Hematologic and Oncologic Complications in the Critically Ill Child

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Admission of a patient to an intensive care unit for management of direct consequences of a hematologic or oncologic disease is occasionally necessary. Such problems included exchange transfusion, sepsis, compression of vital structures by malignant tumor, metabolic derangements, leukostasis, post-operative care, major sickling episodes in vital organs, and disseminated coagulopathy. More often, however, hematologic complications arise in the child critically ill from other causes, such as trauma or infections. The first two sections of this review address blood transfusion and hemostasis, topics likely to have wide application in the care of critically ill children. The last portion discusses problems unique to patients with sickling or malignant disease.

TRANSFUSION THERAPY

Blood transfusion, like medicine, is often a valuable adjunct in the care of the critically ill patient. However, wide availability and ease of administration of blood components may result in overuse and false complacency about the inherent risks of blood products. Physicians and others who prescribe and use transfusions can maximize efficiency and minimize hazards by (1) proper selection of the recipient and the correct blood component, (2) meticulous labeling of blood samples and verification of patient identity, (3) appropriate mechanical handling of blood and infusion apparatus (Table 1), and (4) early recognition and treatment of transfusion reactions. The use of blood products in pediatric medicine and surgery employs, with few exceptions, separated components of blood rather than whole blood (Table 2) [1–4].

Whole blood is indicated for the treatment of massive blood loss with shock, cardiopulmonary bypass, or exchange transfusion. Hypothermia should be prevented, especially in infants, by warming donor blood in an approved warming apparatus. Blood should never be warmed in water or by exposure to unregulated heat, since hemolysis may result and produce consumptive coagulopathy in the recipient. Conversely, blood should never be stored in an unapproved refrigerator because of cellular lysis and protein denaturation which accompany repeated warming and cooling. Microaggregate filters with pore size of 10–40 μ are available [5] and remove debris in stored blood which would not be trapped by the 170 μ mesh filters used routinely in blood administration. The clinical utility of these filters appears to be limited, however, in that they have not decreased the severity of the respiratory distress syndrome in massively transfused adults [6,7]. Microaggregate filters have been associated with hemolysis in neonates [8].
Extreme hypovolemia can be treated with normal saline, Ringer's lactate, 5 percent albumin, or 5 percent plasma protein fraction [9] while blood is being prepared. In the face of brisk or massive hemorrhage, restricting the amount of blood replacement to a certain volume is futile, especially when the patient continues to bleed during the transfusion. In this critical situation, at least one large intravenous catheter must be used to provide adequate access for transfusion, and the rate and volume of transfused products must be gauged by the level of central venous pressure, or pulmonary wedge pressure, and pulse and respiratory rates, blood pressure, urine output, and estimated amount of blood lost.

Exchange transfusion is used to remove circulating nondialyzable toxins, to correct life-threatening anemia or profound coagulopathies, to remove transplacentally acquired antibodies in the neonate, or to temporarily replace inherently abnormal red cells. Whole blood exchange can be accomplished by the "push-pull" method through a single catheter in a large vein, or, in older patients, by phlebotomy from one extremity and replacement into another.

Total blood volume approximates 70–80 ml/kg in most pediatric patients, or 7 percent of body weight in grams in adults [10], and this amount of blood exchanged will effectively remove about 75 percent of the child's own plasma and cells. Formulae have been devised for more precise calculations if needed [11,12].

The routine availability of citrate-phosphate-dextrose-adenine preservative and anticoagulant has virtually eliminated the need for emergency collection of fresh
| Whole Blood                        | Fresh Frozen Plasma | 5% Albumin   | 5% Plasma Protein Fraction | Cryoprecipitate | Packed Red Cells | Platelets | Granulocytes |
|-----------------------------------|---------------------|--------------|-----------------------------|-----------------|-----------------|-----------|--------------|
| Hypovolemic shock from trauma or bleeding | Replacement of multiple or unknown coagulation factors | Hypovolemia Phlebotomy replacement | Hypovolemia Phlebotomy replacement | Deficiencies of factors I, VIII, XIII, fibronectin | Severe anemia | Thrombocytopenia (productive defect) | Infection with severe neutropenia or neutrophil dysfunction |
| Massive blood loss                |                     |              |                              |                 |                 |           |              |
| Exchange transfusion              |                     |              |                              |                 |                 |           |              |
| Cardiopulmonary bypass            |                     |              |                              |                 |                 |           |              |
whole blood [13]. Whole blood less than five days old, or packed cells reconstituted with plasma, can be used to replace blood removed by exchange transfusion. A small fraction, about 15 percent, should be administered as fresh frozen plasma to prevent severe dilutional deficiencies of coagulation factors.

Occasional complications of exchange or massive transfusion are acidosis, hypocalcemia, or hyperkalemia [11,12,14,15]. Acidosis is temporary and mild and usually does not require correction. Hypocalcemia from citrate chelation is unusual but may occur in the face of hepatic disease. Symptoms or electrocardiographic changes can be treated with intravenous calcium gluconate, 0.5–1.0 ml of a 10 percent solution for each 100 ml of blood transfused. Alkalosis and hypokalemia are also effects of citrate toxicity. Hypokalemia is correctable with intravenous potassium solutions. Hyperkalemia may result from anion leakage in blood stored longer than five days and can be prevented by using erythrocytes with shorter storage time. Hyperkalemia has also been reported in fresher blood [16] and as a complication of forcing blood through microaggregate filters [8].

**Blood Components**

*Albumin or plasma protein fraction* (PPF) as 5 percent solutions provide rapid colloidal expansion of blood volume [1,9]. Both materials are widely available and are minimally capable of transmitting hepatitis. Either product is recommended for treatment of hypovolemia without blood loss, particularly when cardiovascular stability is not regained by giving normal saline or other crystalloid.

Both albumin and PPF are administered in amounts required to replete intravenous volume and to stabilize the patient’s vital signs. PPF can produce paradoxical hypotension when infused rapidly.

*Plasma* is frequently required to replace coagulation factors in patients with acquired or congenital deficiencies of clotting proteins [2,3]. Fresh frozen plasma (FFP) contains all coagulation factors and is the component of choice to treat an unknown type of hemophilia or the patient with multiple clotting deficiencies. Patients with congenital deficiencies of factors II, V, VII, XI, and sometimes IX are treated with FFP for hemorrhage.

Massive transfusions for blood exchange or severe hemorrhage should include a portion of FFP (1 unit for adolescents and adults, 10–15 ml/kg for children) for each blood volume transfused to correct dilutional deficiencies of coagulation factors.

*Plasmapheresis*, or the exchange of plasma from an individual without removal of cells, has become possible in adults and older children through the use of the cell separator [17,18]. Plasmapheresis has been used with variable results in critically ill patients with juvenile rheumatoid arthritis, dermatomyositis, lupus, circulating anticoagulants, Goodpasture’s syndrome, myasthenia gravis, cancer, poisoning, and thrombotic thrombocytopenic purpura. The mechanisms of action are removal of immune complexes, immunoglobulin, or various substances inflammatory to tissues, or replacement of factors missing from the patient’s plasma. The therapeutic efficacy and toxicities of this expensive procedure and the relationship to concomitant immunosuppressive chemotherapy are currently obscured by the lack of controlled prospective studies.

*Cryoprecipitate*, prepared from slowly thawed plasma, contains fibrinogen, factor VIII (antihemophilic factor), factor XIII (fibrin-stabilizing factor), and fibronectin, an opsonin derived from fibroblasts. Cryoprecipitate is impure and con-
taminated with plasma proteins and hepatitis virus but offers a concentrated form of factors I, VIII, and XIII for treatment of hemophilia A, von Willebrand disease, factor XIII deficiency, hypofibrinogenemia, or dysfibrinogenemia. Cryoprecipitate comes in "bags," or "units," the amount of material obtained from one unit of plasma, with an estimated volume of 15 ml. These "units" should not be confused with factor VIII units: there are 80-120 factor VIII units in each "unit" of cryoprecipitate.

**Red blood cells**, the most frequently used blood component, are prepared by sedimentation or centrifugation. Packed cells are appropriate transfusional therapy for severe anemia or substantial subacute blood loss without hypovolemia. If extreme viscosity prevents an appropriate rate of flow, normal saline can be added.

For euolemic patients with a hemoglobin > 5 g/dl, 15 ml/kg/24 hours of packed cells can be transfused over one to two hours, provided there is no cardiovascular or renal compromise. If the hemoglobin is < 5 g/dl, the amount transfused should be reduced to the hemoglobin level: for example, the patient with a hemoglobin of 3 can safely receive 3 ml/kg of packed cells. After an equilibration period of four to six hours, another small transfusion can be administered.

The volume of packed cells needed to produce a calculated increment in hematocrit in the child who is **not bleeding** can be estimated by the following formula:

\[
\Delta \text{hematocrit} = \frac{\text{number of ml of packed cells/kg body weight}}{\text{ml/kg of packed cells}}
\]

This calculation assumes a blood volume of 75 ml/kg in the recipient and a hematocrit of 75 percent (25 g of hemoglobin) in each unit of packed cells. The volume transfused should not exceed 20 ml/kg/24 hours, less in individuals with cardiac or renal compromise or severe anemia.

Packed red cells can be washed or frozen to remove the buffy coat and residual plasma and reduce minor transfusion reactions, particularly fever and urticaria [4]. Patients who need repeated transfusions often develop such reactions from plasma proteins or leukoagglutinins and should receive washed, leukocyte-poor red cells for subsequent transfusions. This technique can also be used for IgA-deficient recipients. Frozen glycerolized red cells age little and have long storage life [19]. Frozen cells are indicated for persistent leukoagglutinin reactions and for antigenic compatibility for patients with hemolytic reactions to minor blood groups.

The child with severe autoimmune hemolytic anemia presents the clinician with special problems for transfusional therapy. Since most antibodies acquired to erythrocytes are directed against one or more antigens of the Rh system and/or against complement, it is virtually impossible to obtain compatible erythrocytes by routine cross-matching. The technician or physician performing cross-match procedures for these patients may be reluctant to release incompatible red cells for transfusion. However, erythrocytes which are the most compatible will be hemolyzed no more rapidly than the patient's own cells and are used for emergency transfusion. Some specialists in transfusional therapy recommend a small test dose initially to insure against major blood group incompatibility, since the presence of the autoantibody prevents accurate cross-matching.

