severe anemia</td>
</tr>
<tr>
<td>Degree of jaundice</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
</tr>
<tr>
<td><strong>LABORATORY FINDINGS</strong></td>
</tr>
<tr>
<td>Direct Coombs’ test (infant)</td>
</tr>
<tr>
<td>Maternal antibodies</td>
</tr>
<tr>
<td>Spherocytes</td>
</tr>
<tr>
<td><strong>TREATMENT</strong></td>
</tr>
<tr>
<td>Need for antenatal measures</td>
</tr>
<tr>
<td>Value of phototherapy</td>
</tr>
<tr>
<td>Exchange transfusion</td>
</tr>
<tr>
<td>Frequency</td>
</tr>
<tr>
<td>Donor blood type</td>
</tr>
<tr>
<td>Incidence of late anemia</td>
</tr>
</tbody>
</table>

This naturally occurring phenomenon is the basis for the use of RhG, in which extrinsic anti-D destroys fetal cells before the maternal immune system can be activated to produce antibodies.

Despite this destruction of fetal RBCs, maternal anti-A or anti-B antibodies of the IgG form can freely cross the placenta and adhere to RBCs in the fetal circulation. For this reason, ABO incompatibility can occur in the first pregnancy (40% to 50% of total occurrences involve primigravidas) because TPH and inoculation of the mother with fetal blood are not necessary for the development of these naturally occurring antibodies. Since the A and B antigens on the fetal and neonatal RBCs are not well developed, only a small amount of maternal antibody actually attaches to the antigen. Other body tissues also have antigen sites to which some of the circulating antibodies can adhere, thereby decreasing the potential for RBC destruction. The resulting small amounts of IgG in the plasma do not stimulate activation of the complement system, therefore hemolysis is minimal. This lack of stimulation of the complement system and the above factors may explain why only 3% to 20% of infants of the 15% to 22% who are ABO incompatible with their mothers become symptomatic (Ozolek et al, 1994).

Erythrocyte antibodies are not usually present in the circulating blood until 2 to 8 months of postnatal age, which prevents maternal inoculation with fetal anti-A or anti-B antibodies. Antibody production then increases, reaching a maximum titer at 8 to 10 years of age (Guyton & Hall, 2006a). The newborn becomes inoculated with A and B antigens after birth through ingestion of food and the resulting bacterial colonization. This initiates production of anti-A or anti-B antibodies that circulate in the plasma, depending on the antigens present on the RBCs.

**Clinical Manifestations.** The chief symptom of ABO incompatibility is jaundice within the first 24 hours of life; 90% of all affected infants are female. Hemolysis and anemia are minimal, although signs of a mildly compensated hemolytic state are reflected in certain CBC values. The peripheral blood smear may show evidence of spherocytes, or RBCs lacking the normal central pallor and biconcave, disklike shape of the normal RBC. Because they are smaller than normal RBCs, spherocytes appear thicker. These physical characteristics result in abnormal fragility under osmotic stress. Spherocytes are not distensible or compressible because they lack the normal amount of loose cell membrane, making them more susceptible to destruction in the splenic sinuses.

Additional laboratory findings include a positive direct Coombs' test result in 3% to 32% of cases (Ozolek et al, 1994) and positive results on both direct and indirect Coombs' tests in 80% of cases when micro techniques are used. The direct Coombs' test is a measurement of the presence of antibody on the RBC surface; the indirect Coombs' test is a measurement of antibody in the serum. ABO incompatibility can also be identified by the performance of an eluate test, which involves washing the RBCs of the newborn and testing the wash for anti-A or anti-B antibodies.

On physical examination, hepatosplenomegaly can be observed, a reflection of extramedullary erythropoiesis generated by the fetus in response to significant hemolysis. In an effort to compensate for increased cell destruction, the liver and spleen manufacture RBCs for a longer period than usually is seen in the fetus and newborn. Engorgement of the splenic sinuses by hemolyzed RBCs contributes to splenomegaly.

**Treatment.** Since the antibodies involved in ABO incompatibility occur naturally, elimination of this type of incompatibility is virtually impossible. However, its effects on the fetus and newborn are much less dramatic and life-threatening than those of Rh incompatibility; therefore amniocentesis and monitoring of amniotic fluid bilirubin levels, intrauterine transfusions, and early delivery usually are not necessary. Nevertheless, problems associated with postnatal bilirubin clearance do arise, and phototherapy and possible exchange transfusion become part of the repertoire of care. These two treatment methods are discussed in further detail later in the chapter.

**Rh Incompatibility**

Incompatibilities involving the Rh system are the second most common alloimmune problem, but the severity of complications far surpasses that of ABO incompatibility. Antibodies never occur naturally in the Rh system; exposure to the antigen is necessary to produce antibodies. Such exposure is thought to occur through maternal inoculation with fetal RBCs by transplacental hemolysis or through undetectable hemorrhage during labor, abortion, ectopic pregnancy, or amniocentesis.

Spontaneous TPH occurs in 50% to 75% of all pregnancies, with the greatest and most severe occurrence at the time of delivery. Fetal RBCs can be found in 6.7% of all pregnancies during the first trimester, 15% in the second trimester, and 28.9% in the third trimester (Porter et al, 2003). Spontaneous TPH allows fetal RBCs to pass into the maternal circulation, where antibodies develop in response to any foreign RBC antigen the mother does not possess. The risk of immunization depends on the ABO status of both mother and fetus and the size of the hemorrhage. On the basis of blood type, the risk for maternal Rh immunization in an ABO-compatible Rh-negative mother and Rh-positive fetus is 16%, whereas an ABO-incompatible pregnancy with an Rh-negative mother and Rh-positive fetus runs a 1.5% to 2% risk with each pregnancy. On the basis of the volume of TPH, if the hemorrhage is less than 0.1 ml RBCs, the overall risk for immunization is 3%; if the hemorrhage is greater than 5 ml, the risk increases to 50% to 65%.

The maternal Rh antibody is slow to develop and initially may consist exclusively of IgM, which cannot cross the placenta because of its molecular size. This is followed by the production of IgG, which can cross the placenta into the fetal circulation. The maximum concentration of the IgG form of antibody occurs within 2 to 4 months after termination of the first sensitizing pregnancy (Guyton & Hall, 2006a). If initial immunization occurs shortly before or at the time of delivery, the first Rh-positive infant born to such a mother may trigger the initial antibody response, but the infant will not be affected. However, subsequent exposure to RBCs of Rh-positive fetuses produces a rapid antibody response that consists mostly of IgG. This response results in antibody attachment to antigen sites on the fetal RBCs of these fetuses. The antibody coating of the RBCs forms the basis for a positive result on the direct Coombs’ test. The affected RBCs undergo agglutination, phagocytosis, and eventually extravascular hemolysis in the spleen. The byproducts of hemolysis, especially bilirubin, pass through the placenta into the maternal circulation to be metabolized and conjugated by the maternal liver. The rate of destruction of fetal RBCs depends on the
amount of anti-D antibodies on the cells, the effectiveness of anti-D antibodies in promoting phagocytosis, and the capability of the spleen's reticuloendothelial system to remove antibody-coated cells.

**Erythroblastosis Fetalis**

Hemolysis in the fetus caused by Rh incompatibility results in the disease known as erythroblastosis fetalis (EBF); the major consequences are anemia and hyperbilirubinemia. The name is derived from the presence of immature circulating RBCs (erythroblasts), which are forced into the circulation of affected fetuses to compensate for rapid destruction of fetal blood cells. The severity of the disease depends on the degree of hemolysis and the ability of the fetus's erythropoietic system to counteract the ensuing anemia. In an attempt to compensate for rapid destruction, the fetus continues to use extramedullary organs, such as the liver and spleen, which normally would have ceased RBC production after the seventh month of gestation.

**Clinical Manifestations.** The clinical manifestations of EBF are similar to those of ABO incompatibility but often are more intense (see Table 10-3). Jaundice results from an exaggerated rise in bilirubin, with the premature infant exhibiting an earlier rise and a more prolonged period of elevation. Hepatosplenomegaly may be found on physical examination, along with varying degrees of hydrops. Hydrops fetalis is a severe, total body edema often accompanied by ascites and pleural effusions. Although the pathogenesis is unclear, it is thought to be the result of congestive heart failure and intrauterine hypoxia from severe anemia, portal and umbilical venous hypertension caused by hepatic hematopoiesis, and low plasma colloid osmotic pressure induced by hypoalbuminemia. Low serum albumin levels are a consequence of altered hepatic synthesis, which may be due to local cellular necrosis and compromised intrahepatic circulation. All these factors can lead to portal and venous hypertension and edema. The severity of the anemia and hypoalbuminemia affects the degree of extravasation of fluid into the tissue.

Altered hepatic synthesis can impair production of vitamin K and vitamin K–dependent clotting factors, which can lead to hemorrhage in these infants. Petechiae and prolonged bleeding from cord and blood sampling sites may be initial signs of clotting abnormalities. Hypoglycemia that occurs secondary to hyperplasia of the pancreatic islet cells also is associated with EBF. Products of RBC hemolysis are thought to inactivate circulating insulin, promoting increased insulin release and subsequent pancreatic beta cell hyperplasia. Another theory suggests that potassium or amino acids released from hemolyzed cells may directly stimulate insulin production or indirectly produce this effect by increasing glucagon secretion. Approximately one third of surviving erythroblastotic infants have low blood glucose levels and elevated plasma insulin levels.

**Antenatal Therapy.** Adequate antenatal care is important in safeguarding the fetus that may be affected by EBF. Proper screening of any pregnant woman at her first prenatal visit is essential and should include blood type and Rh factor. If the mother is Rh negative, the father's blood type should also be ascertained. If the father is Rh positive, it is essential to determine Rh immunization of the mother by Coombs’ testing, specifically the indirect Coombs’ test. In addition to blood typing, a concise obstetrical history regarding any previous spontaneous or therapeutic abortions or delivery of an affected infant is important to ensure appropriate management of the current pregnancy. Women who are sensitized require more surveillance throughout the pregnancy than their unsensitized counterparts, and women who have previously given birth to affected infants require the greatest degree of care.

The unsensitized Rh-negative mothers can benefit from antenatal and postpartum administration of RhIgG. The Kleihauer-Betke test for fetal cells in the maternal circulation and the erythrocyte rosetting test that detects Rh-positive fetal cells may be useful screens for determining maternal candidates for RhIgG. Before the inception of RhIgG in 1964, when the first clinical trials were conducted, the frequency of Rh immunization was 7% to 8% in ABO-compatible pregnancies and 1% in ABO-incompatible pregnancies, with close to 50% of all perinatal deaths attributable to EBF. With the use of RhIgG after delivery, the incidence of Rh immunization was dramatically reduced to 1% to 1.8%. Because sensitization was known to occur without evidence of TPH at the time of delivery, the question was raised whether antenatal sensitization occurred in response to frequent, small, and undetectable hemorrhage before or during labor. For this reason, antenatal administration of RhIgG was initiated to eliminate such cases of alloimmunization. Antenatal administration has further reduced the incidence to as low as 0.1%. However, there will always be pregnancies in which RhIgG fails to suppress the formation of antibodies or in which administration is not feasible. Immunization is not effective if sensitization occurs before the initial antenatal screening or if the RhIgG dosage is inadequate to neutralize a massive TPH. For these reasons, it is estimated that the incidence cannot be reduced beyond 4 in 10,000 pregnancies even with the use of RhIgG.

RhIgG is assumed to adhere to any Rh-positive fetal RBCs that have invaded the maternal circulation. Agglutination, hemolysis, and removal of these foreign RBCs occur before the maternal immune system can recognize the invasion and develop antibodies that would transplacentally cross into the fetus.

Several obstetrical conditions, which may require RhIgG prophylaxis, because they can increase the risk of sensitization by increasing the chances of TPH are:

- Therapeutic or spontaneous abortion of any type; the incidence of TPH is higher with therapeutic abortion (three women in 30 may be sensitized)
- Amniocentesis, which has a 10% chance of causing TPH
- Ectopic pregnancies or hydatidiform moles
- Abdominal trauma
- Antepartum bleeding, as with placental abruption or placenta previa

Failure to administer RhIgG after such occurrences may leave these women at risk for sensitization. The American College of Obstetricians and Gynecologists recommends a dose of 50 mcg for high-risk situations that arise before 13 weeks’ gestation and 300 mcg after 13 weeks’ gestation, with the 300-mcg dose repeated at 28 weeks’ gestation.

RhIgG has a half-life of 25 to 27 days and is effective for approximately 2 weeks after antigen exposure. The timing of the dose after delivery is important; administration within 72 hours of delivery is recommended. The dose after delivery allows a maximum estimated fetal transfusion of 30 ml of
whole blood or 15 ml of packed RBCs, which leaves 1% of postpartum mothers without full coverage. If massive TTH is suspected, the dose of RhIgG may need to be increased to provide adequate amounts of anti-D antibodies. After administration of RhIgG, the Kleihauer-Betke test can be performed on the mother's blood to check for RBCs with fetal hemoglobin and to help determine the need for additional RhIgG.

By reducing the incidence of EBF, use of RhIgG has also reduced the number of available immunized donors that supply the polyclonal anti-D antibodies. The recent development of prophylaxis in the form of monoclonal antibodies against Rh D antigen has reached the stage of clinical trials and may afford an alternate source of RhIgG.

Other methods of monitoring the status and treating the fetus with EBF include ultrasonography, flow Doppler studies, amniocentesis, cordocentesis, intrauterine transfusions, and pharmacologic agent administration.

