Clinicians who care for newborns are all too frequently faced with the desperate situation of the seriously bleeding neonate. In this article I will present a practical approach to rapid diagnosis and treatment, founded on utilization of a few laboratory tests and basic clinical judgment.

Most serious bleeding episodes in newborns can be quickly diagnosed and managed. Generally “sick infants” bleed as a secondary phenomenon of their sickness. These newborns require vigorous support with blood products, as well as aggressive therapy for the underlying disorder. “Healthy” infants who bleed usually have primary coagulation defects that are either hereditary or immune-mediated. Therapy for them is designed to correct the specific coagulation defect.

continued
HEMOSTASIS IN THE NEWBORN

The coagulation pathways that lead to normal hemostasis in the adult also apply to the newborn. Platelets adhere to damaged endothelial surfaces and undergo a release reaction that results in the formation of a platelet plug. Soluble plasma proteins react in an orderly cascade (Figure 1) and organize fibrin into a tight clot.

Although there are no qualitative differences between clotting in adults and clotting in newborns, there are significant quantitative differences. Since there is no transplacental passage of soluble clotting factors from the mother to the fetus, all of the clotting factors measured in the cord blood and in the newborn have been synthesized by the fetus. Fetal production of the vitamin-K–dependent factors (II, VII, IX, and X) is relatively poor, and as a result there is a relative deficiency of these factors in the newborn. For example, the cord blood of healthy full-term infants contains only from 30 to 70 per cent of the normal adult values of factors II, VII, IX, and X, and these vitamin-K–dependent factors are even lower in premature infants.

As Figure 1 indicates, these four factors are represented in the laboratory tests for both prothrombin time (PT) and partial thromboplastin time (PTT). Thus, one must remember

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**Figure 1.** The coagulation cascade.

- ☐ vitamin-K–dependent factors
- ☐ other coagulation factors
when examining the neonate’s laboratory tests that the normal values for factors II, VII, IX, and X will differ from adult norms (Table 1). During the first few days of life, the PT and PTT increase further, as the vitamin-K-dependent factors continue to slip. This post-natal decline can be prevented in term infants by prophylactic administration of vitamin K, although premature infants with transient hepatic immaturity may not respond optimally.

In the term infant who has received vitamin K, the PT reaches adult norms in several days, while the PTT can remain prolonged for several weeks. Of those coagulation factors that are not dependent on vitamin K, factors XI, XII, and XIII are only slightly reduced and factors I, V, and VII are normal.

The average normal platelet count in an adult varies from 200,000 to 400,000 platelets per cubic millimeter of blood. In the newborn, the platelet count is generally at least 150,000 or more. Platelets function normally in the newborn as measured by bleeding time.*

**GATHERING THE DATA**

In determining the cause of bleeding in a newborn, a history, physical examination, and laboratory tests are necessary.

**History.** The clues gained from a few pointed questions asked of the parents can be more valuable than any laboratory test. It is crucial to know about six things:

1. **Familial bleeding disorders.** Is there a history of hemophilia, von Willebrand’s disease, etc.?
2. **Was there a bleeding disorder following a previous pregnancy?**
3. **Maternal illness.** Does the mother have lupus erythematosus? Has she had — or does she now have — idiopathic thrombocytopenic purpura (ITP)?
4. **Maternal infection.**
5. **Did the mother take drugs before delivery (e.g., aspirin, coumarin, anticonvulsants)?**
6. **Has vitamin K been given to the infant?**

**Physical examination.** A rapid general physical assessment of the bleeding newborn

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* Some authors have reported transient abnormal function in the test tube, as measured by aggregometry.
should be made, particularly if immediate therapy is necessary and laboratory tests are either slow or unavailable. If the overall gestalt is that the baby is "sick" (acidotic, hypovolemic, hypothermic, septic, hypoxic, hypoglycemic, or very premature), the bleeding is likely to be a secondary phenomenon relating to disseminated intravascular coagulation (DIC) or peripheral platelet destruction. However, if the baby appears "healthy" (term, vigorous, feeding well, not distressed, and without evidence of systemic problems or physical anomalies), it is much more likely to be due to a primary bleeding disorder. In this case, inherited bleeding disorder, immune thrombocytopenia, or vitamin-K deficiency are the possibilities.