**Platelet transfusions** are properly utilized for a severely thrombocytopenic or thrombasthenic patient who is bleeding or for whom surgery or other traumatic therapy is anticipated [4,20]. Young children, in particular, can tolerate extreme thrombocytopenia with a minimum of dangerous spontaneous bleeding. In
premature infants and adolescents, the bleeding risk becomes somewhat higher with platelet counts < 10-20,000/mm³. Cutaneous ecchymoses and petechiae are not harmful and should not be used as an indication for platelet transfusion. The occurrence of raised mucosal purpura on the tongue or buccal mucosa, severe epistaxis, or large scleral hemorrhages, although usually not life-threatening in themselves, tend to identify the patient at a higher risk of serious spontaneous bleeding. Platelet transfusion should be administered immediately for thrombocytopenic patients with neurologic signs, sudden hypotension, melanotic stools, hematemesis, or hemoptysis.

A separate school of thought supports the practice of administering platelet transfusions prophylactically in patients with faulty platelet production [21]. Transfusions are given to maintain a platelet count > 20,000/dl for the duration of thrombocytopenia. Hemorrhagic episodes are reduced initially by this practice, but later are poorly controllable because transfusion-induced autoantibodies allow little or no platelet survival. Surely this approach is warranted, however, in patients who have a separate bleeding tendency or whose disease or age confers a higher risk of bleeding.

If intramuscular injections of medication are necessary, they may be administered sparingly by using a small needle, minimizing the patient's movement during injection, and applying pressure with an ice pack at the injection site.

Patients whose thrombocytopenia results from inadequate platelet production (aplastic anemia, acute leukemia) benefit the most from platelet transfusion. One unit of platelets per square meter surface area will raise the unsensitized patient's platelet count by about 10,000 [4,21]. Normal platelet survival of seven to ten days can be expected initially, but autoantibodies to exogenous platelets develop rapidly, and subsequent platelet transfusions produce lower increments with shorter survival. Histocompatible platelets harvested from a single donor often produce a better yield in these multiply transfused patients. Very slow constant infusions of platelets may also improve hemostasis.

Children with destructive or autoimmune thrombocytopenia have decreased platelet survival from transfusions. In patients with autoimmune disease, corticosteroid therapy often improves hemostasis and may reduce the rate of endogenous platelet destruction.

**Granulocyte transfusions** are indicated for the patient with severe neutropenia (total neutrophil count < 200/mm³) or neutrophil dysfunction in whom prompt recovery is not expected, a severe infection has been documented, and response to appropriate antibiotics has not occurred within 24-48 hours [4,22-24]. White cell transfusions are particularly useful for septicemia or abscesses caused by gram-negative bacteria. Expensive and time-consuming to harvest, granulocytes are obtained by plasmapheresis of a single donor whose white cells are separated by differential centrifugation. Platelets can be retained with the white cells if needed. Granulocytes are transfused over four to six hours and the patient premedicated with acetaminophen and an antihistamine. Fever, chills, and urticaria are common reactions; acute respiratory distress—laryngospasm, anaphylaxis, pulmonary edema—is an unusual but severe complication [24,25].

The efficacy of granulocyte transfusions is evaluated by the patient's control of his infection. Foci of inflammation become more visibly inflamed in the presence of neutrophils, and abscess formation may be enhanced dramatically. The transfused
cells, having a normal circulation time of only a few hours, are not often reflected in the peripheral leukocyte count, since they migrate rapidly to sites of infection. At least four consecutive daily transfusions are necessary for efficacy.

Transfusion Reactions

Substances derived from human blood can certainly be life-saving but are not without risks and should be used with discretion. Potential hazards [26,27] of blood administration include (1) acute or delayed hemolysis from mismatched or damaged erythrocytes; (2) leukoagglutinin reactions (acute pulmonary edema, fever, chills); (3) hypersensitivity to plasma proteins (urticaria); (4) immunization of transfused cellular antigens not present on the recipient's cells; (5) nonbacterial infections—particularly from hepatitis B, non-A, non-B hepatitis, and cytomegalovirus—and occasionally parasites such as malaria [28-31]; (6) bacterial contamination of blood kept at room temperature for more than four to six hours; (7) engraftment of viable lymphocytes into a severely immunosuppressed or immune-deficient child with subsequent host-vs-graft disease [32]; (8) acquired immune deficiency syndrome; and (9) local pain or thrombophlebitis. All transfusion reactions should be reported to the blood bank.

Massive hemolysis from mismatched blood is a life-threatening complication of errors in cross-matching, labeling, or identification [26,33,34]. Acute hemolysis may also result from exposure to hypotonic solutions, thermal or mechanical injury, or oxidant drug exposure to donor cells deficient in G-6-PD. Early in the transfusion, the patient develops chills, myalgias, backache, fever, hemoglobinemia, and hemoglobinuria. Any symptoms suggestive of a major reaction which occurs while the transfusion is in progress require immediate discontinuation of the transfusion and prompt clinical assessment. There may be confusion over whether the symptoms are related to the transfusion in the child who is already ill. Samples of urine and centrifuged blood, obtained by venipuncture or finger puncture, can be examined for the presence of free hemoglobin. If hemoglobinuria or hemoglobinemia is apparent macroscopically—i.e., if the serum or urine is pink or red—intensive hydration should be begun and a brisk diuresis maintained with mannitol, 1-2 g/kg intravenously over 30-60 minutes, or furosemide, 1 mg/kg intravenously. The prevention or reversal of acute hypotension produced by the thromboplastic injury of red cell stroma is the most important aim of treatment. If profound, shock results in acute renal impairment, which may require fluid restriction or dialysis. While prophylactic heparinization has been advocated by some [33], anticoagulation is usually reserved for patients with generalized bleeding from disseminated intravascular coagulation [34].

Simultaneous with the administration of fluids should be an immediate investigation of the reaction by the blood bank. This evaluation requires immediate reporting of the reaction, repeat identification of the recipient, a sample of the recipient's blood, and the remainder of the donor blood with its container and tubing taken to the blood bank.

Delayed immune hemolysis, with the clinical picture of autoimmune hemolytic anemia days to weeks after transfusion, can result from incompatibility of minor blood group antigens [35].

Fever is the most common transfusion reaction among pediatric patients [36]. The transfusion should be discontinued if still in progress. In the absence of rigors,
chills, and myalgias, most pyrogenic reactions are produced by white cells, and there is no hemolysis. If there is any question as to whether hemolysis is present, the patient's serum and urine should be examined.

Patients who have sustained a febrile leukoagglutinin reaction can be spared subsequent reactions by removal of the buffy coat, washing plasma and leukocytes from packed cells, or giving frozen red cells. Fever may also be prevented with one oral dose of acetaminophen, 10 mg/kg, or aspirin, 15 mg/kg.

Acute urticaria [4,36] may accompany febrile reactions or may occur alone, usually at the end of blood administration. Hives are a manifestation of allergy to a component of plasma. The transfusion should be discontinued and the urticaria treated with diphenhydramine, 1–2 mg/kg intravenously, slowly. Urticaria can be prevented with subsequent transfusions by giving washed packed cells or pretreating the patient with oral diphenhydramine.

Acute pulmonary edema, anaphylaxis, and facial edema are rare but major reactions to leukoagglutinins, immunoglobulins, or other plasma proteins [4,25,36]. Recipients with severe IgA deficiency are prone to these reactions and should receive either blood from IgA-deficient donors or washed or frozen red cells.

Antibody formation to donor cells occurs regularly after multiple platelet transfusions and occasionally after red cell transfusions. The result is premature destruction of the transfused elements. HLA-matched platelets demonstrate better survival in vivo under these circumstances but their use requires prescreening of blood donors and expensive, time-consuming plasmapheresis of each donor. Red cell phenotypes of blood donors have been computerized in large cities so that, in some cases, a compatible donor can be located for the patient with multiple antibodies to minor erythrocyte antigens.

Hepatitis continues to be a clinical hazard for recipients of blood products. The availability of commercial antibody to hepatitis B antigen has enabled blood banks to exclude most donors with active hepatitis B infection. Non-A, non-B hepatitis and cytomegalovirus, frequent and ubiquitous subclinical infections in the community, are predominant causes of non-icteric hepatitis in recipients of blood products. The frequency of non-A, non-B hepatitis in volunteer blood programs has been estimated to be about 10 percent [2,29]. The larger the number of donors to a transfused product, the higher the hepatitis risk.

A newly recognized disorder, the acquired immune deficiency syndrome [37], is probably caused by an infectious agent which can be passed through blood products [38]. The disease begins by disruption of the cellular immunoregulatory system, causing a progressive decrement of helper (T4) lymphocytes [39]. An affected patient may then develop adenopathy, fever, weight loss, and malaise— the "pre-AIDS syndrome." Florid AIDS is associated with opportunistic infections, such as Pneumocystis carinii pneumonia or chronic systemic herpesvirus infections, and with malignancies such as Burkitt lymphoma or aggressive Kaposi sarcoma.

Transmission of AIDS in blood products, like hepatitis, appears to be more likely when large numbers of donors are used to make concentrated products for treatment of hemophilia. In addition to hemophiliac patients, a handful of individuals have contracted AIDS from routine uses of blood components.

Recommendations for protection of caretakers of patients with hepatitis or AIDS (or those at risk for either disease) include thorough hand washing, protection from secretions and excretions, and careful handling and disposal of needles and blood samples [40].
Children with severe deficiency of T-lymphocytes, congenital or acquired, have been engrafted with transfused lymphocytes and developed *host-vs-graft disease* [32,41]. About the density of erythrocytes, small lymphocytes sediment with red cells and are interspersed among other cellular components as well. T lymphocytes survive years in the circulation. Most lymphoid elements are disrupted by freezing and thawing but a higher proportion are killed by irradiation with 5,000 r. Although irradiation of blood products for all patients receiving immunosuppressive chemotherapy is probably neither warranted nor practical, those with extreme lymphopenia or a congenital deficiency of T lymphocytes or the thymus may be considered candidates for irradiation of all blood products.