Treatment. On delivery of an infant with EBF, assessment of the newborn's cardiorespiratory status is of utmost importance. Because of ascites, pleural effusions, and circulatory collapse, these infants often require stabilization of the airway by intubation and mechanical ventilation. If peritoneal or pleural fluid prevents adequate chest excursion, paracentesis may be required to remove fluid from the abdominal cavity, or thoracentesis (chest tube insertion) may be needed to drain excess pleural fluid.

Delivery of an infant shortly after intraperitoneal transfusion may not allow adequate time for absorption of blood from the peritoneal cavity. The unabsorbed portion could lead to diminished lung expansion, resulting in respiratory failure or restricted mechanical ventilation. Such infants may require paracentesis for removal of blood from the peritoneal cavity.

After initiation of respiratory support, the infant should be assessed for adequacy of circulating blood volume. If the infant is severely hydropic, the inevitable anemia must be corrected with transfusions of packed RBCs, since an exchange transfusion may not be tolerated until the intravascular RBC volume is replenished. Transfusion is accomplished with O-negative or type-specific Rh-negative blood cross-matched against maternal blood. Initial use of a single-volume or partial exchange may offer a degree of cardiovascular stability before a double-volume exchange is attempted. Congestive heart failure, not present at the time of intravascular volume depletion, may become apparent as the infant is transfused. At times a severely affected infant may benefit from digitalization and diuretic therapy.

Prenatal damage to the liver can adversely affect the production of coagulation factors in such infants, making them prone to bleeding disorders. Hepatic damage can intensify any hyperbilirubinemia present, because the hepatic substances required for conjugation may also be impaired. Laboratory evaluation of the infant affected by EBF should consist of liver function studies, hematocrit determinations, and evaluation of coagulation status.

Nursing care of the infant affected by EBF involves scrupulous attention to the infant's cardiorespiratory status and vital signs. The infant needs to be positioned so as to reduce abdominal pressure on the diaphragm which will permit better chest expansion. Maintaining a normal PO2 and avoiding overventilation may prevent barotrauma to lungs already compromised by pleural effusions. The lungs may be hypoplastic if their growth has been sufficiently compromised by hydrops in utero, making ventilation difficult and predisposing the infant to extraventilatory air. Vital signs usually are assessed every hour until the infant's condition has stabilized. Hematocrit and bilirubin levels should be checked frequently during the first few hours and days of life to maintain adequate circulating blood volumes and to prevent toxic levels of bilirubin by timely initiation of therapy. If the cord bilirubin levels are significantly elevated, exchange transfusion may be necessary shortly after birth.

If bilirubin levels do not require immediate exchange, blood levels should be checked every 4 to 8 hours, depending on the initial cord blood levels and subsequent rate of rise. In Rh incompatibility, exchange is imminent if the rate of rise exceeds 1 mg/hr for the first 6 hours of life. The interval of blood sampling for bilirubin may be increased to 6 to 12 hours after the first 48 hours of life.

The major therapies used to control excessive unconjugated bilirubin levels are similar for all problems resulting in elevated unconjugated bilirubin levels. Phototherapy and exchange transfusion, the most frequently used therapies, are discussed later in the chapter.

Analysis of Laboratory Data. The following laboratory data can be helpful in the diagnosis and treatment of EBF:

- The mother's and infant's blood and Rh types.
- Coombs' reactivity: The infant's RBCs are coated with anti-D antibodies, resulting in a positive direct Coombs' test result; on occasion, the heavy coating of neonatal RBCs with antibody can lead to a false Rh typing (Rh negative); if the direct Coombs' test result is positive, the infant should be considered Rh positive.
- The infant's hematocrit, reticulocyte count, and RBC morphologic characteristics: The presence of immature cells or spherocytes helps distinguish Rh incompatibility from ABO incompatibility.
- Plasma bilirubin levels: The initial cord-blood bilirubin level and the rate of rise determine the appropriate timing of any exchange transfusion needed to control bilirubin levels. Cord bilirubin levels are closely associated with the severity of disease and the mortality rate.

Bilirubin Metabolism and Hyperbilirubinemia

Bilirubin production begins as early as 12 weeks' gestation. It is the primary degradation product of hemoglobin, although 20% to 30% is derived from nonerythroid sources such as tissue heme. Bilirubin is produced after completion of the natural life span of the RBC, but ineffective erythropoiesis or premature destruction of blood cells can increase its production. In RBC destruction, the aging or hemolyzed RBC membrane ruptures, releasing hemoglobin that is phagocytosed by macrophages. The hemoglobin molecule then splits into a heme portion and a globin portion. Bilirubin is derived from the degradation of the heme ring in the heme portion that binds to heme oxygenase. The ferric heme breaks down to the ferrous form and then is cleaved to form carbon monoxide and biliverdin. Biliverdin is further reduced to form bilirubin, and carbon monoxide joins with heme to form carboxyhemoglobin.

The four forms of circulating bilirubin are (1) conjugated bilirubin (which is excretable through the kidneys and intestines), (2) conjugated covalently bound bilirubin (which is attached to serum albumin and not found in neonates
younger than 2 weeks of age), (3) unconjugated bilirubin (which is reversibly bound to albumin), and (4) free bilirubin (which is unconjugated and unbound). Measurement of conjugated (direct) bilirubin identifies the amount of bilirubin that reacts directly with van den Bergh’s reagent. The portion of bilirubin reversibly bound to albumin is lipid soluble. It does not react with van den Bergh’s reagent until it is combined with alcohol, hence the term unconjugated (indirect) bilirubin. Free bilirubin is not attached to albumin and can easily cross the blood-brain barrier, causing the damage seen in kernicterus. Measurements of conjugated and unconjugated bilirubin are important in the evaluation of the hyperbilirubinemic infant and provide valuable information for the diagnosis and method of treatment.

Although bilirubin is found in stool and amniotic fluid, the major route of elimination in the fetus is through the placenta. For this reason, bilirubin must be retained in the form that allows its passage into the maternal circulation. Consequently, the enzyme systems found in the fetus enhance the retention of bilirubin in the unconjugated form. Persistence of some of these fetal mechanisms during the newborn period can contribute to jaundice. Plasma concentrations of bilirubin usually are low in the fetus, except in cases of severe hemolytic disease. All bilirubin in the cord blood of the fetus is the unconjugated variety, which is effectively metabolized, conjugated, and excreted by the maternal liver and gallbladder. The mean cord blood bilirubin concentration in an infant unaffected by hemolytic disease is 1.8 mg/dl, regardless of the infant’s gestational age or weight.

In the newborn, the major routes of bilirubin excretion are through the intestine and the kidneys. As the production of bilirubin exceeds the newborn liver’s capacity to conjugate and eliminate it, plasma levels begin to rise rapidly. Jaundice becomes noticeable when the serum concentration reaches three times the amount normally present in the serum. The conjunctivae become visibly jaundiced at serum levels exceeding 2.5 mg/dl. In the full-term infant, jaundice usually becomes apparent within 2 to 4 days after birth and lasts until the sixth day, reaching a peak concentration of 6 to 7 mg/dl. Although infants born at 37 weeks’ gestation or later are considered term, they are more likely to reach or exceed serum bilirubin levels of 13 mg/dl or higher than are infants born at 40 weeks’ gestation. The preterm infant has cord-blood bilirubin levels similar to those of the term infant, but peak levels are higher, jaundice lasts longer, and levels peak later, at 5 to 7 days. Among preterm infants, 63% reach levels of 10 to 19 mg/dl, and 22% reach levels above 15 mg/dl.

Although the neonatal liver’s conjugating mechanisms are reduced during the first few days of life, the liver is able to metabolize and excrete two thirds to three quarters of the bilirubin circulating throughout the body. Initially bilirubin is transported in the plasma, bound to albumin at two sites—a primary binding site that has a strong bond and a secondary site that has a weak bond. When available albumin binding sites are saturated, bilirubin circulates freely in the plasma. It is this portion of unconjugated bilirubin that can migrate into brain cells, causing damage known as kernicterus. The occurrence of kernicterus is related to the amount of diffusible, loosely bound bilirubin and the availability of albumin binding sites.

When bilirubin reaches the liver, it is transferred from plasma albumin, across the cell membrane of the liver, and into the liver cell. Two proteins, Y and Z, also called ligands, affect bilirubin transfer from plasma to liver. Here the bilirubin is either stored in the cell cytoplasm or removed from the ligands and conjugated in the hepatic endoplasmic reticulum. Conjugation is essential for the excretion of bilirubin into bile. Eighty percent of bilirubin is conjugated with glucuronic acid, becoming bilirubin glucuronide. Glucuronosyltransferase is the important hepatic enzyme required for the production of bilirubin glucuronide. Ninety-five percent of bilirubin in glucuronide is excreted into bile and subsequently into the intestine.

Effective excretion of bilirubin from the intestine depends on the length of time needed for the passage of stool and on the presence of substances that break down conjugated bilirubin. The newborn may have diminished bowel motility and delayed meconium passage, which allow longer exposure of stool to bilirubin glucuronidase, the enzyme responsible for breaking down conjugated bilirubin. The action of this enzyme, in conjunction with the newborn’s lack of the intestinal flora required to reduce bilirubin to urobilinogen, converts the conjugated form to the unconjugated form, which is then reabsorbed by the intestine.

**Kernicterus**

Kernicterus was rarely seen between the 1960s and the 1990s, but its incidence has risen since the mid-1990s with the advent of earlier home discharges. Kernicterus occurs when the albumin binding sites are filled which allows for increased amounts of free bilirubin to pass into the central nervous system (CNS). Free bilirubin easily crosses the blood-brain barrier and is transferred into the brain cells, causing obvious yellow staining of the brain tissue (kernicterus) that is similar to the effect on the skin. The areas of the brain usually affected by the staining are the hypothalamus, dentate nucleus, and cerebellum. Kernicterus is associated with varying degrees of neurologic damage, but a direct correlation cannot be drawn between serum bilirubin levels and the severity of involvement.

Many factors can influence the bilirubin binding capacity and increase the risk of kernicterus at lower bilirubin levels, including the following:

- **The total amount of available serum albumin**: Premature infants normally experience a relative hypoproteinemia and have fewer albumin binding sites available for free bilirubin.

- **The presence of other substances competing for available binding sites**: Certain drugs (e.g., sulfisoxazole, salicylates, sodium benzoate) compete with bilirubin for binding sites or replace bilirubin loosely attached to binding sites.

- **Acidosis and hypoxia**: Increased production of hydrogen ions and implementation of anaerobic metabolism can impede bilirubin binding. Albumin’s ability to bind bilirubin drops to half its potential at a serum pH of 7.1, with free fatty acids produced during anaerobic metabolism competing for albumin binding sites. The simultaneous presence of acidosis and hypoxia, which can open the blood-brain barrier, can expose a sick infant to kernicterus at much lower serum bilirubin levels. Evidence also suggests that tests evaluating bilirubin binding capacity, rather than serum bilirubin concentrations, are better correlated with the appearance of subsequent CNS abnormalities.
Clinical Manifestations. Kernicterus usually becomes evident during the first 5 days of life. Its signs include lethargy or irritability, hypotonia, paralysis of upward gaze, high-pitched cry, poor eating, opisthotonic posturing, and spasticity. It is also associated with deafness, cerebral palsy, and tooth enamel abnormalities. The overall risk for kernicterus is 50% if serum bilirubin levels are 30 mg/dl or higher and 10% if levels are between 20 and 25 mg/dl. Preventing elevated levels of free bilirubin is the primary means of eliminating kernicterus. Prevention may require phototherapy for slowly rising levels but almost certainly demands exchange transfusion if the rise is rapid and marked.

Nonimmune Causes of Hyperbilirubinemia
Elevated bilirubin levels within the first 24 hours of life or levels exceeding 12 mg/dl are not considered physiologic and deserve investigation. Many conditions other than blood group incompatibilities can cause jaundice in the newborn. Most of the commonly seen disorders result in elevated levels of unconjugated rather than conjugated bilirubin. These pathologic conditions can be classified as (1) those that cause increased breakdown of RBCs (e.g., sepsis, drug reactions, and extravascular blood); (2) those that interfere with bilirubin conjugation (e.g., breast milk jaundice, drug interactions, hypothyroidism, acidosis, and hypoxia); and (3) those that cause abnormal bilirubin excretion (e.g., hypoxia or asphyxia, bowel obstruction, ileus, and congestive heart failure). The single factor most implicated in hyperbilirubinemia is prematurity, with the severity of jaundice directly correlated to declining gestational age. The premature infant is thought to be subject to a combination of increased RBC breakdown secondary to reduced RBC life span and impaired bilirubin conjugation as a result of liver immaturity.

Increased Red Blood Cell Breakdown
Several problems that arise in the perinatal period are associated with excessive and premature destruction of the RBCs by hemolysis. Neonatal bacterial and viral infections and intrauterine viral infections, especially those of the TORCH complex (toxoplasmosis, other agents, rubella, cytomegalovirus, and herpes simplex), have been implicated in the hemolytic destruction of RBCs. Certain medications, such as the synthetic analogues of vitamin K or large doses of natural vitamin K, also induce RBC destruction. Other conditions prevalent in the premature and term newborn can result in the extravasation of large amounts of blood (e.g., cephalhematoma and pulmonary or intracerebral hemorrhages). These extravascular collections of blood cells must undergo hemolysis to be reabsorbed by the body. Significant hemolysis, regardless of the cause, increases the bilirubin load on a metabolically immature neonatal liver. This increased load often results in hyperbilirubinemia in the newborn.