Further clues come from the nature of the bleeding:

Small sprays of petechiae, small superficial ecchymoses, and bleeding from the gastrointestinal or central-nervous-system mucosa are commonly associated with thrombocytopenia.

**Localized bleeding** due to trauma — e.g., cephalohematoma, intramuscular hematoma secondary to vitamin-K administration, umbilical stump hematoma, postcircumcision bleeding — can be indicative of factor deficiencies.

**Generalized bleeding** from skin, mucous membranes, venipuncture sites, the gastrointestinal tract, or the renal or central nervous systems can result from DIC, vitamin-K deficiency, and severe liver disease.

**Laboratory tests.** The only laboratory tests that will be needed in the vast majority of cases to clarify a diagnosis of bleeding in the newborn are the platelet count, PT, and PTT. These routine tests are helpful when considered in the context of normal values for age (Table 1) and of the possibilities for laboratory error (Table 2).

**Platelet count** can be measured directly or quickly estimated by examining the peripheral smear. To estimate the platelet counts, count the number of platelets per oil immersion field and multiply by 15,000. Thus, 10 platelets per oil immersion field would indicate a platelet count of 150,000. A normal count will range between three and 10 platelets per field. The count may be falsely lowered by measuring from a heelstick, since the platelets adhere to the cut surface. It is essential to make a simultaneous platelet count on the mother in isolated thrombocytopenia.
**TABLE 2**

CAUSES OF LABORATORY ERRORS IN COAGULATION SCREENING TESTS

<table>
<thead>
<tr>
<th>Error</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count falsely low</td>
<td>Platelets adhered to heelstick, not counted</td>
</tr>
<tr>
<td>PT and PTT falsely long</td>
<td>Decreased plasma/citrate due to either too small a sample or a hematocrit greater than 60%</td>
</tr>
<tr>
<td>PT and PTT falsely long</td>
<td>Contaminated heparin</td>
</tr>
<tr>
<td>PT and PTT falsely short or long</td>
<td>Sample contaminated with tissue thromboplastin from difficult venipuncture</td>
</tr>
</tbody>
</table>

*PT and PTT*. These tests measure all the soluble clotting proteins. These values will be falsely high if too small a blood sample is put into the citrate tube or if the hematocrit is greater than 60. This occurs because of the disproportionately high citrate/plasma ratio and can be corrected by collecting the sample in the tube with half the citrate removed. Another source of error is contamination with heparin in the IV line, which will greatly elevate the PTT and may slightly affect the PT. A difficult, lengthy venipuncture, with associated tissue trauma and contamination of the needle with tissue thromboplastin, may result in an unreliable PT and PTT.

**THE DIFFERENTIAL DIAGNOSIS**

The steps to follow in the differential diagnosis will, of course, depend upon whether the infant presents as a “sick” or “healthy” neonate (Table 3).

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**TABLE 3**

DIFFERENTIAL DIAGNOSIS OF BLEEDING IN THE NEONATE

<table>
<thead>
<tr>
<th>Laboratory studies</th>
<th>Likely diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets</td>
<td></td>
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<tr>
<td>“Sick” infants</td>
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<td>Decreased</td>
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*from Glader and Buchanan*
Sick newborns. Platelet count, P, and PTT are the tests to use.

*Decreased platelets, increased PT, increased PTT.* This is an indication of DIC—a common phenomenon secondary to hypoxia, hypothermia, acidosis, hypovolemia, infection, or tissue necrosis. The clotting mechanism is inappropriately activated, consuming platelets and soluble clotting proteins. Serious generalized bleeding may result, or there may be merely a derangement of laboratory values without clinical manifestations.