**ABNORMALITIES IN HEMOSTASIS**

*Normal Coagulation*

Normal hemostasis requires the functional intercolation of platelets, coagulation factors, fibrinolysins, kininogens, complement, and leukocytes. These interwoven systems are constantly balanced by activators and inhibitors, many of which are found in normal tissues and plasma [42]. Disruption of homeostasis may or may not produce hemorrhage or thrombosis but often is reflected by abnormalities *in vitro*.

The initial event in hemostasis is formation of a platelet plug, or white thrombus, at the site of vascular injury (Fig. 1) [43,44]. Circulating platelets assume a spherical shape and adhere to exposed collagen [45]. Other platelets stick to the adherent cells to produce a reversible primary aggregate.

The platelet release reaction is a multifaceted event in which ADP is secreted from intrathrombocytic granules. Arachidonic acid metabolism is triggered in the platelet and endothelial membranes to produce prostaglandins—primarily thromboxane, a powerful stimulus to aggregation, and prostacyclin, a potent inhibitor [46,47]. Physiologic balance of platelet aggregation is mediated through cyclic AMP, which

**PLATELET FUNCTION**

![Diagram of platelet function](image)

**FIG. 1.** Formation of the normal platelet thrombus.
is lowered by aggregant stimuli and raised by inhibitors. This seesaw can be tipped in either direction by various pharmacologic agents [48-50]. The release reaction amalgamates the platelet plug into a gelatinous mass, from which platelet factor 3 activates thrombin, in turn promoting secondary aggregation. Contraction of thrombosthenin filaments causes retraction of the platelet plug, concomitant with fibrin formation and stabilization.

Clotting is initiated by surface contact, platelet factor 3, thrombin, endotoxin, or tissue thromboplastins [51,52]. Soluble coagulation factors become activated to form fibrin (Fig. 2). The clotting “cascade” is triggered along the intrinsic pathway (measured by the activated partial thromboplastin time, or PTT) by exposure to glass, kaolin, endotoxin, high-molecular-weight kininogen, or kallikrein (Fletcher factor) [53]. Natural inhibitors of coagulation are protein C, alpha-2-macroglobulin, alpha-2-antiplasmin, and the antithrombins, especially antithrombin III. The extrinsic route to fibrin formation is evaluated by the prothrombin time (PT) and consists of activation of the VII–X complex by fixed or circulating thromboplastins: amniotic fluid, placenta, lung, brain, erythrocyte membranes, leukocytes, venoms, toxins, or lipoproteins.

Both the extrinsic and intrinsic routes share a common final path through factors X, V, prothrombin (II), and fibrinogen (I) to the formation of urea-soluble fibrin. Factor XIII then strengthens molecular bonds between polymerized fibrin strands to render them insoluble [54].

Each coagulation factor circulates as the inert procoagulant which requires modification to become active. Many steps of clotting require cofactors, particularly calcium; these have been omitted from Fig. 2 in the interest of clarity. Small amounts of activated factors are stimulatory to the preceding steps of coagulation, but larger amounts are inhibitory.

All coagulation factors except VIII and XIII are synthesized in the liver. The prothrombin time is highly sensitive to subnormal levels and is prolonged in the presence of significant hepatic disease. Inherited deficiencies or severe defects in synthesis of factors I, II, V, or X produce abnormalities in both the PTT and the PT. In addition, II, VII, IX, and X are dependent on the availability of vitamin K for their production.

Normal neonates have low levels of vitamin K-dependent coagulation factors compared to the adult, even when replete with vitamin K [55–57]. Factors XI and XII are also subnormal at birth [58]. Prematurity exaggerates these physiologic hemostatic “abnormalities” [59,60]. Adult levels are reached by several months of age (Table 3).

Physiologic fibrinolysis occurs locally and perhaps even concurrent with coagulation. Plasminogen is converted to plasmin (fibrinolysin) through the effects of urokinase, streptokinase, activated factor XII, and thrombin to digest fibrin into smaller “split,” or “degradation,” products. Plasmin also activates several components of complement. Fibrinolysis is inhibited by alpha-2-antiplasmin, alpha-2-macroglobulin, antithrombin III, and EACA (epsilon-aminocaproic acid). In pathologic defibrination syndromes, fibrinolysis, like coagulation, may become diffuse and uninhibited.

**Assessment of Bleeding**

General clotting and fibrinolytic activity can be evaluated by a prothrombin time (PT), partial thromboplastin time (PTT), and thrombin time or fibrinogen level.
Partial Thromboplastin Time

Surface contact

Endotoxin

HMW kininogen

kinins

Prothrombin Time

Thromboplastins

HMW kininogen

kallikrein

XII

XI

AT III

IX

PC

VIII

VII

X

AT III

PC

V

II

Platelet aggregation

Thrombin Time

XIII

I_s

I_i

Fibrin degradation products

α-AP

Plasmin

(fibrinolysin)

Complement activation

urokinase

streptokinase

EACA, αMG, AT III

Plasminogen

--- = major inhibitors

AT III = antithrombin III

EACA = aminocaproic acid

αMG = α-2-macroglobulin

I_s = soluble fibrinogen

I_i = insoluble fibrinogen

α-AP = α-2-antiplasmin

PC = protein C

FIG. 2. Simplified schematic process of hemostasis and fibrinolysis.
TABLE 3
Normal Coagulation Values in Neonates*

| Coagulation Parameters | Premature Infant | Full-Term Neonate | Age Adult Levels Attained |
|------------------------|------------------|-------------------|--------------------------|
| Platelet count         | Normal           | Normal            |                          |
| (normal 150–300 x 10^3/mm³) |                  |                   |                          |
| Platelet function      | Aggregation      | Aggregation       | ?                        |
| (normal 12–14 seconds) | Prolonged        | Prolonged         | <1 week                  |
| Prothrombin time       | (12–21 seconds)  | (13–20 seconds)   |                          |
| Partial thromboplastin time | Prolonged  | Prolonged         | 2–9 months               |
| (normal 35–45 seconds) | (70–145 seconds) | (45–70 seconds)   |                          |
| Thrombin time          | Prolonged        | Prolonged         | <1 week                  |
| (normal 8–10 seconds)  | (11–17 seconds)  | (10–16 seconds)   |                          |
| Coagulation factors    |                  |                   |                          |
| VIII (nonhepatic)      | Low to normal    | Normal to high    |                          |
| XIII (nonhepatic)      | Normal           | Normal            |                          |
| V                      | Low normal       | Normal            |                          |
| I (fibrinogen)         | Low normal       | Normal            |                          |
| XI                     | Low              | Low               | 1–2 months               |
| XII                    | Low              | Low               | ?                        |
| K-dependent:           |                  |                   |                          |
| II                     | Low              | Low               | 2–12 months              |
| VII                    | Low              | Low               | 2–12 months              |
| IX                     | Low              | Low               | 3–9 months               |
| X                      | Low              | Low               | 2–12 months              |

*Modified from [55]

The combined use of these tests with the Ivy bleeding time provides a rapid examination of hemostasis (Table 4). All can be performed on one adequate sample anticoagulated with sodium citrate.

Many technical problems may be encountered in drawing blood samples. Commonly, venous access is limited or difficult, particularly in infants. Puncture of a deep vein is contraindicated in the bleeding patient. Venous samples obtained with difficulty may contain small clots, heparin-like substances, or thromboplastins from subcutaneous tissues. The presence of clots in the sample renders coagulation studies useless and does not assure that hemostasis is normal. Although direct venous sampling is preferred, heparinized catheters sometimes provide the only vascular access and sometimes can be used if the “dead space” of the line is completely cleared of all solutions by withdrawing at least 2–4 ml of blood prior to obtaining the sample for coagulation studies [61]. However, the heparin effect cannot always be removed by this technique. Heparin contamination affects the PTT and the thrombin time; heparin can be identified in the thrombin time by neutralization with toluidine blue or polybrene.

Accuracy of the PT and PTT is further enhanced by discarding 2 ml of blood prior to withdrawing coagulation studies by venipuncture. The sample should be transported expeditiously to the laboratory in ice.

The ratio of citrate to plasma in the blood sample should be 1:9; adult-sized tubes, which should be utilized as often as possible in pediatric practice, contain 0.5 ml of citrate and are filled with 4.5 ml of blood. This ratio is based upon a normal
**TABLE 4**
A Diagnostic Approach to Hemostatic Abnormalities Based upon Screening with the Prothrombin and Partial Thromboplastin Times

| Normal PTT, Normal PT | Normal PTT, Normal PT | Normal PTT, Normal PT | Normal PTT, Normal PT |
|-----------------------|-----------------------|-----------------------|-----------------------|
| Prolonged PTT, Normal PT | Prolonged PTT, Normal PT | Prolonged PTT, Normal PT | Normal PTT, Normal PT |

| Anticoagulants: | Vitamin K deficiency | *DIC | α2-antiplasmin deficiency |
| ----------------|----------------------|-------|--------------------------|
| Heparin Acquired inhibitor | Liver disease | *Dilution/loss of coagulation factors from massive hemorrhage or exchange transfusion | Factor XIII deficiency |
| Inherited coagulopathy | Factor II, V, VII, X deficiency or anticoagulants | Improperly drawn specimens | von Willebrand disease |
| *von Willebrand disease (PTT may be normal) | Coumarin | Severe liver disease | Vasculitis |
| (VIII, IX, XI, XII) | *Aspirin (high dose) | Deficiencies or inhibitors of factors I, II, V, X | Connective tissue disorders |
| Fitzgerald (HMW kininogen) factor deficiency | | Severe vitamin K deficiency | Surgical or traumatic hemorrhage |
| Fletcher (prekallikrein) factor deficiency | | Dysfibrinogenemia/hypo-fibrinogenemia | |
| Passovoy defect | | |
| Loss of factor IX (nephrosis) | | |
| Decreased synthesis (l-asparaginase) | | |

* *Ivy bleeding time may be prolonged
* Platelet count low

DIC = Disseminated intravascular coagulation

Hematocrit. For patients with polycythemia (hematocrit > 70 percent), an adjustment in either the amount of anticoagulant or the amount of blood must be made [62]. This alteration can be made using the formula:

\[ V(100 - \text{hct}) = S(640 - \text{hct}) \]

where \( V \) = total volume of blood + citrate and \( S \) = amount of citrate anticoagulant, or:

\[ \frac{45}{H} \times 0.05 \text{ ml} = C, \]

where \( H \) = patient's hematocrit and \( C \) = volume of 3.8 percent citrate needed for each 3 ml of blood drawn [63].