Interference with Bilirubin Conjugation
Breast Milk Jaundice. Breast milk jaundice affects approximately 2% to 4% of all breastfed babies and can be divided into two phases, early and late, each with a different time of onset and a different underlying cause. In early-onset breast milk jaundice, the infant is affected within the first few days of life. This condition is thought to be due to a combination of maternal and infant factors that lead to diminished fluid intake and dehydration. Predisposing maternal factors include limited maternal milk supply, engorgement, cracked nipples, poor feeding technique, and maternal illness or fatigue. Neonatal factors include poor suck, illness, lethargy that accompanies hyperbilirubinemia, and dehydration. Poor intake leads to poor stool output and increased enterohepatic resorption of bilirubin. The recommended treatment is phototherapy and alleviation of dehydration. Frequent breast feedings with avoidance of supplementation, in addition to lactation counseling, are advised.

Late-onset breast milk jaundice is a separate entity that is attributed to a change in the chemical or physical composition of breast milk; it usually occurs after the first 3 to 5 days of life (Wong et al, 2006). Bilirubin levels can reach 12 to 20 mg/dl between 8 and 15 days and may remain elevated for as long as 2 months. The infant appears healthy, and no evidence of RBC hemolysis is seen. This jaundice is believed to be caused by substances in breast milk that interfere with bilirubin conjugation or increase enterohepatic circulation, resulting in resorption of bilirubin from the intestine. Two substances found in breast milk, pregnanediol and nonesterified fatty acids, are thought to inhibit glucuronyl transferase, the enzyme necessary for bilirubin conjugation in the liver. However, the role of these two substances in the interference with glucuronyl transferase remains questionable.

Recent studies suggest the presence of an unknown substance in breast milk that enhances the breakdown of conjugated bilirubin deposited in the intestine before it can be eliminated in the stool. Conjugated bilirubin is broken down to the unconjugated form and reabsorbed by the small and large bowel. Unconjugated bilirubin diffuses easily into the blood supply of the bowel, where it is redistributed into the circulation.

When breastfeeding is discontinued, the bilirubin level falls within 24 to 48 hours, dropping to half its previous peak level by 48 hours. With resumption of breastfeeding, the bilirubin level starts to rise but at a much slower pace. Interruption of breastfeeding is not recommended; instead, continued and frequent breastfeeding is encouraged. However, the health care provider has the option to supplement nursing with formula or to interrupt breastfeeding and substitute formula, depending on the degree of bilirubin elevation. Supplementation of nursing with water or glucose water does not appear to have any effect on bilirubin levels in healthy term infants.

Drugs That Interfere with Bilirubin Conjugation.
Certain medications ingested by the mother and passed transplacentally to the fetus (e.g., salicylates, sulfa preparations) can interfere with the ability of albumin to bind bilirubin. Administration of these drugs to the newborn can produce the same effect. Other medications, such as sodium benzoate, a commonly used preservative, compete with bilirubin for albumin binding sites.

Hypothyroidism. Hypothyroidism is one of the more common metabolic disorders associated with hyperbilirubinemia. Of all infants with hypothyroidism, 20% have elevated bilirubin levels lasting 3 to 4 weeks, with normalization of levels requiring up to 4 months. The suspected mechanism for jaundice is theorized to be a delay in glucuronosyltransferase synthesis or impairment of hepatic proteins that bind bilirubin and remove it from the plasma. The plasma membrane of liver cells may also be altered, resulting in decreased bilirubin influx into the hepatic cells.
**Acidosis and Hypoxia.** As previously stated in the discussion of kernicterus, a drop in serum pH alters albumin’s ability to bind bilirubin. The accompanying increase in the production of free fatty acids promotes competition between fatty acids and bilirubin for binding sites. In animal models, respiratory acidosis but not metabolic acidosis increases movement of bilirubin across the blood-brain barrier.

**Abnormal Bilirubin Excretion**

Any disease state resulting in abnormal bilirubin excretion can raise serum bilirubin levels significantly. This is seen in hepatic dysfunction secondary to such entities as hypoxia or asphyxia, bowel obstruction, ileus, and congestive heart failure. However, these conditions have a tendency to elevate both the conjugated and unconjugated bilirubin levels. The diminished bowel motility associated with these conditions lengthens the time during which beta-glucuronidase, which is naturally present in the gut, can act on conjugated bilirubin in the stool. This enzymatic reaction converts conjugated bilirubin into the unconjugated form, which is reabsorbed into the stool. This enzymatic reaction converts conjugated bilirubin into the unconjugated form, which is reabsorbed into the stool. This enzymatic reaction converts conjugated bilirubin into the unconjugated form, which is reabsorbed into the stool. This enzymatic reaction converts conjugated bilirubin into the unconjugated form, which is reabsorbed into the stool. This enzymatic reaction converts conjugated bilirubin into the unconjugated form, which is reabsorbed into the stool. This enzymatic reaction converts conjugated bilirubin into the unconjugated form, which is reabsorbed into the stool.

**Treatment of Hyperbilirubinemia**

**Phototherapy.** The actual mechanisms by which phototherapy reduces unconjugated bilirubin and the exact mode of bilirubin excretion are not clearly understood. Photodegradation and photoisomerization are the two mechanisms thought to change bilirubin into water-soluble and excretable forms. Photodegradation involves the oxidation of bilirubin pigment deposited in the skin and its conversion into colorless products that can be excreted into the urine. Of the total body bilirubin concentration, 15% can undergo photodegradation through oxidation. Photoisomerization involves the conversion of bilirubin polymers present in the skin into excretable isomers. When the natural form of bilirubin is exposed to blue light at certain wavelengths, it undergoes photoisomerization. This changes it from a tetrapyrrole, a lipid-soluble substance, into five water-soluble isomers. Four of these isomers are excreted into bile without undergoing conjugation. Two are unstable isomers that are incorporated into bile and must be promptly eliminated from the gastrointestinal tract as a component of stool or they revert back to their natural forms, resulting in resorption of bilirubin from the gut and recirculation into the plasma. Two other isomers remain relatively stable and account for most of the bilirubin found in bile. The fifth isomer, lumobilirubin, is a stable, water-soluble form of bilirubin that is eliminated through urine and bile.

Phototherapy is also thought to enhance hepatic excretion of unconjugated bilirubin and to increase bowel transit time. When phototherapy is begun early, a 20% to 35% reduction in the serum bilirubin concentrations is noted by day 2 of life and a reduction of 41% to 55% by day 4. This reduction is more significant than the naturally occurring drop in the untreated infant.

Although no significant adverse effects are attributed to the use of phototherapy, it is not without associated side effects. Some of these problems include dermal rash, lethargy, abdominal distention, possible eye damage, dehydration caused by increased insensible water loss through the skin and digestive tract, thrombocytopenia, hypocalcemia, and secretory diarrhea possibly as a result of a temporary intestinal lactose deficiency. Another effect of phototherapy seen in infants with a significant direct bilirubin component is “bronze baby” syndrome. This syndrome is thought to be due to skin deposition of a photoproduct of bilirubin decomposition, possibly copper porphyrins, which cause bronzing of the skin and urine. Although no harmful effects can be attributed to the bronzing, it can last for several weeks to several months and is somewhat alarming to parents.

Phototherapy is not adequate therapy for a rapidly rising bilirubin level, but it is effective in the treatment of moderate hyperbilirubinemia that has not reached or exceeded levels known to be associated with kernicterus and in reducing the need for exchange transfusions after the first 12 hours of life. Intensive phototherapy can produce a decline of 1 to 2 mg/dl of total serum bilirubin within 4 to 6 hours (Bergman et al, 1994). This is a reflection of the length of exposure necessary for phototherapy to exhibit its effectiveness. The American Academy of Pediatrics (AAP) adopted a set of guidelines for the initiation of phototherapy and exchange transfusion in the term, healthy newborn (AAP, 2004) (Figure 10-7). Suggested bilirubin levels for initiation of therapy based on birth weight, including very low birth weight, are found on a chart devised by King and Jung (1990) (Figure 10-8). Recommended levels for the use of phototherapy or exchange transfusion must be adjusted downward for prematurity, acidosis, hypoxia, respiratory distress, asphyxia, and neurologic decompensation (Figure 10-9). Diminished bilirubin-binding capacity of albumin, decreased amounts of circulating albumin, and increased permeability of the CNS expose these infants to increased amounts of free bilirubin, which can easily cross the blood-brain barrier.

Although administration of intravenous immunoglobulin (IVIG) to the mother has produced contradictory results, its administration to infants with Rh hemolytic disease may be beneficial. Administration of IVIG to a group of infants with Rh incompatibility was associated with a reduction in the rate of exchange transfusion to 12.5%, compared with 69% in the control group. It is hypothesized that IVIG may interfere with receptors in the reticuloendothelium that are required to induce hemolysis. The optimum dosage has yet to be determined.

However, administration of albumin to an infant undergoing phototherapy may reduce the amount of bilirubin available in the skin for photoisomerization. In an attempt to saturate the increased available albumin binding sites, free bilirubin is drawn into the vascular compartment from the skin, where phototherapy exerts its effect. For this reason, use of albumin in the infant undergoing phototherapy should be carefully weighed.

**Collaborative Management.** Infants who require phototherapy benefit most from blue light in the wavelength range at which photoisomerization occurs most efficiently: that is, 420 to 460 nm. In addition to the appropriate wavelength, effective illumination must be maintained. Spectroradiometric readings of 4 to 6 mcW/cm²/nm are considered in the effective therapeutic range. For optimum therapy, phototherapy units should be checked for adequacy of light levels by nursing or bioengineering staff. Prolonged exposure to phototherapy lights may cause retinal damage, which can be minimized with adequate eye protection. Phototherapy units and eye
FIGURE 10-7

- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin <3.0 g/dL (if measured).
- For well infants 35-37 6/7 wk can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for infants closer to 35 wks and at higher TSB levels for those closer to 37 6/7 wk.
- It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2-3 mg/dL (35-50 mmol/L) below those shown but home phototherapy should not be used in any infant with risk factors.

FIGURE 10-8
The rate of increase in bilirubin levels, gestational age, and the newborn's general condition determine the type of treatment for hyperbilirubinemia and the rapidity of its initiation. This chart is a useful guideline for initiating phototherapy or exchange transfusion in hyperbilirubinemic infants. From Pernoll M et al (1986). Neonatal hyperbilirubinemia and prevention of kernicterus. In Pernoll M et al, editors. Diagnosis and management of the fetus and neonate at risk, ed 5. St Louis: Mosby.
Therapy for inhibition of bilirubin synthesis, but clinical trials have preliminarily shown that metalloporphyrins may be effective in controlling hyperbilirubinemia in the term and preterm infant. Metalloporphyrins are inhibitors of heme oxygenase, the enzyme involved in the degradation of heme to biliverdin, an intermediate in the synthesis of bilirubin. Tin- and mesoporphyrin and tin-protoporphyrin are the two heme oxygenase inhibitors used in clinical trials as a prophylaxis and as treatment. Although these studies have shown beneficial effects, they are still in the initial stages of investigation.

Exchange Transfusion. Once done frequently in neonatal intensive care units, exchange transfusions are now rarely done. An exchange transfusion may be necessary, if bilirubin levels start to approach those associated with kernicterus despite phototherapy, to protect the CNS status of the jaundiced infant. The object of this procedure is to remove bilirubin and the antibody-coated RBCs from the newborn’s circulation. In addition, exchange transfusion removes some of the circulating maternal antibodies and Rh-positive fetal RBCs while potentially normalizing the hematocrit. After a single-volume exchange, 75% of the newborn’s RBC mass is removed; a double-volume exchange removes 85% to 90% of the cells. However, bilirubin removal is much less effective; only 25% of the infant’s total body bilirubin is removed during a double-volume exchange. This probably occurs because the major portion of bilirubin is in the extravascular compartment, an area not affected by the exchange of blood volume. Rebound in bilirubin levels occurs within 1 hour of the exchange, with posttransfusion levels rising as high as 55% of pre-exchange values.

Although EBF remains the primary condition requiring exchange transfusion, the procedure also can be used to reduce levels of circulating metabolic toxins or exogenous drugs and to re-establish a normal hematocrit without further volume overload in anemia-induced congestive heart failure. The mortality rate for exchange transfusions is 1%. This rate includes death during the procedure or within 6 hours after its completion but excludes hydropic, kernicteric, or moribund infants.

The following criteria are used to determine the need for and timing of exchange transfusions, particularly in infants with EBF (Bergman et al, 1994):

**Pharmacologic Agents.** Phenobarbital is thought to accelerate bilirubin excretion by increasing its uptake and conjugation by the liver and by increasing its excretion by enhancing bile flow. However, no increased benefit is noted that cannot be achieved with phototherapy alone. No medications have been approved in the United States as therapy for inhibition of bilirubin synthesis, but clinical trials...
• A cord blood bilirubin level over 4.5 mg/dl in term infants and 3.5 mg/dl in preterm infants
• A hemoglobin level under 8 g/dl and a bilirubin level over 6 mg/dl within 1 hour of delivery in a term infant
• A hemoglobin level under 11.5 g/dl and a bilirubin level over 3.5 mg/dl within 1 hour of delivery in a preterm infant
• An increase in bilirubin levels by 0.5 mg/dl/hr despite phototherapy
• A bilirubin level over 20 to 25 mg/dl in an uncompromised term infant (see Table 10-4), 18 mg/dl in the high-risk term newborn, and 10 to 18 mg/dl in the preterm infant, depending on gestational age and condition (Table 10-7)
• A bilirubin level over 10 to 17 mg/dl in a stressed or very immature preterm infant, over 10 to 12 mg/dl if hypoxia and acidosis are present

Identical criteria are used to determine the need for repeated exchange transfusion.