Therapy is aimed at treating the underlying disorder (e.g., shock, sepsis, etc.) In symptomatic patients, replacement of the consumed clotting factors is necessary. Fresh platelet concentrates are given every 12 to 24 hours along with 10-15 cc/kg of fresh-frozen plasma (Table 4). In patients who continue to bleed despite intensive replacement therapy, exchange transfusion may be helpful. Heparin therapy is usually not helpful in this setting unless the major manifestations of the DIC are thrombosis (e.g., purpura fulminans) and not hemorrhage. Under these circumstances heparin is used at 10-15 U/kg/hour as a continuous infusion. Once heparinization is complete, replacement therapy is continued.

*Increased platelets, normal PT and PTT.* Peripheral destruction of platelets without DIC is commonly seen in infants with bacterial or viral infection or tissue necrosis (e.g., toxic enterocolitis). In fact, thrombocytopenia is one of the most common early warnings of sepsis in a child. Therapy is directed at treating the underlying disorder and supporting with platelet transfusion in symptomatic patients.

*Normal platelets, increased PT, increased PTT.* This may be a sign of either severe liver disease or of heparinization.

Patients with severe liver disease may have a generalized bleeding disorder secondary to multiple clotting-factor deficiencies. They are generally unresponsive to vitamin-K administration and, because of poor clearance, will have increased fibrin-split products. Thrombocytopenia may result from hypersplenism, making the differential diagnosis between liver disease and DIC difficult. Obvious clues are elevated liver enzymes and direct hyper-

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**TABLE 4**

**THERAPY FOR NEWBORN BLEEDING DISORDERS**

**Platelet transfusions**

*Indications:* (1) thrombocytopenia + bleeding
(2) platelet count \( \leq 20,000 \)

*Source:* random donor platelets for all cases except isoimmune thrombocytopenia (use mother’s platelets resuspended in AB+ plasma)

*Dose:* 1 unit will result in platelet count \( \geq 100,000 \)
unless there is rapid peripheral destruction

*Frequency:* normal survival = 8 days, less if rapid peripheral destruction occurs

*Hazards:* will clot off arterioles if injected into arterial system and cause liver damage if injected into portal system; give through peripheral IV only

**Fresh-frozen plasma transfusion**

*Indications:* bleeding with low clotting factor levels

*Dose:* 10-15 ml/kg.

*Frequency:* q. 12 hours

**Steroids**

*Indications:* bleeding from thrombocytopenia with failure to correct platelet count with transfusion

*Dose:* prednisone, 2 mg/kg. (or its equivalent)

*Frequency:* daily

**Exchange transfusion**

*Indications:* serious bleeding from thrombocytopenia and/or clotting-factor deficiency uncontrollable by replacement therapy

*Technique:* use either
(1) fresh whole blood or
(2) stored blood with platelet supplement, repeat as necessary
bilibinemia. Therapy includes support with fresh-frozen plasma and vitamin K.

Rarely, a newborn will be inadvertently heparinized by the heparin used to keep several IV lines open. Reversal of the heparin effect can be accomplished by administering protamine on a milligram-for-milligram basis.

**Normal platelet count, normal PT, normal PTT.** These values will be found in severely sick or premature infants who have massive intracranial or pulmonary hemorrhages without evidence of coagulation defect. They presumably have local vascular damage, with resulting bleeding. Treatment with blood products is of no help.

**Healthy newborns.** Hemorrhage may be due to thrombocytopenia, hemorrhagic disease of the newborn, inherited coagulation disorders, trauma, or vascular anomalies.

**Decreased platelets, normal PT, normal PTT.** Healthy infants with early onset of platelet-type bleeding and thrombocytopenia usually have immune-mediated thrombocytopenia. This is a passively acquired disorder, with antiplatelet antibody passing from mother to fetus. There are two main types, isoimmune thrombocytopenia and immune thrombocytopenia due to maternal idiopathic thrombocytopenic purpura.

**Isoimmune thrombocytopenia** is analogous to Rh incompatibility. The mother is lacking platelet antigen PLA-1, and the fetus is PLA-1–positive. Fetal platelets have crossed into the mother's circulation early in pregnancy and have caused her to make anti-PLA-1 antibody. This antibody crosses the placenta and destroys the baby's PLA-1–positive platelets. Although most of these infants tolerate their thrombocytopenia without problem, some do suffer severe intracranial hemorrhage either just before or just after delivery. The diagnosis rests on clinical grounds, since determination of platelet type is not a routinely available test. A history of a previously affected sib is most helpful.