The platelet phase of coagulation is best measured by an Ivy or a Duke bleeding time. The Ivy bleeding time is a standardized superficial cut or puncture in the forearm [64]. Capillary pressure is raised to 40 mm Hg with a blood pressure cuff, and the wound is blotted lightly every 30 seconds until bleeding ceases. In small children or restless patients, the forearm should be stabilized by an assistant. The puncture method is two 3-mm punctures placed one to two inches apart. The Duke method uses a puncture of the ear lobe. Normal Ivy bleeding time is < 6 minutes for puncture methods and up to 12 minutes for some template methods. A prolonged bleeding time suggests thrombocytopenia, platelet dysfunction, or an abnormality in the vessels or connective tissue.
ACQUIRED ABNORMALITIES OF HEMOSTASIS

Decrease of coagulation and fibrinolytic factors may occur because of decreased synthesis, loss, increased catabolism, or inactivation by inhibitors. Inadequate synthesis may result from hypoproteinemia, deficiency of cofactors such as vitamin K, disruption of protein synthesis (l-asparaginase) [65] or protein-vitamin K interaction (coumarin), or liver failure (Table 5).

Vitamin K deficiency causes hemorrhagic disease in the following situations: (1) newborn infants not treated with prophylactic vitamin K; (2) older infants with malabsorption [66] or biliary atresia; (3) children of any age who develop acute malabsorption of vitamin K because of alteration or eradication of bowel flora by antibiotics [67]; and (4) some patients with hepatocellular injury [68]. Therapy consists of replacement of vitamin K by intramuscular, subcutaneous, intravenous, or oral routes. One mg given parenterally is more than sufficient to treat all infants and most young children. In the bleeding patient, intravenous administration may be preferred. Since intravenous use can produce hypotension or dyspnea, vitamin K should be given slowly, allowing at least one minute for each milligram to infuse. Although bleeding may cease, several hours are required for correction or improvement of the prothrombin time.

Competitive antagonism to vitamin K is a pharmacologic effect of coumarin [69] and a toxicity of phenytoin [70]. Both drugs can cause serious hemorrhage and should be immediately discontinued if bleeding occurs. Major hemorrhage is treated with large doses (1–20 mg) of vitamin K and transfusions of fresh frozen plasma.

Inadequate synthesis of coagulation factors also may result from hypoproteinemia or interference with protein synthesis from drugs such as l-asparaginase. Replacement of clotting proteins can be accomplished by using fresh frozen plasma in simple or exchange transfusions.

Loss of coagulation factors occurs through exchange transfusion or massive hemorrhage and can be prevented or corrected by using 10–15 ml/kg of fresh frozen plasma for each total-body volume (80 ml/kg) of blood replaced.

Children with nephrosis occasionally lose coagulation and fibrinolytic factors in the urine [71].

| TABLE 5 | Profile of Usual Hematologic Data in Acquired Hemostatic Failure |
|---------|---------------------------------------------------------------|
|         | DIC      | Liver Disease | Heparin Effect | Vitamin K Deficiency |
| Platelet count | 1 | Normal | Normal | Normal |
| Microangiopathic hemolysis | | | | |
| PT | 1 | 1 | Normal to 1 | Normal to 1 |
| PTT | 1 | Normal to 1 | Normal to 1 | Normal to 1 |
| Thrombin time | 1 | Normal to 1 | Normal to 1 | Normal to 1 |
| Factor I (fibrinogen) | Normal to 1 | Normal to 1 | Normal | Normal |
| V | 1 | Normal to 1 | Normal | Normal |
| VII | 1 | 1 | Normal | Normal |
| VIII | Normal to 1 | Normal to 1 | Normal | Normal |
| Fibrin degradation products | 1 | Normal | Normal | Normal |
Acute hepatic failure, exemplified by the Reye syndrome, often produces coagulopathies [72]. These coagulation deficiencies may be due to deficient synthesis of liver-dependent factors, deficiency or poor incorporation of vitamin K, or systemic fibrinolysis syndrome (DIC). Vitamin K and fresh frozen plasma, 10–15 ml/kg, are effective therapies unless DIC is continuous (see “Thrombosis”).

Post-operative hemorrhage after cardiopulmonary bypass is a frequent and troublesome complication in the pediatric intensive care unit [73–75]. Factors which increase the risk of bleeding are cyanotic cardiac lesions [63,76], abnormal hemostasis prior to surgery, prolonged time required on extracorporeal circulation, pre-operative use of salicylates or warfarin, vitamin K deficiency, hepatic injury, hypotension, and low cardiac output. Virtually all post-operative patients have dysfunctional platelets and a prolonged bleeding time. Heparin, used throughout the bypass procedure, is reversed with protamine sulfate at the conclusion. Protamine is catabolized more rapidly than heparin, producing a “heparin rebound” effect for which more protamine—25 percent of original dose, or 10–50 mg intravenously over five to ten minutes—may be required. Vitamin K, fresh frozen plasma, or platelet transfusions may be necessary to correct vitamin K deficiency, inadequate synthesis of coagulation factors, DIC, or post-bypass thrombathesia. Occasionally, generalized fibrinolysis may be a major factor and may improve with the use of anti-fibrinolytic therapy such as epsilon-aminocaproic acid [77]. If the coagulopathies are corrected and the patient continues to bleed, surgical exploration is indicated.

Functional defects in platelets are common and arise from such disturbances as uremia, contact with foreign surfaces, or medications.

Uremic patients often have defective platelet aggregation which is reversible with dialysis or transplantation [78,79]. Plasma factors responsible for this abnormality include guanidinosuccinic acid and phenols [80,81]. Cardiopulmonary bypass regularly reduces platelet adhesion and sometimes disturbs aggregation, with or without thrombocytopenia [82].

Since the discovery of malfunction of aspirinated platelets, a host of drugs has been studied, in particular certain ones now in use specifically to inhibit platelet adhesion and/or aggregation. These include aspirin, dipyridamole, nonsteroid anti-inflammatory agents, tricyclic antidepressants, anticoagulants, high-dose penicillins, diuretics, propranolol, some antihistamines, and some corticosteroids [83]. Although some of these drugs alter platelet-endothelial cell interaction, most prevent the release reaction by inhibiting enzymes pivotal in prostaglandin production. Severe thrombopathic bleeding is best treated by removal of an offending drug and local therapy. Occasionally, transfusions of normal platelets are necessary to provide hemostasis.

Thrombocytopenia results from inability to make platelets, from loss through massive hemorrhage or exchange transfusions, or from premature destruction or consumption.

Productive defects (aplastic anemia, bone marrow malignancy) are treated with transfusions of platelet concentrates (see “Transfusions”). Sensitization and formation of autoantibodies occur quickly, however, and the platelet yield and circulating time are progressively diminished. Hemostasis is sometimes possible in the patient refractory to random-donor platelets through the use of HLA-matched single-donor platelets; slow continuous infusions of random-donor platelets; avoidance of iatrogenic injury such as intramuscular injections and vigorous pulmonary toilet; and nasal and oral care, including prevention of mucosal cracking and ulceration.
and the use of topical thrombin or fibrin-promoting substances, epsilon-aminocaproic acid, nasal packing, or sedation.

Destructive thrombocytopenia is not so amenable to platelet transfusions, and therapy must be directed at the underlying cause (see "Thrombosis"). Autoimmune, or idiopathic, thrombocytopenia, a common disease, rarely causes life-threatening hemorrhage, but can be difficult to control in those instances. Treatment is aimed not only at attempting to replace platelets with large and frequent platelet transfusions, but also at dampening reticuloendothelial phagocytosis and suppressing production of antiplatelet antibody [84]. Therapies include high-dose steroids (4–8 mg/kg/day of prednisone); intravenous IgG, 200–500 mg/kg/day for four to five days [85,86]; intravenous vincristine as both an immunosuppressant and stimulant of platelet production; other immunosuppressants such as cyclophosphamide, azathioprine, or cyclosporin; danazol [87]; vinblastine-tagged platelets; splenectomy; and possibly plasmapheresis or exchange transfusion with immunosuppressive drugs [88,89].

Inhibitors

Antibodies, or inhibitors, to specific coagulation factors occur most frequently among boys with factor VIII deficiency but may also develop sporadically in healthy children or as one of the manifestations of systemic lupus erythematosus [90–95].

Inhibitors occur in 10–20 percent of boys with hemophilia A. The potency and level of antibody to factor VIII vary considerably among patients and in the same individual. These inhibitors are measured in Bethesda units, 1 B.U. being the amount of antibody which inactivates 0.5 unit of factor VIII. Boys with very low levels of inhibitor may not exhibit an anamnestic rise on repeated exposure to factor VIII—these selected patients can be treated with doses of factor VIII sufficient to overcome the inhibitor and produce adequate hemostasis. Low-titer inhibitors known to exhibit an anamnestic rise may be overcome with large doses of factor VIII for a few days before the anamnestic rise occurs [96]. With inhibitor levels > 30 B.U., the amounts, cost, and efficacy of factor VIII infusions become prohibitive.

Treatment of serious hemorrhage in the patient with a high-titer inhibitor is difficult [97,98]. Even large amounts of factor VIII are immediately inactivated unless the level of antibody can be lowered quickly by exchange transfusion or plasmapheresis. Any effort to remove circulating antibody should be accompanied by treatment with an immunosuppressant such as cyclophosphamide. Factor VIII from other species, such as porcine factor VIII, can be used to provide hemostasis for a short period before inhibitors or allergic reactions develop.

Concentrates of the vitamin K complex—factors II, VII, IX, and X—stop bleeding in about 50 percent of episodes in VIII-deficient patients [99–101]. This phenomenon occurs because activated clotting factors, especially Xa, can bypass the need for factor VIII to produce hemostasis. The clinical effect is variable and cannot be monitored by the PTT. The prothrombin complexes are thrombogenic in high dosage and can be administered only in short infusions over 20–30 minutes. Empiric dosage formulations are 25–75 units/kg every 8–12 hours.