**Side Effects of Exchange Transfusion.** Exchange transfusion can have a marked effect on the cardiovascular status and the intravascular compartment, which is reflected in pressure changes, volume fluctuations, and biochemical balance. Significant morbidities such as anemia, air embolism, infection, bradycardia, necrotizing enterocolitis, thromboembolism and death can also occur as a result of an exchange transfusion. These are discussed more in depth on the website.

**Collaborative Management of the Infant Undergoing an Exchange Transfusion.** In addition to the general nursing care required by a sick infant, specific stabilization procedures are necessary for a successful exchange transfusion. A sample protocol for required care during an exchange is presented on the website.

**Anemia Pathophysiology**

An infant is considered anemic if the hemoglobin or hematocrit value is more than two standard deviations below normal for their gestational age group (Luchtman-Jones et al, 2002). During the neonatal period, several abnormalities can evoke states of both acute and chronic anemia in the newborn.

These forms of anemia often precede and occur independently of the natural propensity for physiologic anemia that exists as a common entity among all infants, both term and preterm. The conditions that most commonly trigger these pathologic anemias are acute or chronic episodes of hemorrhage, acute or chronic RBC destruction and hemolysis, and blood sampling for laboratory analysis.

**Acute Anemia.** The physical presentation of acute anemia is more intense than that seen in the chronic form, because the causes of acute anemia are more emergent, life-threatening, and disruptive to the homeostasis of the infant (Box 10-2). The resulting cardiovascular collapse, followed closely by respiratory failure, can overwhelm the neonate with...

---

<table>
<thead>
<tr>
<th>TABLE 10-7</th>
<th>Maximum Total Serum Bilirubin Concentration Allowed before Exchange Transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth Weight (g)</td>
<td>Uncomplicated Course</td>
</tr>
<tr>
<td>Under 1000</td>
<td>10</td>
</tr>
<tr>
<td>1000 to 1249</td>
<td>13</td>
</tr>
<tr>
<td>1250 to 1499</td>
<td>15</td>
</tr>
<tr>
<td>1500 to 1999</td>
<td>17</td>
</tr>
<tr>
<td>2000 to 2500</td>
<td>18</td>
</tr>
<tr>
<td>2500 or over</td>
<td>25</td>
</tr>
</tbody>
</table>


---

**BOX 10-2**

**Causes of Acute Anemia in the Newborn**

**Obstetric Accidents, Malformations of the Placenta and Cord**
Rupture of a normal umbilical cord
• Precipitous delivery
• Entanglement

Hematoma of the cord or placenta
Rupture of an abnormal umbilical cord
• Varices
• Aneurysm

Rupture of anomalous vessels
• Aberrant vessel
• Velamentous insertion
• Communicating vessels in multilobed placenta

Incision of placenta during cesarean section

**Placenta previa**
**Abruptio placentae**

**Occult Hemorrhage Before Birth**

Fetoplacental
• Tight nuchal cord

Cesarean section

Placental hematoma

Fetomaternal
• Traumatic amnioentesis
• After external cephalic version, manual removal of placenta, use of oxytocin

Spontaneous
• Chorioangioma of the placenta
• Choriocarcinoma

Twin to twin
• Chronic
• Acute

**Internal Hemorrhage**

Intracranial
Giant cephalhematoma, subgaleal, caput succedaneum

Adrenal
Retroperitoneal
Ruptured liver, ruptured spleen

Pulmonary

**Iatrogenic Blood Loss**

only marginal reserves. Immediate intervention and replacement of lost intravascular volume often are required to achieve stabilization. An infant experiencing an acute anemic episode (hemorrhage being the most common cause) has symptoms reflecting compromise of the cardiorespiratory system: shock, poor peripheral perfusion, poor respiratory effort or respiratory distress, tachycardia, pallor, lethargy, and hypotension. Before signs of acute anemia become apparent, the hemoglobin level must fall precipitously below 12 g/dl.

Acute blood loss results in a recognizable sequence of symptoms based on the volume loss:

- **7.5% to 15% volume loss**: Little change is noted in heart rate and blood pressure, but stroke volume and subsequent cardiac output are reduced. Peripheral vasoconstriction occurs, resulting in diminished blood flow to the skeletal muscles, gut, and carass.
- **20% to 25% volume loss**: Hypotension and shock become apparent. Cardiac output is reduced, and peripheral vasoconstriction is present. Low tissue oxygen levels and acidosis become apparent.

**Chronic Anemia.** Prolonged, or chronic, anemia may not require rapid intravascular volume expansion, but it is by no means completely benign, as is seen with EBF or chronic twin-to-twin transfusion (Box 10-3). In both of these conditions, infants may require removal of intravascular volume and replacement with volume of a higher hematocrit before stabilization is achieved. Because these infants have had considerable time to adjust to chronic blood loss or hemolysis, the changes in vital signs may reflect poor oxygen-carrying capacity rather than hypovolemia. On physical examination, pallor usually is accompanied by hepatosplenomegaly, a reflection of the body’s attempt to compensate for blood loss through extramedullary hemopoiesis. The blood smear may also reflect the long-standing nature of the problem; RBCs appear hypochromic and small, and a greater number of immature RBCs are seen.

**Common Causes of Pathologic Anemia in the Newborn**

**Hemorrhage.** Hemorrhage is one of the most common causes of pathologic anemia in the newborn. There are many different types of hemorrhage, but they can be classified into four distinct categories, each which will be discussed below.

**Fetal-Maternal Transfusion Caused by Transplacental Hemorrhage.** This phenomenon occurs in approximately 50% to 75% of all pregnancies and can be an acute or chronic process. An estimated 5.6% of pregnancies involve a fetal-maternal transfusion in the range of 11 to 30 ml of blood; another 1% involve an exchange of more than 30 ml. Fetal-maternal transfusions can be verified by the presence of fetal cells in the maternal circulation, which can be detected with the erythrocyte rosette test and the Kleihauer-Betke acid elution test for fetal hemoglobin in maternal blood. The erythrocyte rosette test specifically detects fetal RBCs. The Kleihauer-Betke test consists of an acid wash of a maternal blood smear followed by staining. Fetal hemoglobin resists elution from intact RBCs in an acid solution. Intact cells containing fetal hemoglobin can be distinguished microscopically, when stained, from adult erythrocytes. The presence of stained erythrocytes suggests contamination of maternal blood by fetal blood. This test is useful in identifying fetal RBCs in the mother’s blood as long as no underlying condition increases the amount of fetal hemoglobin in the mother’s blood.

**Twin-to-Twin Transfusion.** This phenomenon, which can be both acute and chronic, occurs in 15% to 33% of all monochorionic (monzygotic) twins, in which the placentas tend to be fused. The anastomosis usually is between an artery of one placenta and the vein of the other, although vascular connections may be artery to artery or vein to vein. In the chronic form of twin-to-twin transfusion, the size difference between twins can be helpful in determining the donor and the recipient. When the weight difference exceeds 20%, the smaller twin is always the donor. When the weight difference is less than 20%, either twin may be the donor. In such cases, hematocrit values prove useful in determining the donor and the recipient. The donor twin is anemic, and the blood count

**BOX 10-3**

**Causes of Chronic Anemia in the Newborn**

- **Immunity disorders**
  - Rh incompatibility
  - ABO incompatibility
  - Minor blood group incompatibility
  - Maternal autoimmune hemolytic anemia
  - Drug-induced hemolytic anemia
- **Infection**
  - Bacterial sepsis
  - Congenital infections
  - Syphilis
  - Malaria
- **Cytomegalovirus
  - Rubella
  - Toxoplasmosis
  - Disseminated herpes**
- **Disseminated intravascular coagulation**
- **Macroangiopathic and microangiopathic hemolytic anemias**
  - Cavernous hemangioma
  - Large-vessel thrombi
  - Renal artery stenosis
  - Severe coarctation of aorta
- **Galactosemia**
- **Prolonged or recurrent acidosis of a metabolic or respiratory nature**
  - Hereditary disorders of the red cell membrane
  - Hereditary spherocytosis
  - Hereditary elliptocytosis
  - Hereditary stomatocytosis
  - Other rare membrane disorders
- **Pyknocytosis**
- **Red cell enzyme deficiencies**
  - Most commonly glucose-6-phosphate dehydrogenase deficiency, pyruvate kinase deficiency, 5’-nucleotidase deficiency, and glucose-6-phosphate isomerase deficiency
- **Alpha-thalassemia syndrome**
- **Alpha chain structural abnormalities**
- **Gamma-thalassemia syndromes**
- **Gamma chain structural abnormalities**

reflects increased hemapoiesis, as evidenced by an elevated reticulocyte count and increased numbers of immature RBCs. The recipient develops polychromasia but can exhibit signs of congestive heart failure and pulmonary or systemic hypertension. Laboratory data usually show a difference of 5 g/dl between donor and recipient hemoglobin values. Stillbirths are common in twin-to-twin transfusion, and both twins are at risk.

Obstetrical Accidents. Many obstetrical problems, especially those that occur before labor and delivery, can result in chronic as well as acute blood loss. Long-standing problems, such as placenta previa or partial abruption, usually result in anemia. However, acute hemorrhage rather than anemia is the case in problems that occur at the time of delivery. Examples are severe abruptio, severing of the placenta during cesarean section, or umbilical cord rupture as a result of sudden tension on a short or tanged cord. A tight nuchal cord can reduce blood volume in a newborn by approximately 20%. Holding a newly delivered infant above the placenta can also reduce the hematocrit and blood volume because of the gravitational drainage of blood from the newborn into the placenta.

Internal Hemorrhage. A drop in the hematocrit during the first 24 to 72 hours that is not associated with hyperbilirubinemia usually is attributed to internal hemorrhage. Bleeding can occur in various parts of the body secondary to birth trauma or pre-existing anomalies. The areas of potential hemorrhage in the head include the subdural, subarachnoid, intraventricular, intracranial, and subperiosteal spaces. Infants can lose an estimated 10% to 15% of their blood during an intraventricular or intracranial hemorrhage. In cases of traumatic delivery or vacuum extraction, extensive scalp bleeding can result in significant blood loss, which can be estimated by measuring the increase in the head circumference. Each centimeter of increase represents an estimated 38 ml of blood lost from the intravascular compartment. Hemorrhage into the liver, kidneys, spleen, or retroperitoneal space can also occur in association with traumatic and breech deliveries.

Hepatic rupture occurs in approximately 1.2% to 5.6% of stillbirths and neonatal deaths; half of the hemorrhages are subcapsular. Infants with this disorder tend to be stable for 24 to 48 hours and then suddenly deteriorate. This deterioration seems to coincide with rupture of the capsule and hemoperitoneum. Hepatic rupture carries a poor prognosis, but rapid surgery preceded by multiple transfusions can save the infant. Splenic rupture is associated with severe EBF and should be suspected at the time of exchange transfusion if the central venous pressure is low rather than elevated. Signs of splenic rupture include scrotal swelling and peritoneal effusion without free air. Adrenal hemorrhage is seen more often in the infant of a diabetic or prediabetic mother and is characterized by a flank mass with bluish discoloration of the overlying skin.

Red Blood Cell Destruction and Hemolysis

Maternal-Fetal Blood Group Incompatibilities. Isoimmunization, as in ABO and Rh incompatibility, accounts for most cases of neonatal hemolysis. A reduced RBC life span caused by hemolysis usually is associated with a rise in the bilirubin level, 1 g of hemoglobin yielding 35 mg of bilirubin. Infants who have received intrauterine transfusions or exchange transfusions for blood group incompatibilities are predisposed to a hyporegenerative anemia that develops within the first few months of life. The pathophysiology is considered to be bone marrow suppression, possibly as a result of the increased amount of hemoglobin A received during the blood transfusions.

Acquired Defects of the Red Blood Cells. This hemolytic problem is seen in bacterial sepsis and viral infections, especially of the TORCH variety. Drug-induced RBC destruction, caused by either maternal ingestion or direct administration of the drug to the newborn, is another common cause of hemolysis. An example of this would be the hemolysis that could occur with administration of iron supplements to an infant with vitamin E deficiency.

Congenital Defects of the Red Blood Cells. Defects resulting in destruction of the RBCs can involve the cell membrane, enzymatic system, or hemoglobin component, as in glucose-6-phosphate dehydrogenase deficiency, thalassemia, and hereditary spherocytosis. Although these conditions can cause hemolysis in the newborn period, they are rare diseases.

Blood Sampling. Blood loss that occurs secondary to sampling is one of the two most frequent causes of chronic anemia in infants, the other being physiologic anemia of the newborn and premature infant. Among two groups of preterm infants admitted to neonatal intensive care units, the average blood loss from sampling during the first 4 to 6 weeks of life was 46 to 50 ml/kg; the severity of illness correlated with the amount of blood removed for sampling. Prudent blood sampling may eliminate unnecessary blood volume depletion and reduce the need for replacement transfusion therapy. Accurate recording of blood lost to sampling can prove beneficial in the assessment of a sick infant’s circulatory status and volume needs. However, perfusion status and hematocrit values may be better determinants of the need for volume expansion or blood transfusions.