Therapy for these infants with platelet counts under 30,000 or with clinical symp-

toms is the prompt administration of maternal platelets carefully washed and resuspended in AB-positive plasma. These compatible platelets will have a normal survival and be gone in several days. Random donor platelets are not helpful, since 97 per cent of the population is PLA-1–positive. Although

97 per cent of the population is PLA-1–positive

the thrombocytopenia may persist for a few months, subsequent maternal platelet transfusions are not indicated unless the child is symptomatic. For subsequent pregnancies, elective cesarean section is recommended to reduce the incidence of intracranial hemorrhage.

When **immune thrombocytopenia** is due to maternal idiopathic thrombocytopenic purpura, the antiplatelet antibody formed by the mother is directed not only against the infant's platelets but against her own as well. This is a much more serious situation, since there are no compatible platelets that will survive in the affected newborn. The diagnosis is a clinical one, based on the early

continued
finding of thrombocytopenia in a healthy baby with either accompanying thombocytopenia in the mother or with a maternal history of idiopathic thrombocytopenic purpura or systemic lupus erythematosus. Fortunately, most infants do not become symptomatic, but some suffer intracranial hemorrhages either just before or after delivery.

The chance that thrombocytopenia will develop in the infant varies inversely with the mother’s platelet count — the higher the count, the less likelihood the newborn will develop the disorder.10 (The mother with ITP who has a normal platelet count may still have circulating antibody, and her infant may thus be affected.)

Elective cesarean section is indicated for all gravidae with active ITP and probably indicated for most with a past history of the disorder.

Treatment of the symptomatic infant or of one with fewer than 20,000 platelets per cubic millimeter of blood is prednisone (2 mg./kg./day). Severely affected infants may respond to exchange transfusion and platelet transfusion.

Nonimmune thrombocytopenia is due to bone marrow failure. This condition is exceedingly rare in newborns. When it is present, the most easily recognized syndrome is the thrombocytopenia-absent radii syndrome (TAR), which is easily diagnosed on the basis of several congenital and skeletal anomalies of the upper extremities (illustration, page 55).11 Normal platelets, increased PT, increased PTT. These findings are associated with hemorrhagic disease of the newborn. Most infants are relatively deficient in vitamin K at birth, and the condition grows worse during the first few days of life unless it is corrected with prophylactic administration of this vitamin.

The classic picture of hemorrhagic disease of the newborn is of an otherwise healthy infant who has diffuse bleeding on the second, third, or fourth day of life. Treatment for severe bleeding includes fresh-frozen plasma.

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coming next month:

THE PEDIATRICIAN AND THE ANEMIC CHILD

- Anemia in the newborn
- Hypoplastic anemias
- Nutritional anemias
- Sickle-cell disease

Blanche Alter, M.D., Samuel E. Lux IV, M.D., Bertram Lubin, M.D.,
William C. Mentzer Jr., M.D., Elliott Vichinsky, M.D.,
Winfred C. Wang, M.D., Lawrence C. Wolfe, M.D.
Guest Editor: Bertil E. Glader, M.D., Ph.D.
Normal platelets, normal PT, normal PTT. Hemorrhages in most healthy infants with these findings will be due to local trauma or to local vascular anomalies. A healthy child with normal clotting studies will rarely have a deficiency of factor XIII (fibrin-stabilizing factor), which could result in a bleeding disorder characterized by delayed localized bleeding from trauma (e.g., one or two days after birth or after circumcision).

Specific assays of factor XIII are available for the infant with a factor XIII deficiency. Hemorrhage in a healthy infant with normal findings may also be due to maternal aspirin ingestion—a qualitative platelet disorder with a normal platelet number that results in bleeding. After the aspirin clears, platelet transfusion will reverse the bleeding tendency.

BIBLIOGRAPHY