Chronic management of the hemophiliac with a high-titer inhibitor includes (1) avoidance of factor VIII to prevent anamnestic antibody boosts, (2) daily infusions of high-dose factor VIII to suppress the inhibitor [102], (3) cyclophosphamide therapy [103], and (4) liberal use of prothrombin-complex concentrates.
Sporadic inhibitors to factors VIII or IX [104] sometimes develop acutely in otherwise healthy children. The appearance of these antibodies is often preceded by a viral illness. Supportive care is usually all that is required for this transient anticoagulant. Threatening hemorrhages can be managed with steroids, exchange transfusions (or possibly plasmapheresis), and appropriate replacement therapy.

CONGENITAL ABNORMALITIES IN HEMOSTASIS

Although bleeding in critically ill patients is usually ascribed to complications of major illness or injury, pediatric patients may also have a congenital hemorrhagic tendency. An accurate personal and family history of bleeding contributes heavily to the assessment. Bruising, petechiae, epistaxis, and menorrhagia suggest defective platelet function, while surgical hemorrhage or excessive hematoma formation may reflect deficiency of a coagulation factor.

Coagulation Factors

Several coagulation deficiencies exist which produce striking prolongation of the PTT but not clinical bleeding. These include factor XII (Hageman factor), prekallikrein (Fletcher factor), and high-molecular-weight kininogen (Fitzgerald factor) deficiencies [105].

Most patients with hemophilia have deficiencies of factors VIII or IX, both of which are sex-linked; a few have other forms of hemophilia, most of which are recessively inherited. Low levels of factor VIII, IX, XI, and XII produce an abnormally prolonged PTT but a normal PT, whereas VII deficiency gives a markedly long PT and a normal PTT (Fig. 2). Because of the sensitivity of the prothrombin time and the short biologic half-life of factor VII, deficient factors in the final common pathway usually produce a more pronounced abnormality in the PT than the PTT unless the deficiency is severe.

Treatment for the bleeding patient with hemophilia is to replace the appropriate clotting factor. In the younger who has an undefined type of hemophilia with a negative family history, “shotgun” therapy can be given with fresh frozen plasma (FFP) after blood samples have been obtained on which to perform appropriate factor assays. FFP contains all coagulation factors but, due to volume constraints in young children and infants, only low hemostatic levels of coagulation factors are achieved.

Factor VIII deficiency, or hemophilia A, is the most common severe congenital bleeding diathesis. Factor VIII is present in FFP (about 1 unit/ml), cryoprecipitate (about 7 units/ml), or lyophilized concentrates (10–35 units/ml) [106]. While volume considerations become less problematic as the potency of the material increases, the hepatitis risk increases. One unit of factor VIII/kg in these products will raise the patient's VIII level 2 percent; or, using a plasma volume of about 50 ml/kg, 100 percent VIII activity can be produced by giving 50 units/kg of factor VIII. In treating a major hemorrhage or providing hemostasis for surgery, this initial dose should be followed by continued replacement, either as a constant infusion or as bolus doses of 25 units/kg every 6 to 12 hours [107]. Ten to 20 percent of boys with hemophilia A develop an antibody, or inhibitor, against exogenous factor VIII; the management of these difficult problems has been discussed above.

Factor IX deficiency, hemophilia B, is less frequent than factor VIII deficiency, and is rarely complicated by inhibitor formation. Factor IX has a half-life of 24 hours in vivo. Each unit of factor IX per kilogram produces a rise of 1½ percent in
the patient. This substance is absent from cryoprecipitate but present in fresh frozen plasma or lyophilized concentrates, which also contain factors II, VII, and X. The concentrates, manufactured from large donor pools, are intensely contaminated with hepatitis B virus and should be used only in those patients who require large amounts of factor replacement.

_Rare hemophilies_ due to factor II [108], VII, V, or X deficiency are inherited as autosomal recessive genes. The PT is prolonged with deficiency of factor VII, while both PT and PTT may be affected by low levels of factors II, V, and X. Bleeding is unusual in the heterozygote, common in the homozygote. Treatment or operative coverage is fresh frozen plasma. The frequency of plasma infusions varies with the biologic half-life of each factor.

Deficiency of factor XI, a recessive gene common among Jews, may be mild (30–60 percent) in heterozygotes or severe (< 20 percent) in homozygotes [109]. Although spontaneous bleeding is uncommon, post-operative hemorrhage is not. Fresh or stored plasma is corrective for a few days.

Factor XIII deficiency is characterized by bleeding from the umbilical stump in infants, poor wound healing and post-operative hematomas, hemorrhagic pseudotumors, intracranial hemorrhage, infertility, and a high rate of spontaneous abortion. The deficiency is corrected by giving fresh frozen plasma, cryoprecipitate, or factor XIII concentrate every 3–4 weeks [54].

Afibrinogenemia (factor I deficiency) or hypofibrinogenemia in the congenital form is an uncommon cause of inherited bleeding diathesis. The PT and PTT are prolonged, clot formation poor or absent _in vitro_, and platelet adhesion often abnormal as well. Acquired hypofibrinogenemia may result from disseminated fribrinolysis or from autoantibody formation. Defective factor I, dysfibrinogenemia, is associated with similar laboratory findings and sometimes clinical bleeding [82].

The Passovoy defect is an unknown cause of mild prolongation of the PTT, bruising, menorrhagia, and hemorrhage after minor trauma or surgery. Levels of coagulation factors, high-molecular-weight kininogen, and prekallikrein are normal [110].

A paradoxical inherited bleeding disorder has been described in families with alpha-2-antiplasmin deficiency [111,112]. The PT and PTT are normal, but clot lysis time, urea solubility, and fibrin degradation products are abnormal.

*Platelet Disorders*

Thrombopathy, or platelet dysfunction, may be congenital or acquired [113–116]. Of the congenital thrombopathies, the most severe is Glanzmann's thrombasthenia, in which multiple aggregation defects are present. This is inherited as an autosomal recessive; affected persons have severe epistaxis, bruising, and menorrhagia. Other inherited thrombopathies (May-Hegglin anomaly, Bernard-Soulier syndrome) may be associated with thrombocytopenia and circulating megathrombocytes or platelet fragments. A release reaction defect results in thrombopathic bleeding in some patients with albinism [117].

The most common inherited abnormality of platelet function is von Willebrand disease, in which the platelet adhesive defect is caused by lack of the "von Willebrand factor" in plasma [118–120]. This defect is associated with low levels of factor VIII antigen and coagulant and is thought to be a deficiency or qualitative abnormality in the antigenic factor VIII molecule. Platelet aggregation is normal.
with all chemicals except ristocetin. Usually transmitted as an autosomal dominant, von Willebrand disease is extremely common and must be considered in any patient with a positive or suspicious family history of bleeding. It is notoriously difficult to diagnose because of independent fluctuations in bleeding time and factor VIII levels from very abnormal to completely normal values; at least two sets of normal data should be obtained before this diagnosis is discarded.

The surgical or bleeding patient with von Willebrand disease can be treated with fresh frozen plasma, 10–15 ml/kg, or with cryoprecipitate, \( \frac{1}{2} \) “bag” or “unit” per kilogram, followed by \( \frac{1}{4} \) “bag”/kg every 12 hours for two days, then daily. Desaminovasopressin (DDAVP) administration, intravenously or intranasally, corrects the von Willebrand defects and is used increasingly to prevent the need for blood products [121]. The bleeding time can be used as a guide to frequency of treatment.

Vasculitis, capillary abnormalities such as telangiectasia, connective tissue disorders (Ehler-Danlos, scurvy), Down’s syndrome, and viral diseases are all conditions in which platelet function may be normal and the bleeding time normal or prolonged. These patients may have petechiae, bruising, or purpura. Vasculitic lesions may be severe and crippling or superficial and mild. Oral, nasal, or intestinal telangiectasia may cause troublesome bleeding.

THROMBOSIS

Thrombosis results from a hypercoagulable state in which the balance between clotting and fibrinolysis has been disturbed [122–124]. The thrombotic tendency may result from (1) endothelial alteration (vasculitis, sickle cell disease), (2) presence of a foreign body or surface (catheters), (3) slowed blood flow with stasis (dehydration, hyperviscosity), (4) hyperfunctional platelets, (5) increased coagulant activity, particularly from thromboplastins, or (6) deficiency of fibrinolysins or coagulation inhibitors such as antithrombin III [125] or protein C [126–128].

Newborn infants appear to have an increased risk of both local and generalized clotting activity, even though their platelet function is sluggish [129] and many coagulation factors are low. Premature infants and those born to diabetic mothers are especially vulnerable to thrombosis [130].

Localized venous thrombi are unusual in children and adolescents and may represent a congenital deficiency of antithrombin III [125], protein C, or, paradoxically, some of the milder coagulation factors [122,124].

Thrombosis of large or small cerebral vessels may complicate severe hydration, cyanotic congenital heart disease, or sickle cell anemia. Hyperviscosity with hyperfibrinogenemia may play a central role in the pathogenesis of cerebrovascular accidents in these disorders. Treatment is correction of hyperviscosity by exchange transfusions or phlebotomy [76].

The tips of indwelling venous catheters often become enveloped in a fibrin “sleeve,” potentially a site for obstructive thrombosis. Thrombus formation can be reduced by irrigating the catheter with a heparin solution [131,132].

Any patient with deep venous thrombosis should be heparinized or treated with a fibrinolytic drug such as streptokinase [133,134]. In adults with pulmonary emboli or deep vein thrombosis, streptokinase has been more effective than heparin in reducing the occlusion without increased bleeding risk [135].

Arterial thrombi are precipitated by foreign bodies (catheters) or surfaces (artificial cardiac valves) which promote local platelet aggregation and clot formation.
Platelet-inhibiting drugs appear to decrease this risk in patients with unremovable artificial surfaces in the heart or vascular tree [136–138]. Heparin irrigations or continuous infusions decrease the frequency of thrombotic occlusion of peripheral catheters and of pulmonary infarction from catheters in the pulmonary artery [139].

Regional thrombosis, or microthrombus formation in a particular organ or region of the body, is exemplified by the hemolytic-uremic syndrome. Thrombi are well formed by the time the diagnosis is apparent, and supportive care remains the mainstay of therapy. The efficacy of fibrinolytic agents [133,134] is unknown and extremely difficult to evaluate in such an uncommon and variable disease.