Differential Diagnosis

History. Acute and chronic anemia often can be distinguished from each other and from other problems by analyzing the family history for anemia or jaundice. The maternal history should be carefully examined for evidence of drug ingestion that may affect RBC life span or production, bleeding during the pregnancy or labor, or other incidents surrounding the delivery that may contribute to blood loss in the newborn.

Laboratory Findings. The type of anemia often can be identified on the basis of laboratory studies that evaluate RBC content and form.

- Hematocrit and hemoglobin levels can define the type as well as the degree of anemia. Blood loss during acute hemorrhage is rapid, with little evidence of the compensatory hemapoiesis seen in chronic anemia. RBCs are of normal size and have a normal hemoglobin mass, and no significant increase is seen in the number of immature RBCs. Hemoglobin values initially may not reflect hemorrhage because the intravascular volume contracts and masks volume loss. It may take several hours for intravascular equilibration to occur before the hemoglobin accurately reflects the extent of the hemorrhage. The site of hemoglobin or hematocrit sampling is important for obtaining accurate information, because capillary sticks on an infant in shock reflect venous stasis. A more accurate sample at this time would be from an arterial or venous source.

- Reticulocyte counts are useful in differentiating chronic and acute forms of anemia. Increased numbers of
immediate RBCs reflect the degree of hematopoietic activity in response to anemia. Increased hematopoiesis requires a time lapse between the occurrence of anemia and stimulation of the hematopoietic centers.

- Peripheral blood smears are helpful in evaluating iron content and the size and shape of the RBC, which vary in different forms of anemia.
- Blood typing, Rh determination, and Coombs’ testing can help identify blood group incompatibilities as causes of anemia.

**Treatment**

**Collaborative Management of the Infant with Acute Anemia.** The following measures are used to stabilize the condition of an infant with acute anemia:

- Basic resuscitation of the infant experiencing precipitous blood loss often includes stabilization of the airway by means of intubation and ventilation.
- Rapid line placement for fluid replacement, volume expansion, and blood sampling may require use of the umbilical vein or artery. Central venous pressure measurements can be helpful in assessing the degree of volume loss and the amount of replacement needed.
- If acute volume expansion is required, low-titer, type O-negative blood, plasma, albumin, or saline initially can be used in increments of 10 to 20 ml/kg until a type and cross-match replacement is available. Failure to respond may indicate continuing internal hemorrhage.
- After the infant’s condition has been stabilized, laboratory tests and a physical examination should be performed to determine the cause of the anemia and to rectify the problem.
- Examination of the placenta and maternal blood sample testing for fetal hemoglobin may prove useful in determining the cause of the blood loss.

As with all newborns, the principles of care (provision of warmth, monitoring of vital signs, ongoing assessment, and accurate determination of intake and output) are essential to the well-being of the infant who has suffered acute blood loss. After initial stabilization, nursing care must include modifications that either eliminate recurrence of precipitous events or prevent further blood loss. Providing safe care to such infants requires adequate knowledge of the principles and procedures involved in volume expansion and the use of blood products. A review of the use of blood products can be found at the conclusion of this chapter.

**Collaborative Management of the Infant with Chronic Anemia.** The major focus of therapy for the infant with chronic anemia is control or elimination of the cause of the anemia. Several forms of chronic anemia in term and preterm infants are linked to dietary deficiencies that can be eradicated by replacement therapy. Chronic forms of anemia requiring symptomatic therapy can also be treated with transfusion therapy and erythropoietin.

**Dietary Supplementation.** The three major dietary factors that affect RBC production are iron, folate, and vitamin E. Because all three increase in amount with increasing gestational age, premature birth predisposes the immature infant to anemia as a result of insufficient stores.

Without benefit of iron supplementation, the hematopoiesis necessary to maintain a normal hemoglobin level depletes the infant’s iron reserves by the time birth weight is doubled.

Various factors can further contribute to iron deficiency anemia, such as low birth weight, low initial hemoglobin levels, and blood loss through trauma, hemorrhage, or sampling. In the term infant, exhaustion of iron reserves normally occurs by 20 to 24 weeks’ postnatal age, but this happens much earlier in the preterm infant. Iron stores needed for hemoglobin production are present in insufficient quantities at birth in the premature infant, making supplementation necessary during the first 2 to 4 months to prevent iron deficiency anemia.

In any gestational age group, iron depletion first becomes evident in reduced serum ferritin levels (serum ferritin being a measure of accumulated iron stores) and in the disappearance of stainable iron from the bone marrow. A subsequent reduction in the mean corpuscular volume (i.e., the size) of the RBC is followed by a drop in the hemoglobin level. Although prophylactic iron supplementation does not prevent the initial fall in hemoglobin, administration of 1 to 2 mg/kg/day of supplemental iron should supply term and preterm infants with adequate reserves; 3 to 6 mg/kg/day is recommended in iron-deficient infants or those receiving erythropoietin.

The relationship between serum ferritin levels and the administration of multiple transfusions to a population of newborn infants was evaluated to determine iron supplementation needs in this group. In a study by Arad and associates (1988), serum ferritin levels were measured in four groups of infants: (1) preterm infants transfused with more than 100 ml of packed cells, (2) preterm infants transfused with less than 100 ml, (3) nontransfused preterm infants, and (4) nontransfused term infants. At 4 to 5 months of age, the preterm infants receiving more than 100 ml of RBCs had the highest ferritin levels of all four groups. This would suggest that LBW infants receiving large volumes of RBCs could amass iron stores sufficient for new RBC production during the first 4 to 5 months without the need for additional iron supplementation.

Folate is the generic description for folic acid and its related compounds. Folate is an essential part of the B-complex vitamins involved in the maturation of RBCs, particularly the synthesis of DNA, which controls nuclear maturation and division. Because bone marrow is one of the body’s fastest growing and proliferative tissues, folic acid deficiency diminishes its ability to produce RBCs, resulting in a megaloblastic anemia.

High amounts of folate are present at birth in both term and preterm infants, but these levels drop rapidly, especially in LBW infants. It is estimated that approximately 68% of infants weighing less than 1700 g have subnormal levels of folate at 1 to 3 months of age. However, only a few infants actually develop anemia. Human milk and soy-based products contain an adequate amount of natural folate, but commonly used commercial products must be artificially enriched. Premature infant formulas are adequately enriched to satisfy a premature infant’s folate needs provided that intake is sufficient. Because folate is absorbed in the duodenum and jejunum, any disease or medication that affects the absorptive surface of these areas can impair folate absorption.

Vitamin E, an antioxidant, is valuable in protecting the RBC membrane from destruction due to lipid peroxidation. Deficiency of this nutrient shortens the life span of the cell by exposing the unprotected, unsaturated membrane lipids to peroxidation and hemolysis. Infants are born in a state of relative vitamin E deficiency that is more intense in the smaller and more premature infants. Vitamin E is required in
increasing amounts as the intake of polyunsaturated fatty acids increases. Deficiency becomes apparent in infants of birth weights less than 1500 g at approximately 4 to 6 weeks of age, resulting in decreased hemoglobin levels ranging from 7 to 10 g/dL. Administration of iron supplementation in the presence of this deficiency intensifies the hemolytic response. Signs and symptoms, as with many neonatal diseases, mimic those of other disease entities that occur in the neonatal period. One of the more obvious symptoms is edema of the feet, lower extremities, and scrotal area. The appearance of the RBC may vary, but abnormalities usually include fragmented or irregularly shaped cells, presence of spherocytes, and thrombocytopenia. Infant formulas are now enriched with adequate amounts of vitamin E, provided formula intake is sufficient.

Transfusion Therapy. Of all preterm infants admitted to an NICU, approximately 90% receive one transfusion in the first 6 weeks of life; 50% receive cumulative transfusions in excess of their total circulating RBC mass. In determining which infants may need subsequent transfusions after the first 2 weeks of life, gestational age of less than 30 weeks is the best predictor, regardless of severity of illness, number of transfusions during the first week, complications, or hematocrit level at birth. Only 14% of infants of more than 30 weeks' gestation require transfusions after 2 weeks of age.

Although a critically ill infant generally is maintained with a hematocrit above 40%, the benefits of transfusion therapy in the convalescent infant remain controversial. When the effects of transfusion therapy in the convalescent infant were studied, the elimination of symptoms attributed to anemia was not a consistent finding. In premature infants with hematocrits below 30%, apnea, bradycardia, dyspnea, feeding difficulties, poor weight gain despite good calorie intake, lethargy, tachypnea, tachycardia, and increased cardiac output and oxygen consumption appear to be relieved by transfusion therapy in some studies. There appears to be no overall relationship between hematocrit values and physiologic symptoms such as apnea, bradycardia, or changes in heart and respiratory rates, nor does abatement of these symptoms follow transfusion therapy.

In light of the controversy surrounding transfusions, evidence of impaired tissue oxygenation remains the ultimate criterion for the use of blood products. Measurement of lactic acid levels may prove helpful in determining which infants may benefit from transfusion therapy. When the oxygen-carrying capacity of hemoglobin is insufficient for tissue needs, anaerobic metabolism occurs, leading to excess production of lactic acid. Monitoring of lactic acid levels and transfusing only those infants with elevated levels may aid in establishing more sound criteria for transfusion therapy.

Several methods of blood preparation and use have been evaluated to minimize donor exposure and reduce the potential for transmitted disease. Studies suggest that packed RBCs with a shelf life of more than 5 days, and up to 42 days, are safe for use in neonatal transfusions (Gael, 2005; Basile & Southgate, 2004). This finding, combined with use of a sterile connection device that allows multiple aseptic entries into a unit of blood, would permit use of a designated unit for each infant at risk for multiple transfusions, thereby significantly reducing donor exposure (Gael, 2005). The desire to limit donor exposure must inevitably be balanced by the limited availability of banked blood. Multiple users on a blood unit may reduce wastage but may possibly expose an infant to multiple donors.

Blood administered to the newborn is often irradiated, which causes cell membrane disruption and potassium leakage from the cell. The decision by the U.S. Food and Drug Administration to change its recommendations for the maximum storage time of irradiated blood from 42 to 28 days affects the length of use of a designated unit (Quinnan, 1993). Although older blood appears to be safe to administer, it is not recommended for rapid transfusions, administration of large aliquots, exchange transfusions, or treatment of coagulopathies.

The establishment of transfusion criteria can effectively minimize donor exposure. These guidelines help determine which infants would benefit from transfusion on the basis of symptoms, hematocrit value, and severity of illness.

Recombinant Human Erythropoietin Therapy. Cloning of the human erythropoietin (HuEPO) gene in 1985 resulted in the production of large amounts of HuEPO for use as an exogenous stimulant of erythroid progenitor cells in patients with anemia. HuEPO acts primarily on CFU-E, derivatives of the hematopoietic stem cells in the bone marrow and the precursors of the RBCs (Figure 10-10). Studies from the United States and England have shown the use of recombinant erythropoietin to be an effective replacement for transfusion therapy in raising the hemoglobin level in hyporegenerative anemia and end-stage renal disease. Further studies of preterm infants have demonstrated that HuEPO maintains the hematocrit level during the phase of normal anemia of the premature infant, with good proliferation of erythroid progenitor cells in response to HuEPO.

HuEPO has attained recognition as a standard of care for anemia of prematurity, because several clinical trials have established its effectiveness in reducing both the number of transfusions and the cumulative volume of transfused blood needed in treated patients (Messer et al, 1993; Ohls et al,
1993, 1995; Maier et al, 1994; Meyer et al, 1994). Donato and associates (2000) noted increased reticulocytosis in infants started early on erythropoietin but failed to see a reduction in transfusion requirements in those infants.

The usual response in preterm infants given HuEPO is an increase in blood levels of erythropoietin and reticulocytes, as well as RBC volume, 2 to 3 weeks after initiation of therapy. The accepted dosage of erythropoietin is 200 to 250 units/kg, given subcutaneously three times a week for 2 weeks, although a definitive therapeutic dosage has yet to be determined.

HuEPO has been evaluated for its effectiveness as an alternative to transfusion therapy for treatment of anemia in premature infants caused by (1) blood sampling, with administration beginning within the first 2 days of life (Maier et al, 1994; Ohls et al, 1995); (2) physiologic anemia of prematurity, with therapy starting at 1 to 4 weeks of age (Emmerson et al, 1993; Messer et al, 1993; Meyer et al, 1994; Shannon et al, 1993); and (3) anemia of bronchopulmonary dysplasia, with treatment starting at 3 months of age (Ohls et al, 1993).

Serum ferritin levels decline rapidly after initiation of HuEPO therapy in infants with normal pretreatment ferritin levels, despite prophylactic iron supplementation of 2 mg/kg/day. This predisposition to the development of iron deficiency anemia underlines the need for increased iron supplementation in infants treated with HuEPO. Also documented as a side effect of HuEPO therapy are transient thrombocytosis shortly after the initiation of therapy and transient neutropenia. The transient neutropenia can last as long as 2 months after discontinuation of therapy. It has been postulated that this phenomenon is due to a stimulant effect of HuEPO on megakaryocyte progenitors and a negative effect on granulocyte-monocyte progenitor cells. Before HuEPO was proven effective in raising hematocrit levels, its use was projected to eliminate the need for one third of all transfusions in premature infants.