Disseminated coagulation and fibrinolysis (DIC) [140] may complicate massive trauma, shock, low cardiac output, severe hypoxia, hemorrhagic shock-encephalopathy syndrome, venoms, head trauma [141], hemolytic transfusion reactions, administration of prothrombin-complex concentrates, or infection [74,142–144]. Infection is the most common precipitating event in children beyond the neonatal period, while hypoxia, acidosis, or infection triggers DIC in the neonate [60,145]. Bleeding and organ failure may or may not occur, and therapy is indicated if either complication is present. The best treatment for DIC is reversal of the underlying cause.

The classic form of disseminated fibrinolysis is thrombocytopenia, low levels of coagulation factors and fibrinolysins reflected in prolongation of the PT and PTT, microangiopathic hemolytic anemia, circulating degradation products of fibrin, and hemorrhage due to depletion of clotting proteins [146]. DIC produces a low level of factor V. Factor VIII, like fibrinogen, is an acute phase reactant, raised by inflammation and lowered by consumption, producing variable levels in DIC [147]. Thrombocytopenia is variable, tends to occur early in the course of DIC, and resolve last [148].

Neonates have physiologically low levels of factors II, VII, IX, X, XI, and XII at, and shortly after, birth, even with prophylactic administration of vitamin K [57,59,149]. Levels of factors V and VIII are normal in healthy infants (Table 3).

Treatment of the bleeding patient with DIC depends upon (1) adequacy of therapy for the primary illness, especially reversal of shock, and (2) whether the process of generalized coagulation continues unabated or subsides. If the process is subsiding, simple replacement of platelets and coagulation factors in the form of platelet concentrates and FFP should be sufficient to stop bleeding. Platelets normally survive in vivo about one week; a modified platelet survival study can be performed by obtaining a platelet count before, and one to two hours after transfusion, then daily. Similarly, coagulation factors in FFP should shorten the PTT for at least two hours and control bleeding for 24 hours or longer. Lack of clinical hemostasis or requirements for repeated transfusions of platelets and FFP at shorter intervals strongly suggest continuing DIC and document the patient’s candidacy for heparinization (see section following).

DIC must sometimes be distinguished from the coagulopathy of severe liver failure, in which levels of factors II, V, VII, IX, and X are depressed, producing prolongation of the PT and PTT (Table 5). Factor VIII, produced in endothelial cells, is high in liver disease and low in DIC. Liver failure in the absence of DIC does not produce microangiopathic red cell distortion, thrombocytopenia, and high levels of circulating fibrin degradation products.

Platelet consumption alone may occur in specific diseases of the newborn—cavernous hemangioma (Kassaback-Merritt syndrome) and necrotizing enterocolitis.
Thrombocytopenia is also a common manifestation of congenital viral and bacterial infections and is not necessarily a component of DIC in that setting.

**Heparin and Heparinization**

Heparin is a heterogeneous, high-molecular-weight mucopolysaccharide commercially prepared from animal viscera. The American USP unit is slightly more potent than the British, or international, unit. Commercial preparations of heparin contain at least 120 international units per milligram, and most products contain 130–170 international units/mg. Because of this variability, units rather than milligrams should be used whenever possible [150]. The pharmacologic half-life is variable and depends on dosage, the patient's level of antithrombin III, presence of pulmonary embolism, and ill-defined individual factors. Because of its large molecular size, heparin crosses into neither the placenta nor breast milk.

The activity of heparin depends upon the availability of antithrombin III (AT III), a physiologic inhibitor of thrombin (factor II), factor X, and other activated coagulation factors. Heparin alters AT III and/or prothrombin to facilitate rapid binding of AT III to prothrombin, thereby inactivating prothrombin. In situations in which AT III levels are diminished, such as inherited deficiency or consumptive coagulopathy, the activity of heparin will be commensurately absent or decreased [151,152].

Heparinization should be approached with caution in patients who have other conditions which in themselves produce risks of hemorrhage. These include a pre-existing bleeding diathesis, thrombocytopenia, concomitant anti-platelet drugs, intramuscular injections, uremia, or wounds. Conversely, patients with a previous history of thromboembolism or females taking oral contraceptives have higher risks of thrombus formation when post-operative or nonambulatory.

Side effects of heparin include hemorrhage (up to 20 percent), thrombocytopenia [153], and osteoporosis. Heparin is rapidly neutralized by protamine sulfate, which can be given in the event of serious hemorrhage. The amount of protamine required to reverse heparin effect decreases with time elapsed from heparin administration. After 30 minutes, 0.5 mg of protamine neutralizes 100 units of heparin [154].

Monitoring of the effect of heparin can be accomplished by several methods: (1) whole-blood clotting time which, although convenient, is imprecise and requires a waterbath; (2) thrombin time and the extent to which it can be reversed with protamine; (3) measurement of inhibition of factors II and Xa, which is costly and time-consuming; (4) plasma heparin assay; (5) the activated partial thromboplastin time, a reproducible, widely available method [152]; or (6) the activated whole-blood clotting time, a rapid, accurate bedside test [155,156]. Patients treated with prophylactic, or low-dose, heparin do not require monitoring, since the amounts of heparin administered do not produce abnormal values in tests of coagulation. Therapeutic dosages should produce a PTT of 50–80 seconds, or about 1½ times normal [157], or an activated whole-blood clotting time of 150–180 seconds [155].

**Prophylactic heparinization** There are a few situations in pediatrics in which preventive heparinization is indicated [158]. The child or adolescent with a history of thromboembolism who does not have a congenital deficiency of antithrombin III, and possibly young women taking oral contraceptives who require major abdominal or thoracic surgery, may benefit from low or “ultra-low” dose heparin (Table 6) [159]. The use of heparin to prevent thrombosis in orthopedic surgery is controversial: thrombus formation may be precipitated by trauma, and a heparin-induced
hematoma in the operative wound may negate the effects of surgery [150,158]. Prophylactic heparinization is sometimes used in acute promyelocytic leukemia (see "Complications of the Leukemias and Solid Tumors") [160].

**Therapeutic heparinization** Indications for heparinization in children include the following: (1) **Purpura fulminans**—These acute ischemic vasculitic lesions characteristically accompany meningococcemia but occasionally complicate acute viral illnesses. Heparinization appears to reverse the rapid progression of these lesions and may substantially reduce the necessity to amputate digits or distal extremities from ischemic necrosis. To be effective, treatment must be started as soon as purpura fulminans appears [147,161]. (2) Established **thrombosis** in a deep vein—Heparinization prevents growth of the clot and reduces the risk of pulmonary embolization. Since heparinization carries some risk of hemorrhage, documentation of deep vein thromboses should be obtained when possible. Lytic therapy with streptokinase is a new therapeutic alternative [135]. (3) Acute fibrinolysis (disseminated intravascular coagulation) causing significant bleeding in spite of replenishment of coagulation factors and platelets—During heparin administration, continued replacement of platelets and fresh frozen plasma is necessary. Heparin therapy for DIC may reverse fibrinolysis but does not affect survival, for which reversal of the underlying condition is necessary [149]. (4) Pulmonary embolism—If massive or if accompanied by shock, very large doses of heparin may be required (Table 6) [147]. Streptokinase therapy in lieu of heparin has shown promise in recent studies [135].

Therapeutic heparinization is accomplished by an initial loading dose of 50–75 units/kg, followed by a daily dose of 300–600 units/kg/24 hours, delivered by continuous intravenous infusion or by intermittent subcutaneous or intravenous injection every four hours [150,158]. Adults and adolescents can receive daily doses of 30,000–45,000 units. Infants require 20–25 units/kg/hour, somewhat higher than older children [162]. Continuous intravenous infusion requires a mechanical pump for accurate delivery but may cause fewer bleeding complications, is easy to monitor, and permits rapid dose adjustments [163]. Individual variation in heparin effect is wide, particularly when levels of AT III may be low, as in DIC or pulmonary embolism. The dosage of heparin, therefore, must be adjusted to each individual patient. Since hemorrhagic complications of heparinization almost always occur after the second day, the dose of heparin should be decreased by one-half to

| Dosage Route | Duration |
|--------------|----------|
| 1 unit/kg/hr Constant IV | Only while IV needed |
| 100 units/kg q 12 hr Intermittent SQ | Until ambulatory |
| (Adults 5,000 units q 12 hr) | |

| Prevention of thrombus progression (deep vein thrombosis) | Continuous IV or intermittent IV or SQ | Until ambulatory or 3–6 months |
| High dose | 50–75 units/kg initially followed by 300–600 units/kg/day | |
| (massive embolism with shock) | 1,200–1,400 units/kg/day | Up to 6 months |
two-thirds after the first 48 hours. Oral anticoagulants can be begun at this point. Optimal duration of anticoagulation is not known. Patients with purpura fulminans or DIC will not need prolonged treatment, since these conditions resolve or progress rapidly. Patients with deep vein thrombosis or pulmonary embolism require treatment at least until ambulatory and perhaps up to six months [164]. If oral anticoagulants are used, they should be initiated while the patient remains heparinized, since several days are required for warfarin to produce therapeutic prolongation of the prothrombin time. Heparin should be continued at least until the PT becomes prolonged, and some advise continuation of heparin for six days after the therapeutic level of warfarin has been reached. Discontinuation of heparin without oral anticoagulation is followed within several days by a hypercoagulable state caused by rebound elevations in antithrombin III. Whether gradual discontinuation of heparin prevents this hypercoagulability is uncertain.

**COMPLICATIONS OF SICKLING DISORDERS**

Major sickling disorders (homozygous SS disease, hemoglobin SC disease, S-beta thalassemia) require intensive care when the patient is threatened by precipitous generalized sickling, overwhelming infection, or severe organ dysfunction.

Precipitous sickling may complicate any illness in which septicemia, hypoxia, dehydration, acidosis, or shock occur. Since all red cells in patients with sickle cell anemia contain about 90 percent hemoglobin S, generalized sickling is promoted by these circumstances, and rapid death may ensue. Treatment of precipitating conditions and correction of hypoxemia, dehydration, and infection are paramount in reversing the escalated sickling process.

Exchange transfusion is the most rapid practical method of preventing or correcting generalized sickling. A one-volume exchange transfusion (80 ml/kg) with packed red cells and fresh frozen plasma accomplishes the following: (1) correction of anemia and improvement of oxygen delivery [165], (2) reduction of sickle-prone cells to 30 percent of the red cell population [166], (3) possible replacement of opsonins, and (4) reversal of splenic reticuloendothelial function in young children with functional asplenia [167]. The risks of exchange or of simple transfusions are those of transfusional hepatitis, allergic or leukoagglutinin reactions, and formation of hemolytic antibodies from minor blood group incompatibilities.

Pain, particularly from bone infarction, is a hallmark of acute vaso-occlusive episodes and should be treated appropriately [168]. Since vaso-occlusive crises usually last several days, the preferred drug or drug combination should be given regularly, rather than as required, in full pharmacologic doses for at least 24 hours. Infarcts are extremely painful, and treatment usually requires narcotics (with or without a synergist), bed rest, local heat, and sometimes oxygen. Morphine sulfate given by continuous intravenous infusion [169] is a very effective regimen which provides a constant level of analgesia. When large amounts of narcotics are required for relief of intense pain, hypoventilation, atelectasis, and pulmonary infarction or pneumonia often follow. Adequate pulmonary toilet is a mandatory part of preventing complications in these patients.

The following clinical situations are circumstances in which patients may require exchange transfusion and intensive care:

1. General anesthesia (surgery) or heavy sedation
2. Shock
3. Multiple or massive traumatic wounds
4. Acute splenic sequestration or extreme anemia
5. Incipient or acute organ failure [170–172]
6. Severe pneumonia involving multiple lobes
7. Cerebrovascular accident
8. Massive infarction of the musculoskeletal system
9. Disseminated intravascular coagulation [173, 174]

Anesthesia

General anesthesia, heavy sedation, or the use of hyperosmolar radiographic contrast solutions for angiography all predispose to sickling. The increased incidence of intra-operative and post-operative death and morbid complications arises primarily from hypoxia, dehydration, infarction, infection, and poor wound healing [175–180], rather than specific drugs used for anesthesia. Many of these patients have been untransfused pregnant or parturitional women. Individuals with clinically milder sickling disorders, such as sickle cell beta-thalassemia or hemoglobin SC disease, appear to be as much at risk for anesthetic, surgical, and obstetric complications as the patient with sickle cell anemia, illustrating that the presence of sickle-prone cells is a greater factor than anemia alone [181].

The risk of these catastrophes can be minimized by meticulous attention to oxygenation, temperature, hydration, infection, and pulmonary hygiene. For patients who refuse blood products or who have developed hemolytic antibodies, these measures must suffice. For the majority, however, pre-operative exchange transfusion can be accomplished expeditiously and virtually eliminates the risk of generalized or regional sickling.

Sepsis/Meningitis

Bacterial septicemia and meningitis are the major causes of death in young children with sickling disorders [182–185]. Prior to the recognition of this hazard, one-third of all patients with sickle cell anemia died before five years of age from sepsis or meningitis caused by S. pneumoniae or H. influenzae. The loss of splenic reticuloendothelial function in early childhood renders these young patients incompetent to trap blood-borne polysaccharide-encapsulated bacteria and to mount early formation of opsonins [186–191]. Bacteremia becomes potentially fatal septicemia in the child with a sickling disorder. Blood-borne infections have not been totally prevented even with routine use of pneumococcal vaccines and prophylactic penicillin.

Septicemia and meningitis usually appear initially as a febrile illness. Extreme pyrexia alone—fever ≥ 104°F, or 40.3°C—is sufficient reason to institute aggressive therapy for presumptive systemic bacterial infection, even if the child “looks well.” At least half of the children seen with extreme hyperpyrexia in one institution did, in fact, have bacterial growth from blood or CSF [192]. Any febrile child with lethargy or any other systemic symptom disproportionate to his degree of fever should also be treated promptly.

Since systemic bacterial infection in patients with sickle cell diseases can progress to septic shock and death within a few hours, high doses of intravenous antibiotics should be given immediately when sepsis, meningitis, or severe pneumonia is suspected. Antibiotic therapy should precede a time-consuming evaluation, such as X-rays, lumbar puncture, and urine collection. One dose of antibiotics will rarely sterilize a diagnostic sample of urine or CSF and may be life-saving for the child. S.
pneumoniae and H. influenzae are the most likely causative agents; the choice of antibiotics may vary with geographic location and the presence of resistant organisms in the community.

Severe infections predispose to sickling, and measures to reverse sickling are second in importance only to antibiotic therapy. Hydration is an acute need. Dehydration occurs quickly in children with sickle cell anemia because hyposthenuria—loss of renal tubular concentrating capacity—is a common defect in children and older infants and cripples compensatory mechanisms to conserve fluid in the face of exaggerated evaporative and respiratory losses.

Exchange transfusion with packed cells and colloid or crystalloid can rapidly dilute sickled cells, correct anemia, possibly provide opsonins (plasma), and reverse functional asplenia. Although this maneuver certainly should be used in the hypotensive infected patient, the rate of the patient’s deterioration may exceed the time required to prepare for exchange transfusion. Exchange transfusion may be used to greater advantage in the young patient with presumed sepsis and systemic symptoms (lethargy, vomiting, severe diarrhea, diffuse discomfort, agitation) before generalized sickling is precipitated.

Septic shock signifies rapid deterioration and impending death from the combined effects of overwhelming septicemia, acute adrenal insufficiency (Waterhouse-Friderichsen syndrome) or DIC, and generalized sickling. Administration of fluids, and possibly corticosteroids, may be supportive.

The stabilized or improving child should continue to be treated with intravenous antibiotics for at least five days, until blood and CSF cultures have matured. Septicemia and meningitis may precede cellular responses in blood and CSF, and the absence of left shift and pleocytosis are insufficient grounds for excluding the presence of severe bacterial infection [193].

**Acute Splenic Sequestration**

The spleen in young children with sickling diseases is anatomically enlarged, even though the reticuloendothelial function is faulty [187,188]. The enlarged spleen may on occasion transform into a highly elastic organ, pooling vast amounts of blood in the splenic sinusoids. This phenomenon, acute splenic sequestration, is a major cause of death in infants and young children with sickle cell diseases and usually complicates an infectious illness [174,189].

The speed at which splenic sequestration occurs determines the clinical presentation of the child. Massive, sudden enlargement of the spleen produces hypovolemic shock and severe splenomegaly. Subacute splenic sequestration is manifest as severe anemia, with or without congestive heart failure, in the presence of massive splenomegaly.

The appropriate management of the infant in shock is rapid administration of a colloid solution, preferably blood. During transfusion, the spleen may actually shrink and return sequestered blood into the circulation.

Life-threatening splenic sequestration may recur. Splenectomy or chronic transfusions have been advocated as definitive treatment.

**Severe Anemia**

Exaggeration of the anemia already present in sickle cell anemia is a common hematologic complication of the disease and on occasion may be severe. Extreme anemia, with hemoglobin values as low as 1 g/dl, may result from aplastic episodes,
hyperhemolysis, or splenic sequestration. The presence of congestive heart failure may mitigate against the use of simple transfusion. Modified exchange transfusion provides a safe alternative and can be accomplished by concomitant administration of packed cells in one vein and withdrawal of an equal volume from another vein or artery. If a large venous route is easily accessible, the classic “push-pull” technique can be used.

If congestive heart failure is mild or absent, multiple small transfusions of packed cells, spaced several hours apart for equilibration, is advised. The safe amount of packed-cell transfusions in this situation can be guided by the severity of the anemia and adjusted by the following formula: ml of packed cells/kg/transfusions = hemoglobin level (e.g., for a hemoglobin of 2.5 g/dl, give 2.5 ml/kg/transfusion). When the hemoglobin value is 5 or greater, the amount of blood given in each transfusion may be increased to 10-15 ml/kg, provided congestive heart failure is no longer present and renal function is not compromised.

**Acute “Chest Syndrome”**

Chest pain is a common presentation of infarction and infectious episodes in older children and adolescents. The patient is acutely febrile, uncomfortable, and often tachypneic, dyspneic, or grunting. Tenderness of the ribs or sternum may be elicited.

The etiologies of the “chest syndrome” are multiple and may be elusive when the patient is first examined. Pneumonia may be suspected from a history of purulent sputum, pleuritic pain or fever, auscultatory examination, and X-rays. A radiographic pulmonary infiltrate may reflect lung infarction as well as pneumonia. The “whiteout” or “ground glass” radiographic appearance (Fig. 3) of pneumonic infiltrates in sickling syndromes mirrors pathologic studies showing both infarction and infection in consolidated areas of the lung [194-197].

Pulmonary infarctions may or may not show a radiographic infiltrate early and may or may not become superinfected with pyogenic organisms [194,195]. Ventilation-perfusion scans of the lung in the presence of a normal chest X-ray may help clarify the presence of infarction. A similar picture may occur from pulmonary embolism of fat from infarcted bone marrow or a blood clot from deep vein thrombosis [198].

FIG. 3. Right upper lobe infiltrate in a young child with sickle cell disease. The “ground glass” appearance is a frequent radiologic finding, suggesting the presence of both infarct and infection.
Myocardial infarction infrequently is a cause of acute chest pain in the young but should be considered and evaluated with an electrocardiogram [199,200].

Generalized truncal infarction of the skeletal system is a common cause of severe chest pain. Because large and strategic areas of infarction are commonly found in the “chest syndrome,” adequate hydration, oxygenation, analgesia, and pulmonary toilet constitute initial management. If the patient is desaturated or critically ill, or if multiple pulmonary lobes are involved, exchange transfusion is recommended. Antibiotic therapy may be reserved for signs of infection or fever over 38.5°C, but is often required at some point in the patient’s hospital course.

Cerebrovascular Accident

Stroke is a major complication of sickling in older children and adolescents [201–203]. Vessels of any size may be affected, and the lesion may be one of vascular occlusion or of hemorrhage from collateral vessels or aneurysms. Stenotic lesions usually develop in larger vessels; plaque deposition or endothelial proliferation may serve as a nidus for occlusion by sickled cells or thrombus [204]. If stenosis develops gradually, fragile collateral vessels are formed to bypass the occluded vessel. Extensive collateralization, the moya-moya syndrome [205], may result in hemorrhage into the subarachnoid or subdural space.