**Physiologic Anemia of the Newborn and Anemia of the Premature Infant**

Shortly after birth, the physiologic regulator of RBC production, erythropoietin, falls to barely perceptible levels because the relative intrauterine hypoxia that stimulated its release in utero is no longer present. Erythropoietin levels remain low until another hypoxic stimulus occurs, one created by the normal drop in the hemoglobin level that marks physiologic anemia of the newborn. This drop in the hemoglobin level is due to decreased marrow production of RBCs secondary to diminished circulating erythropoietin levels, a shorter life span of the neonatal RBC with destruction of fetal hemoglobin, and hemodilution caused by growth.

The drop in hemoglobin that prompts the postnatal rise in erythropoietin directly correlates with the infant's gestational age and birth weight (Figure 10-11). The smaller and more immature infant reaches a lower nadir at an earlier postnatal age. The hemoglobin level in the term newborn reaches a nadir of 11.4 g/dl ± 0.9 in the first 2 to 3 months of life and plateaus at this level for approximately 2 more months before it gradually increases. Although there is no significant difference in cord blood hemoglobin levels between term infants and preterm infants born after 32 weeks' gestation, the drop in hemoglobin occurs earlier in the preterm infant, is more precipitous, and reaches a lower nadir. Starting at 2 weeks of age, the preterm infant has a drop in hemoglobin of 1 g/dl/wk for the first several weeks; the nadir at 6 to 8 weeks of age is 2 to 3 g/dl lower than that of the term infant. An infant weighing 1000 to 1500 g at birth will have a mean hemoglobin nadir of 8 g/dl at 4 to 6 weeks of age.

Infants who have undergone exchange transfusion or multiple transfusions also have a greater fall in the hemoglobin level in the first 3 months of life. This phenomenon, theoretically may be due to improved oxygen delivery to tissue associated with the replacement of fetal with adult hemoglobin. Adult hemoglobin has less affinity for oxygen because of the structural difference of the globin portion of the hemoglobin molecule. This, coupled with the increased amount of 2,3-diphosphoglycerate present in the blood, allows adult hemoglobin to release oxygen to the tissue more easily. Improved tissue oxygenation effectively lowers serum erythropoietin levels (Figure 10-12), resulting in decreased RBC production. Consequently, an infant undergoing intrauterine transfusion, exchange transfusion, or frequent postnatal transfusions has improved tissue oxygenation and a decreased erythropoietin level.

The switch in the predominant site of erythropoietin production during fetal life from the liver to the kidneys occurs concurrently with the change in hemoglobin to a more mature form. Hepatic production of erythropoietin in response to hypoxia is not as rapid as the kidneys' response, an adjustment that actually spares the fetus from polycythemia in utero. However, persistence of this hepatic pathway after premature birth may explain why the premature infant's hematocrit...
values reach a lower nadir that persists longer compared with the term infant. Although erythropoietin levels are reduced in the early newborn period, the erythroid progenitor cells in the bone marrow are exceedingly sensitive to erythropoietin and respond rapidly as blood levels increase. The normal erythropoietin level in infants beyond the newborn period is 10 to 20 munits/ml.

Physiologic anemia does not usually require any form of treatment. With good nutrition, the hemoglobin level in the term infant should start to rise by 3 months of age. With adequate nutrition and iron supplementation, the hemoglobin level in the preterm infant should start to increase by 5 months of age, eventually attaining hematocrit values comparable to those of the term infant. It is the preterm infant with symptomatic anemia of prematurity who poses the question of transfusion vs HuEPO therapy, a question that has not yet been answered conclusively.

**Polycythemia**

**Pathophysiology**

Polycythemia, defined as a peripheral venous hematocrit over 65%, occurs in 4% to 5% of the total population of newborns, in 2% to 4% of term infants appropriate for gestational age, and in 10% to 15% of infants either small or large for gestational age. It has not been observed in infants of less than 34 weeks’ gestation. Although the fetus lives in a low-PO2 environment that should induce a polycythemic response, it protects itself by keeping hematocrit levels below 60%. This may be a function of slower fetal hepatic response to hypoxia compared with rapid renal response after birth. The average hematocrit on the first day of life is approximately 50% in the term infant and the preterm infant of more than 32 weeks’ gestation and 45% in the preterm infant of less than 32 weeks’ gestation. During the first 4 to 12 hours of life, hemoglobin and hematocrit values tend to rise and then equilibrate, especially in infants receiving large placental transfusions.

The choice of sampling site can affect hematocrit values considerably, particularly during the early newborn period when peripheral circulation may be somewhat sluggish. Infants younger than 1 day of age either lack or have diminished cutaneous vasoregulatory mechanisms that reduce peripheral perfusion. Polycythemia further impairs peripheral circulation by increasing blood viscosity and reducing the flow rate. As blood viscosity increases, vascular resistance increases in the peripheral circulation and the microcirculation of the capillaries throughout the body. Compared with venous samples, the hematocrit levels of capillary samples are 5% to 15% higher, and those of umbilical vesel or arterial samples are 6% to 8% lower.

Three major factors determine blood viscosity: hematocrit, plasma viscosity (osmolality), and deformability of the RBCs. With hematocrit levels below 60% to 65%, blood viscosity increases in a linear fashion, but viscosity exponentially increases at higher hematocrit levels.

Variations in the components of plasma affect blood viscosity independent of the hematocrit. Abnormal composition of plasma protein, electrolytes, and other metabolites can either decrease or increase plasma viscosity. Such an increase in the presence of a high hematocrit further increases blood viscosity and reduces the blood flow rate. The ability of cells to modify their shape to successfully traverse the peripheral vascular bed and microcirculation also affects the blood flow rate. The degree of deformability of the cell determines its ability to pass through small vascular spaces; the greater the deformability of the cell, the quicker its passage. Less deformable cells can increase blood viscosity by occluding small vessels, causing sludging in the microcirculation that can lead to thrombosis and tissue ischemia.

The two major types of polycythemia are (1) the active form, which is caused by the production of an excess number of RBCs in response to hypoxia and other poorly defined stimuli; and (2) the passive form, which is caused by RBC transfusion to an infant secondary to maternal-fetal transfusion, twin-to-twin transfusion, or delayed cord clamping.

**Active Polycythemia.** Tissue hypoxia, regardless of the cause, elicits an increase in erythropoietin that stimulates RBC production. In the fetus, erythropoietin is produced initially by the liver and then by the kidneys, the adult production site. The kidneys’ potential to release erythropoietin is active by 34 weeks’ gestation. At this time, a renal erythropoietic factor reacts with a substance in the plasma to produce erythropoietin, the RBC stimulating factor. Hypoxia of the tissues adjacent to the renal tubules, where erythropoietin is thought to be produced, is the potent stimulator of this factor’s release.

Many factors can lead to tissue hypoxia associated with the active form of polycythemia. These factors include the following:

1. Maternal factors that result in reduced placental blood flow
   - Pregnancy-induced hypertension
   - Older maternal age
   - Maternal renal or heart disease
   - Severe maternal diabetes (hematocrit values of 64% or higher are found in 42% of infants of a diabetic mother and 30% of gestational infants of a diabetic mother)
5. Metabolic symptoms
4. Hematologic symptoms
3. Respiratory symptoms
2. Cardiovascular symptoms
1. Neurologic symptoms

include the following:

- Oligohydramnios
- Maternal smoking (the mechanism is thought to be production of carbon monoxide that crosses the placenta and induces a state of tissue hypoxia in the fetus)

2. Placental factors
   - Placental infarction
   - Placenta previa
   - Viral infections, especially TORCH
   - Postmaturity
   - Placental dysfunction that results in a small-for-gestational-age (SGA) infant

3. Fetal syndromes
   - Trisomies 13, 18, and 21
   - Beckwith-Wiedemann syndrome

**Passive Polycythemia.** Passive polycythemia is a result of increased fetal blood volume caused by maternal-fetal transfusion; twin-to-twin transfusion, with one twin being polycythemic and the other anemic; or delayed cord clamping. A diagnosis of maternal-fetal transfusion can be considered when (1) the infant’s blood is found to contain larger amounts than expected of adult hemoglobin, IgA, or IgM; (2) RBCs in the infant’s blood have maternal blood group antigens, if the mother’s and the infant’s blood groups are different; or (3) XX cells are found in an XY infant. In twin-to-twin transfusion, morbidity and mortality are comparable in both groups of affected infants, with one twin being anemic and the other polycythemic. By far, however, the most common cause of fetal transfusion is delayed cord clamping with positioning of the newborn below the level of the placenta. Delayed cord clamping can increase the circulating volume by as much as 60% and can raise the hematocrit value by 10%.

**Clinical Manifestations**

Symptoms of polycythemic hyperviscosity, which usually are evident within the first few days after birth, reflect compromise of various organ systems. The most commonly seen findings include the following:

1. Neurologic symptoms
   - Lethargy
   - Hypotonia
   - Tremulousness
   - Exaggerated startle
   - Poor suck
   - Vomiting
   - Seizures
   - Apnea

2. Cardiovascular symptoms
   - Plethora
   - Cardiomegaly
   - Electrocardiographic changes (right and left atrial hypertrophy, right ventricular hypertrophy)

3. Respiratory symptoms
   - Respiratory distress
   - Central cyanosis
   - Pleural effusions
   - Pulmonary congestion and edema

4. Hematologic symptoms
   - Thrombocytopenia
   - Elevated reticulocyte level
   - Hepatosplenomegaly

5. Metabolic symptoms
   - Hypocalcemia
   - Hyperbilirubinemia
   - Hypoglycemia

Hypoglycemia found in conjunction with polycythemia can be a reflection of (1) increased glucose consumption by an overabundant number of RBCs; (2) increased cerebral extraction of glucose secondary to hypoxia; (3) a state of hyperinsulinemia caused by increased erythropoietin levels; or (4) decreased hepatic glucose production as a result of sluggish hepatic circulation. Hyperbilirubinemia associated with polycythemia is a reflection of increased byproducts of RBC destruction.

The complications of polycythemia center around the increased resistance to blood flow related to hyperviscosity; blood flow to all organ systems is impaired by sluggish circulation. Pulmonary blood flow can be dramatically compromised, resulting in pulmonary hypertension, retained lung fluid, and respiratory distress syndrome. Taxation of the heart by an increased vascular load can lead to congestive heart failure and left to right shunting across the foramen ovale or ductus arteriosus. Sludging of blood in the microcirculation of the kidneys can lead to renal vein thrombosis and renal failure. Impairment of blood flow to the bowel can lead to necrotizing enterocolitis.

**Treatment**

Although most infants with polycythemia are asymptomatic or minimally symptomatic, the hematocrit level and the presence of symptoms, even if minimal, should form the basis of treatment. Because hematocrit levels of 65% can lead to neurologic abnormalities and levels of 75% or higher are always associated with neurologic changes, an infant with a venous hematocrit of 65% or higher should be considered for partial exchange transfusion.

Partial exchange results in dramatic improvement in symptomatic infants, relieving congestive failure and improving CNS function. It also corrects hypoglycemia, relieves respiratory distress and cyanosis, and improves renal function.

Partial exchange transfusion should be done as the venous hematocrit (Hct) approaches 65% and as symptoms appear; 5% albumin or crystalloid is suggested as replacement for the removed aliquot of blood. With the advent of stricter precautions for prevention of viral transmission by blood products, use of fresh-frozen plasma would not seem advisable.

The formula for calculating the partial replacement of blood volume is

\[
\text{Replacement} = \frac{\text{Observed Hct} - \text{Desired Hct}}{\text{Observed Hct}} \times \text{Blood volume}
\]

**Collaborative Management of the Infant with Polycythemia**

The care of any newborn infant should include a screening hematocrit determination for polycythemia by 12 hours of age. This allows both detection of any infant with polycythemia and adequate observation before symptoms become apparent. Because the initial sample usually is obtained by heel stick or finger stick, detection of a high value should be followed by venipuncture confirmation. The infant should be kept adequately hydrated and closely monitored for hypoglycemia and hypocalcemia. A hematocrit value over 65% should prompt careful observation of the infant for any symptoms associated with hyperviscosity. If symptoms appear, the infant
should undergo partial exchange transfusion. During the partial exchange, the same care should be provided as that given during a single-volume or double-volume exchange transfusion.

**COMMON COAGULATION DISORDERS IN THE NEWBORN**

**Hemorrhagic Disease of the Newborn**
The liver produces most of the clotting factors, including those of the prothrombin complex. Adequate function of this complex requires the specific action of vitamin K, which is continuously synthesized by bacteria in the bowel. Vitamin K is not directly involved in the synthesis of these factors but is required for the conversion of precursor proteins produced by the liver into active factors having coagulant capabilities. Vitamin K is especially necessary for conversion of prothrombin binding sites into forms that can bind calcium, which is required for the completion of many steps in the clotting cascade.

Vitamin K-dependent factors reach approximately 30% to 70% of adult levels in the cord blood of term infants but quickly drop to half that amount if the infant is not given vitamin K. Because these factors are gestational age dependent, the more premature the infant, the lower the levels at birth. The exaggerated drop after birth may be due to poor placental transfer of maternal vitamin K, immature liver function, and delayed synthesis of vitamin K by the bowel. Vitamin K-dependent factors slowly rise but do not reach normal adult levels until approximately 9 months of age. Administration of approximately 25 mcg (0.025 mg) of vitamin K can prevent this decline and normalize the prothrombin time.

Hemorrhage during the early neonatal period that can be attributed to a deficiency of vitamin K–dependent factors is classified as hemorrhagic disease of the newborn, of which there are three identified forms. The early form, the least common, is not directly involved in the synthesis of these factors but is required for the conversion of precursor proteins produced by the liver into active factors having coagulant capabilities. Vitamin K is especially necessary for conversion of prothrombin binding sites into forms that can bind calcium, which is required for the completion of many steps in the clotting cascade.

Vitamin K-independent factors reach approximately 30% to 70% of adult levels in the cord blood of term infants but quickly drop to half that amount if the infant is not given vitamin K. Because these factors are gestational age dependent, the more premature the infant, the lower the levels at birth. The exaggerated drop after birth may be due to poor placental transfer of maternal vitamin K, immature liver function, and delayed synthesis of vitamin K by the bowel. Vitamin K–dependent factors slowly rise but do not reach normal adult levels until approximately 9 months of age. Administration of approximately 25 mcg (0.025 mg) of vitamin K can prevent this decline and normalize the prothrombin time.

Controversy continues over whether intramuscular or oral prophylaxis should be used. At one time, intramuscular administration of vitamin K was linked to the occurrence of childhood cancers; however, this charge has not been substantiated by research. The use of one or two oral doses of vitamin K as an effective treatment is also disputed, and research is needed to determine its efficacy. Research continues in an effort to determine the appropriate timing and number of oral doses of vitamin K and to develop a better oral preparation. Alternative therapies are also being investigated, including antenatal maternal dosing to prevent antenatal intraventricular hemorrhage and postnatal maternal dosing as prophylaxis in the breastfed infant.

Kumar and colleagues (2001) reported that premature infants have high plasma vitamin K levels in the first 2 weeks of life as a result of intramuscular and parenteral supplementation. These researchers measured vitamin K levels in infants who were given 1 mg of vitamin K intramuscularly at birth and who then were given vitamin K parenterally at a dosage of 60 mcg/day for those less than 1000 g and 130 mcg/day for those weighing more than 1000 g. This research suggests
that further studies need to focus on vitamin K levels in the premature infant and attempts need to be made to determine the adequate dose.

Active bleeding caused by hemorrhagic disease of the newborn may require blood replacement or the use of fresh-frozen plasma for immediate clotting factor replacement.

Hemophilia Pathophysiology

Hemophilia A and B are the most common inherited bleeding disorders. Classic hemophilia (hemophilia A) is the most frequently inherited coagulation abnormality, accounting for 90% of all genetically linked coagulopathies and 80% to 85% of all hemophiliacs, whereas hemophilia B occurs in 10% to 15%. Both diseases are passed from mother to son as an X-linked trait. Hemophilia A is caused by factor VIII deficiency and hemophilia B is caused by a factor IX deficiency. Both factors are essential in normal thrombin production. They are needed for the activation of pathway of factor X, which converts prothrombin to thrombin. The absence of either factor severely impairs the body’s ability to generate both thrombin and fibrin. A hemophilic’s problem is not that of deficiency, the infant should also be evaluated for von Willebrand disease.

Diagnosis

Infants affected with hemophilia have a prolonged partial thromboplastin time and decreased factor, but the prothrombin time, thrombin time, and platelet count are relatively normal. The major symptom of hemophilia is bleeding, most often from the circumcision site, scalp, umbilicus, and brain. Not all severe hemophiliacs bleed after circumcision in the early newborn period. The reason for this is unknown, but it has been suggested that tissue thromboplastin release, caused by the circumcision clamp on the foreskin, may initiate the extrinsic pathway and clotting cascade, preventing excessive bleeding.

Prenatal diagnosis is possible, but the results are not always accurate. Diagnosis involves measurement of the ratio of factor antigen to coagulant antigen on blood samples of fetuses of more than 20 weeks’ gestation. If diagnosed with Factor VIII deficiency, the infant should also be evaluated for von Willebrand disease.

Treatment

The ultimate goal of treatment for hemophilia is to raise the defective or deficient factor to a level that will prevent bleeding. In order to have replacement products be as free as possible of transfusion-transmissible diseases, it is recommended that recombinant products be used rather than plasma-derived products. Recombinant factor VIII concentrates are preferred for hemophilia A, whereas either plasma-purified factor IX or a monoclonal immunosuppressant is preferred for hemophilia B.

Desmopressin (DDAVP, 1-desamino-8-D-arginine vasopressin) is now the treatment of choice for mild to moderate hemophilia A, in patients who have shown a response to the drug in trials. This medication is not effective in the treatment of hemophilia B. The effectiveness and applicability of this therapy in the newborn is still unknown, but currently it is not recommended if the infant is younger than 3 months of age. Amicar, an antifibrinolytic agent, is also showing some benefit in the treatment of hemophilia.

Thrombocytopenia

The normal range of platelets is 150,000 to 450,000/mm$^3$; the average count in the newborn is approximately 250,000/mm$^3$. Platelet counts below 150,000/mm$^3$ are considered abnormal and should be subject to investigation for a possible pathologic process. Platelet function in the neonate reaches normal adult levels between the fifth and ninth postnatal days. Although 14% of all preterm infants and 4% of all term infants are thrombocytopenic, with platelet counts below 150,000/mm$^3$, not all of these infants are ill.

Thrombocytopenia is the most common bleeding disorder in the newborn; 20% of all NICU admissions have platelet counts below 50,000/mm$^3$, and 80% of sick infants have counts below 100,000/mm$^3$. However, the pathogenesis of the thrombocytopenia can be determined in only 60% of these infants. Abnormalities of the platelet count are due to increased destruction or decreased production, and the underlying cause is mediated by maternal, placental, neonatal, or iatrogenic factors. In most thrombocytopenic newborns, platelet counts are low as a result of increased destruction rather than bone marrow depression. The overall mortality rate for infants with thrombocytopenia is 34%; 22% of these infants exhibit a bleeding diathesis. Infants with a platelet count below 20,000/mm$^3$ are at particularly high risk for bleeding.

Maternal Factors

Thrombocytopenia is the most common form of hemostatic problem present during pregnancy; 5% to 7% of healthy mothers have platelet counts below 150,000/mm$^3$. Some of the maternal factors associated with thrombocytopenia are maternal drug ingestion (e.g., chloramphenicol, hydralazine, tolbutamide, and thiadiazides), maternal eclampsia and hypertension, placental infarction, and immune-mediated maternal platelet antibodies.

Immune-Mediated Maternal Platelet Antibodies

Idiopathic Thrombocytopenia. With immune-mediated thrombocytopenia, in which maternal antibodies destroy platelets, 80% of cases are caused by the autoimmune form, or maternal idiopathic thrombocytopenic purpura (ITP), which strikes women during the second to third decade of life. ITP, now also referred to as autoimmune thrombocytopenia, is a pre-existing condition in which maternal lymphocytes produce IgG antiplatelet antibodies (PAIgG) that attack maternal platelets, usually reducing the platelet count to below 150,000/mm$^3$. These antibodies are specifically directed at platelet antigen and bind to platelets, which are then phagocytosed by cells carrying a specific receptor, the Fc receptor. The greatest number of cells with this receptor are found in the reticuloendothelial system of the spleen, which is
also the major site of PAIgG production. ITP is often confused with HELLP syndrome, which, in addition to a low platelet count, involves hemolysis and elevated liver enzymes. Because IgG can cross the placenta, fetal platelets can also be destroyed by the transplacental passage of platelet antibodies, resulting in thrombocytopenia in the fetus and newborn. The mortality rate is 1% to 10% in these affected infants, and the condition can persist postnatally for as long as 4 months.

**Neonatal Alloimmune Thrombocytopenia.** The remaining 20% of immune-mediated thrombocytopenias are caused by an alloimmune (isoimmune) reaction in which maternal antibodies are produced against foreign fetal platelets (paternally inherited), whereas maternal platelet levels remain normal. This reaction occurs when fetal platelets, which have an antigen not found on maternal platelets, pass into the maternal circulation. The resultant generation of maternal antibodies in response to the fetal platelets is similar to the mechanism behind Rh incompatibility. Unlike Rh incompatibility, alloimmune thrombocytopenia affects 33% to 50% of first pregnancies. The mother develops IgG antibodies that eventually cross into the fetal circulation, resulting in platelet destruction. The PIA1 alloantibodies are responsible for 50% to 80% of neonates with alloimmune thrombocytopenia. This phenomenon occurs in approximately 1 in 2000 to 1 in 5000 live births. The mortality rate of 10% to 15% in alloimmune thrombocytopenia is higher than that in ITP, because bleeding tends to be more severe. The incidence of intracranial hemorrhage in utero is reported to be as high as 10% to 15%, with most cases occurring between 30 and 35 weeks’ gestation. Treatment consists of transfusion of maternal platelets, exchange transfusion, and use of IVIG. Platelets usually normalize in the newborn by 4 weeks of age.

**Antenatal Treatment.** Antenatal treatment is not universally agreed on, but several sources suggest administration of corticosteroids 1 to 2 weeks before delivery and administration of multiple aliquots of IVIG within 7 to 9 days of delivery. Steroids and IVIG are theorized to work in similar fashion by (1) diminishing the production of antiplatelet antibodies, (2) interfering with antibody attachment to the surface of the platelets, and (3) reducing platelet destruction by interfering with phagocytic receptors in the reticuloendothelial system. Suggested steroid therapy consists of prednisone (1 to 2 mg/kg/day, orally) for 2 to 3 weeks. When the desired increase in platelet count occurs, usually within 3 weeks, the dose is tapered to a level that will maintain a platelet count over 50,000/mm³. IVIG can be administered in several different doses and for different lengths of time, but the regimen most often used is 400 mg/kg/day given intravenously for 5 days, with an increase in the platelet count expected within 7 to 9 days. In patients who are unresponsive to these two therapies, splenectomy may be necessary to remove the major site of antibody production and platelet destruction.

Serious bleeding during labor and delivery occurs only in infants with platelet counts below 50,000/mm³. Scalp sampling in fetuses of mothers with ITP and delivery by cesarean section of infants with platelet levels below 50,000/mm³ are recommended.

**Postnatal Treatment.** Postnatal treatment consists of platelet transfusion, exchange transfusion with blood less than 2 days old, steroid therapy (prednisone, 1 to 5 mg/kg/day), and IVIG. The major difference in therapy between ITP and alloimmune thrombocytopenia is the use of washed, irradiated, maternal platelets in infants with alloimmune thrombocytopenia.

**Neonatal Factors**

Neonatal factors associated with thrombocytopenia include asphyxia, an Apgar score of less than 7, disseminated intravascular coagulation, exchange transfusion, infection, smallness for gestational age, necrotizing enterocolitis, hyperbilirubinemia and phototherapy, meconium aspiration, cold injury, polycythemia, pulmonary hypertension, and cardiopulmonary bypass procedure. Treatment of thrombocytopenia caused by neonatal factors consists initially of amelioration of the underlying problem, followed by symptomatic treatment with platelet transfusion. Transfusion therapy should be considered if platelet counts are in the range of 50,000/mm³ to 100,000/mm³ and active bleeding is present. Platelet transfusion should be considered when the level is below 50,000/mm³ even if active bleeding is not present.

A helpful formula for estimating the rise in platelets after transfusion is as follows: one tenth the volume (in milliliters) of a unit of platelets per kilogram of weight raises the platelet count by 50,000/mm³.

**Disseminated Intravascular Coagulopathy**

Disseminated intravascular coagulation (DIC) is marked by a generalized deficiency of coagulation factors and platelets, which leaves the infant predisposed to hemorrhage. Because this condition is triggered by a pre-existing illness and does not occur independently, treatment consists of identification and resolution of the underlying problem. Releases of tissue factor and substantial injury to endothelial cells are the two major mechanisms that precipitate DIC (Mitchell & Cotran, 1999). The factors most often associated with bleeding that occurs secondary to DIC are obstetrical complications, respiratory distress syndrome, hypoxia, hypotension, necrotizing enterocolitis, and sepsis. Occasionally thrombosis of large vessels can trap platelets and consume an amount of clotting factors sufficient to cause DIC. Mortality rates reach 60% to 80% in infants with DIC who experience severe bleeding.

The hematologic picture of DIC (Table 10-8) reflects a depletion of platelets, prothrombin, fibrinogen, angiotensin III (AT III), protein C, and Factors V, VIII, and XIII. The prothrombin time and partial thromboplastin time are prolonged and are not corrected by the addition of fresh-frozen plasma to the blood sample. The fibrinolytic system is also stimulated, as evidenced by the presence of degradation products of fibrinolysis (i.e., fibrin degradation products or fibrinolytic split products). A commonly used test, measurement of d-dimer, serves as an evaluation of the activation of the fibrinolytic system in that it measures degradation of cross-linked fibrin. However, the d-dimer test may not be very helpful in the newborn because the result commonly is positive in infants who do not have a consumptive coagulopathy.

Successful treatment of DIC depends on alleviation of the underlying cause. Palliative treatment consists of replacement of deficient clotting factors with fresh-frozen plasma and cryoprecipitate, platelet transfusions, and exchange transfusion. Heparin is used infrequently because it carries a higher risk of hemorrhage; it is used only when large-vessel thrombosis occurs.
Differential Diagnosis of Newborn Coagulopathies

Analysis of a number of factors often can aid in the identification of the specific coagulopathy affecting an infant. Careful evaluation of the following factors can pinpoint the correct diagnosis and influence the choice of therapy or intervention:

- A familial history of a bleeding disorder, such as hemophilia
- A maternal history of a bleeding disorder, as in autoimmune thrombocytopenia
- An obstetrical history that suggests a possible abnormality, as in maternal alloimmunization or hypofibrinogenemia
- An adverse neonatal history, such as with hypoxia or asphyxia
- Failure to administer prophylactic vitamin K at birth
- Physical manifestations of a bleeding disorder (e.g., obvious bleeding, the presence or absence of petechiae or ecchymosis) and the infant’s overall condition
- Laboratory data that identify specific abnormalities, such as specific coagulation factor deficiencies, thrombocytopenia, and prolonged prothrombin time, partial thromboplastin time, and clotting times

Collaborative Management of a Coagulopathy

Care of an infant with a bleeding diathesis should be aimed at prevention of further injury or bleeding. Supportive care of fragile tissue and limiting the number of blood draws from sites other than central catheters are of great importance in the infant who lacks adequate clotting factors to control bleeding. Appropriate administration of platelets, clotting factors, or blood products requires the correct equipment, the correct method of administration, and conscientious monitoring of vital signs to ensure effective therapy without causing further harm to the infant. Wise decisions regarding replacement blood products are now important in light of the severe and potentially lethal sequelae of acquired infection. Adopting guidelines for transfusion therapy may safeguard infants and eliminate unnecessary exposure to blood products (Table 10-9). Monitoring of laboratory tests to determine continuing needs and the efficacy of therapy is important throughout the infant’s course of therapy.

When blood or blood products are administered, the infant must be evaluated continuously for signs of fluid overload and untoward reaction. Although blood reactions are rare in the newborn, they tend to occur within the first 15 minutes of blood or blood product administration. Signs of such reactions include rashes, tachycardia, hypertension, hematuria, cyanosis, and hyperthermia. Throughout the acute course of illness, the hematocrit values and the state of perfusion, rather than the percentage of the infant’s blood volume removed, should govern the decision on whether to transfuse. Symptoms of hypovolemia include metabolic acidosis, hypotension, poor perfusion, tachycardia, cyanosis, and shock.

BLOOD COMPONENT REPLACEMENT THERAPY

Whole Blood

This product is not used for routine volume expansion because of the hematocrit dilution that occurs. It is used in surgical procedures that require large volumes of blood for replacement, for exchange transfusions, and for priming heart-lung oxygenators for extracorporeal membrane oxygenation.

Packed Red Blood Cells

Blood is “hard spun” to concentrate cells and allow the supernatant to be removed. Because of this form of preparation, less volume can be administered. Packed RBCs can be reconstituted with normal saline, 5% albumin, or fresh-frozen plasma. Packed RBCs can be used in exchange transfusions or in the treatment of anemia in the acutely ill or symptomatic convalescent infant.

Washed Red Blood Cells

For additional protection, RBCs can be washed to remove as much of the plasma, nonviable RBCs, WBCs, and metabolic wastes as possible. To further eliminate the possibility of a graft-versus-host reaction, cells can be irradiated with 5000 rad; this prevents T-lymphocyte proliferation and, when done in conjunction with washing, can remove up to 95% of T lymphocytes.

Frozen Deglycerolized Red Cells

Frozen storage of deglycerolized RBCs allows preservation of rare units of blood, but the cost of preparation increases considerably. In addition, this product tends to have a higher potassium content and hemoglobin concentration. Centrifuging it, removing the supernatant, and diluting it to the desired hematocrit tend to control these problems.

Fresh-Frozen Plasma

A whole unit of fresh-frozen plasma can be thawed, but once entered, it is good for only 6 hours. If, however, it is packaged in aliquots, such as a quad pack, before freezing and then thawed, the quad pack unit is good for 24 hours once it has thawed. Fresh-frozen plasma provides a rich source of coagulation factors; 10 to 15 ml/kg, which contains 1

<table>
<thead>
<tr>
<th>TABLE 10-8</th>
<th>Hematologic Findings in Disseminated Intravascular Coagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematologic Feature</strong></td>
<td><strong>Finding</strong></td>
</tr>
<tr>
<td>Uniformity of clotting defect</td>
<td>Variable</td>
</tr>
<tr>
<td>Capillary fragility</td>
<td>Usually abnormal</td>
</tr>
<tr>
<td>Bleeding time</td>
<td>Often prolonged</td>
</tr>
<tr>
<td>Clotting time</td>
<td>Variable</td>
</tr>
<tr>
<td>One-stage prothrombin time</td>
<td>Moderately prolonged</td>
</tr>
<tr>
<td>Partial thromboplastin time</td>
<td>Prolonged</td>
</tr>
<tr>
<td>Fibrin degradation products</td>
<td>Present</td>
</tr>
<tr>
<td>Factor V</td>
<td>Diminished</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Often diminished</td>
</tr>
<tr>
<td>Platelets</td>
<td>Often diminished</td>
</tr>
<tr>
<td>Red cell fragmentation</td>
<td>Usually present</td>
</tr>
<tr>
<td>Response to vitamin K</td>
<td>Diminished or absent</td>
</tr>
<tr>
<td>Associated disease</td>
<td>Severe; may include sepsis, hypoxia, acidosis, or obstetric accident</td>
</tr>
<tr>
<td>Previous history</td>
<td>Associated diseases; administration of vitamin K</td>
</tr>
</tbody>
</table>

international units/ml of all clotting factors, raises the overall level of clotting factor activity by 20% to 30%. Fresh-frozen plasma often can normalize prolonged prothrombin and partial thromboplastin times in the newborn who has a generalized deficiency in quantity and activity of available clotting factors.

**Platelets**
The number of platelets available for circulation after transfusion depends on the storage time. In transfusions using platelet bags less than 7 days old, the rise in platelet levels is comparable to the rise seen with the use of fresh platelets. Use of packs older than 7 days achieves only 70% of the rise seen with the use of fresh platelets. Platelets also can be concentrated by centrifuge if smaller volumes are required. An important caveat: platelets require a special administration set for proper infusion.

**Granulocytes**
Granulocytes, which are used for infusion in septic infants with severe neutropenia, are prepared from fresh donor blood through the process of plasmapheresis. WBCs are removed from the unit of blood, but a large number of RBCs remain. For this reason, the donor unit must be typed and cross-matched to the infant for blood type and Rh compatibility. WBCs are usually irradiated to eliminate donor T cells in an effort to prevent graft-versus-host responses. The use of granulocyte transfusions remains controversial.

**Cryoprecipitate**
This form of plasma preparation is rich in Factors VIII and XIII and fibrinogen and is useful in the treatment of hemophilia. Because it is a single-donor collection, the risk for infection is lower than with pooled substances. Each unit of cryoprecipitate transfused raises fibrinogen levels by 200 mg/dl per 100 ml of the infant’s blood volume.

**Factor Concentrates**
Factor concentrates are used as specific therapy for identified factor deficiencies. They are obtained from pooled plasma and expose the recipient to multiple donors, thereby increasing the potential for infection, especially with hepatitis B, CMV, and AIDS. Eighty percent of cases of hepatitis B-infected blood can be identified by the third-generation screening tests, and blood screening is also available for CMV. Because the risk for transmission of HIV is increased by pooled concentrates, it is now recommended that concentrates be treated with heat, solvent, steam, detergent, or ultraviolet light to kill any virus that may be present. Currently it is unclear whether such treatment alters or inactivates the clotting activity of factor concentrates.

<table>
<thead>
<tr>
<th>Hematocrit (%)</th>
<th>Ventilator Requirements or Symptoms</th>
<th>Transfusion Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hct ≤ 35/Hb ≤ 11</td>
<td>Infants requiring moderate or significant mechanical ventilation (mean airway pressure over 8 cm; H2O and fractional concentration of oxygen in inspired gas [FiO2] over 40%)</td>
<td>15 ml/kg of packed red blood cells (PRBCs) over 2 to 4 hours</td>
</tr>
<tr>
<td>Hct ≤ 30/Hb ≤ 10</td>
<td>Infants requiring minimal mechanical ventilation (any mechanical ventilation or continuous positive airway pressure [CPAP] ≥6 cm; H2O and FiO2 ≤ 40%)</td>
<td>15 ml/kg PRBCs over 2 to 4 hours</td>
</tr>
</tbody>
</table>
| Hct ≤ 25/Hb ≤ 8 | Infants receiving supplemental oxygen who do not require mechanical ventilation, but for whom one or more of the following is a factor:  
  - Tachycardia (heart rate over 180) or tachypnea (respiratory rate over 80) for 24 hours or longer  
  - Increased oxygen requirement from the previous 48 hours; specifically, a fourfold or greater increase in nasal cannula flow (e.g., 0.25 to 1 L/min) or an increase in nasal CPAP of 20% or more from the previous 48 hours (e.g., 10 to 12 cm H2O)  
  - Elevated lactate concentration (2.5 mEq/L or higher)  
  - Weight gain of less than 10 g/kg/day over the previous 4 days while receiving at least 100 kcal/kg/day  
  - Increase in episodes of apnea and bradycardia (more than nine episodes in a 24-hour period or two or more episodes in 24 hours requiring bag and mask ventilation) while receiving therapeutic doses of methylxanthines  
  - Surgery | 20 ml/kg PRBCs over 2 to 4 hours (if infant is fluid sensitive, divide into two 10 ml/kg volumes) |
| Hct ≤ 20/Hb ≤ 7 | Infants without any symptoms who have an absolute reticulocyte count under 100,000 mcl* | 20 ml/kg PRBCs over 2 to 4 hours (if infant is fluid sensitive, divide into two 10 ml/kg volumes) |

*The absolute reticulocyte count is determined by multiplying the number of red blood cells by the percentage of uncorrected reticulocytes.

Case Study

IDENTIFICATION OF THE PROBLEM

A 6-day-old infant is admitted to the neonatal intensive care unit (NICU) with a history of jaundice and lethargy from her local pediatrician’s office. A total serum bilirubin (TSB) test drawn at the pediatrician’s office had a result of 42 mg%.

ASSESSMENT: HISTORY AND PHYSICAL EXAMINATION

The baby girl was born at 36 weeks’ gestation at 3.16 kg to a 24-year-old gravida 1, para 1 mother of Macedonian descent. The pregnancy was complicated by positive maternal group B bacterial streptococcal cultures, and the mother was treated with penicillin chemoprophylaxis. The baby was born by a spontaneous vaginal delivery without complications. The baby was vigorous at birth with Apgar scores of 8 and 9. The mother’s blood type was O Rh positive, and the infant’s type was A Rh positive. The Coombs’ test was positive. The breastfed infant had an unremarkable course but was noted to be jaundiced at 30 hours of age. A TSB test was done with a result of 12.9 mg%. She was discharged home at 40 hours of age.

On admission to the NICU, the infant was noted to be severely jaundiced but pink. Her vital signs were within normal limits (NL), with an axillary temperature of 98.4° F, heart rate of 130 beats/min, respiratory rate of 62 breaths/min, and blood pressure of 58/35 mm Hg with a mean of 45 mm Hg. Her weight on admission was noted to be 2.78 kg, a 12% loss. Her examination was nonremarkable, except for her decreased response to stimuli, poor muscle tone, poor suck, and a decreased Moro reflex. Her glucose screen was 55.

DIFFERENTIAL DIAGNOSIS

Many conditions are known to cause jaundice and lethargy in the newborn. The most common are hyperbilirubinemia, ABO incompatibility, G6PD, hypothyroidism, dehydration secondary to inadequate breast feeding, sepsis, and kernicterus.

DIAGNOSTIC TESTS

To determine the cause of the jaundice and lethargy, a CBC with differential, repeat TSB, electrolytes, calcium, glucose, liver function tests, and T4/TSH, G6PD screen, a hemoglobin electrophoresis, and blood culture all need to be ordered.

WORKING DIAGNOSIS

The baby’s repeat bilirubin was 43%; her CBC showed a WBC of 12.1/mm³, with 35% segs and 4% bands; her hemoglobin was 10.1 g%; her hematocrit was 28.5%; and her reticulocyte count was 2%. The G6PD screen was adequate. Electrolytes, liver function tests, calcium, and glucose were within normal limits, and free T4 was 1.3 ng/dl (NL: 0.9 to 2.1), but TSH was 24.98 milli–international units (NL: 1.7 to 9.1). The hemoglobin electrophoresis was “A, F.” These test results suggest a working diagnosis of hyperbilirubinemia secondary to ABO incompatibility and hypothyroidism.

DEVELOPMENT OF MANAGEMENT PLAN

The main goal for an infant with a bilirubin of 43% is to reduce the bilirubin level as quickly as possible to prevent kernicterus. While the blood is being typed and cross-matched, the infant needs to be placed in a neutral thermal environment, made NPO, have a peripheral IV placed, begin D10 with 0.2 normal saline with 20 mEq KCl/L at 120 ml/kg/hr, and started on antibiotics. An attempt should be made to do a cutdown of the umbilical cord to place an umbilical vein and arterial catheter for the exchange transfusion. Double phototherapy lights need to be started as well.

IMPLEMENTATION AND EVALUATION OF EFFECTIVENESS

A double volume exchange transfusion was done over several hours. The infant received a calcium and glucose boluses during the transfusion for low calcium and glucose. Phototherapy lights were continued after the transfusion. Her laboratory tests of TSB, electrolytes, CBC with differential, glucose, and calcium were repeated after the exchange transfusion was completed. Her postprocedure TSB level was 24.6%.

During the exchange the baby became apneic, which required her to be intubated and ventilated for 2 days. She received antibiotics for 3 days and phototherapy for 5 days and was started on Synthroid for her abnormal TSH.

On day of life 12, the TSB was 10.1 mg%. On examination, the infant was slightly hypertonic. A BAER was normal, but an MRI was consistent with kernicterus. She was discharged home with a referral made to the neonatal developmental clinic and early intervention to follow her developmental status.
REFERENCES