Cerebrovascular accidents, like stroke in the elderly, produce a variety of clinical symptoms: seizures, paresis, headache, change in sensorium, aphasia, transient ischemic attacks, or collapse. High doses of dexamethasone are used to control cerebral edema. Exchange transfusion as an emergency maneuver is of critical value in the management of patients with arterial occlusion in reducing the proportion of sickle-prone cells in the circulation, preparing the patient for angiographic studies, and improving cerebral blood flow and oxygenation. Improvement in the neurological status of treated patients is common. Once the proportion of sickle cells has been reduced to < 30 percent, regular transfusions on a monthly basis are used to help ensure continual recovery and to prevent other similar episodes [206–208].

A hemorrhagic event is a much more difficult form of CVA to manage successfully. Emergency and chronic transfusion programs should be helpful in reducing the severity and preventing the propagation of multiple stenotic areas around which collateral networks have developed.

Pregnancy

Obstetric complications of the untransfused adolescent with sickle cell disease, sickle-beta thalassemia, or SC disease include increased morbidity and mortality rates from sickling and infections [209–213]. The high incidence of fetal wastage and perinatal mortality, whether or not the fetus is affected by a major hemoglobinopathy, stems largely from placental insufficiency. Live-born infants of affected mothers are usually small for gestational age and suffer the problems of the chronically malnourished neonate.

If the pregnant patient has not been maintained on a chronic transfusion program and becomes critically ill, exchange transfusion is indicated. Since the blood volume is increased, commensurately larger transfusions are needed. Although controversial [214,215], chronic transfusion programs are recommended by many hematologists. Certainly the pregnant woman who has sustained one major illness from her blood disorder should be maintained on a transfusion program until delivery.
**Intractable Pain**

Single episodes of vaso-occlusive “crises” which persist for longer than five to seven days without improvement and which involve large or weight-bearing areas of the skeleton may be managed with exchange transfusion, in addition to hydration and analgesia [216]. Transfusion is not recommended as initial therapy in children and adolescents with painful episodes, since most “crises” resolve spontaneously in two to five days. The persistent painful episode requires a careful re-evaluation for possible osteomyelitis, since bone infections mimic bone infarcts early in the illness and are difficult to distinguish clinically or radiologically. If osteomyelitis is indeed present, exchange transfusion may be used to prepare the patient for orthopedic drainage and to hasten recovery and wound healing.

**COMPLICATIONS OF THE LEUKEMIAS AND SOLID TUMORS**

Patients with cancer usually are admitted to the intensive care unit if they are potentially curable [215–218] and require stabilization or treatment for complications of disease or antineoplastic therapy. With rare exceptions, children and adolescents in the terminal phase of their illness should not be admitted to the intensive care unit but given a quiet room where maximal attention can be devoted to comfort.

**Metabolic Complications**

Metabolic derangements are common major complications of active malignancy. Hyperuricemia, hyperphosphatemia [219], hypoglycemia [220], hypocalcemia [221], hypercalcemia [222,223], hyperkalemia, and acidosis [224–226] are metabolic abnormalities caused by the release of urates, phosphates, and potassium from tumor cells, particularly those of acute lymphocytic or undifferentiated leukemia, Burkitt lymphoma, and neuroblastoma. The existence of such abnormalities prior to treatment reflects rapid cellular turnover and cell death. Commencement of chemotherapy or radiotherapy may accentuate the metabolic derangements, particularly if renal function and hydration are compromised.

The child with a large tumor or leukemic burden (high leukocyte count, malignant effusions, extreme hepatosplenomegaly) is the patient at highest risk to develop metabolic and renal complications of cell lysis. Specific antitumor treatment should be delayed or instituted cautiously while vigorous hydration and allopurinol administration is begun. Serial determinations of serum urate, phosphate, calcium, urea nitrogen, creatinine, and electrolytes are needed until the abnormalities resolve. Electrocardiography is often helpful.

Renal function may be compromised from leukemic or tumor infiltration or from urate nephropathy. Infiltrated kidneys are large, with abnormal consistency on ultrasonic evaluation, and may show delayed or absent concentration and excretion of radiographic dyes. Radiotherapy to one or both kidneys can be instituted on an emergent basis and can be expected to reduce infiltrative disease within a few days, using cumulative doses of 500–1,000 r. Any renal function is better than none with regard to urate excretion, and dialysis by either the peritoneal or vascular route is inferior to urination. However, if the kidneys are nonfunctional, dialysis is necessary to stabilize the patient for antineoplastic therapy.

The hypocalcemia produced by extreme hyperphosphatemia may require calcium supplementation.

Hyperkalemia, exaggerated by systemic acidosis, should be assessed by electrocar-
diographic changes and the presence of ileus or weakness [227]. Extreme or symptomatic hyperkalemia is treated by rectal administration of potassium-binding colloids. Hyperkalemia may be worsened by concomitant administration of packed red cells, which leak potassium during storage.

Other metabolic distortions may occur as a result of the effects of chemotherapeutic drugs or antibiotics. Vincristine and large doses of cyclophosphamide, for example, regularly produce the inappropriate ADH syndrome. Serum sodium levels as low as 125 mEq/l may occur but rarely produce clinical symptoms. Since reversal will occur within a few days, fluid restriction is usually not needed unless this syndrome further complicates abnormal electrolyte regulation from other causes such as intracranial disease, diuretics, or antibiotics.

Effusions

Pleural effusions and ascites may result from lymphatic obstruction, implantation of malignant cells on serous surfaces, or infection. The cause and type of effusion often has major implications for planning both emergency management and definitive treatment, and for assessing the patient’s prognosis. A diagnostic thoracentesis or paracentesis should be performed with removal of a limited amount of fluid to relieve respiratory symptoms. One should refrain from “tapping the space dry” unless the instillation of sclerosing agents is planned, since removal of large amounts of fluid from extravascular spaces may result in cardiovascular instability or protein depletion.

Sympathetic or obstructive fluid collections are best managed by treating the source of obstruction. These effusions are seen most commonly with Hodgkin disease in the presence of a large anterior mediastinal mass. Nonmalignant ascites may complicate nodal or hepatic metastases of Wilms’ tumor or abdominal sarcomas.

Fluid from malignant effusions usually contains tumor cells which can be identified by an experienced microscopist. Cellular morphology becomes rapidly distorted if the fluid is allowed to stand, and correct identification of cells may become impossible. The fluid should be placed into specific fixatives if immediate processing is not available. Cell block preparations for cytology can be supplemented by cytocentrifugation, a technique which allows more prompt evaluation of the morphology of exuded cells. Even though the malignant nature of the cells may be ascertained from fluid microscopy, the exact identity of the tumor often requires biopsy of a tumor mass. The timing of the biopsy, as well as the choice of sites, should be ascertained by the oncologist and the surgeon before antitumor therapy is begun. In rare circumstances the child may be so ill that treatment must be instituted before a biopsy can be obtained.

Malignant effusions are best managed by treating the regional or systemic malignancy rather than by directing therapeutic approaches toward the effusion itself. Occasionally, when radiotherapy or chemotherapy has suboptimal effectiveness, more direct methods of controlling a recurrent effusion may be required [228]. Placement of an indwelling catheter for continuous drainage in the newly diagnosed patient with respiratory compromise from pleural effusions allows time for systemic treatment to become effective. If systemic therapy does not prevent the reaccumulation of fluid, sclerosing agents (tetracycline, nitrogen mustard, quinacrine, talc) can be instilled into the pleural cavity. The effusion must be thoroughly drained via a chest tube, with the patient rotated in various positions to effect maximal removal. Loculations may require separate drainage. The sclerosing
substance is then instilled through the chest tube, the patient rotated again in various positions to assure wide application to pleural surfaces, and the excess medication removed.

**Cardiac Complications**

Cardiac emergencies can result from infectious myocarditis or pericarditis, noninfectious inflammation or fibrosis from radiotherapy, or drug-induced cardiomyopathy [229,230].

Pericardial effusions, like pleural effusions, may be reactive, infectious, or neoplastic. Etiologic diagnosis requires examination of pericardial fluid by microscopy and culture. Chronic inflammation and thickening of the pericardium may result from radiotherapy, particularly when radiosynergistic drugs such as actinomycin D and doxorubicin have been used. Recurrent tamponade requires surgical removal of the pericardium or drainage of pericardial fluid into the abdominal or pleural space. Malignant infiltration of the heart and pericardium is managed best by radiation therapy.

Constrictive or inflammatory pericarditis as a result of mediastinal irradiation can be ameliorated with corticosteroids.

Cardiomyopathy induced by doxorubicin or daunorubicin is more likely to occur in the patient with pre-existing cardiopulmonary disease, previous irradiation to the lower mediastinum, and a cumulative dose exceeding 450 mg/m² [231,232]. Acute congestive heart failure (Fig. 4) is fatal in about 20 percent of children, and most patients who recover have varying degrees of cardiac dysfunction [233]. Less information is available about the course of chronic cardiomyopathy due to these drugs. Electrocardiographic abnormalities include ST-T wave changes, low voltage, and arrhythmias, many of which appear transiently during the course of chemotherapy [234]. Echocardiography, the method most commonly applied to monitor heart function while chemotherapy is in progress, shows reduction in left ventricular performance [235]. Newer radionuclide imaging techniques [236,237] and possibly endocardial biopsy [238] may provide more accurate assessment of the cardiac injury.

![FIG. 4. Acute congestive heart failure from doxorubicin-induced cardiomyopathy.](image-url)
Digitalis and other ionotrophic drugs should be employed with other usual methods of cardiopulmonary support. Data from rodent studies have suggested that alphatocopherol, or vitamin E, treatment may prevent the progression of the myopathic injury [239].

**Central Nervous System**

Seizures, palsies, and other acute neurological events are relatively common complications of cancer and its therapy [240,241]. Meningeal infiltration or intracranial tumors produce signs of increased intracranial pressure, with or without focal neurological signs.

Tumors of the central nervous system are a leading cause of malignant morbidity in children [242]. These consist of astrocytomas of varying neoplastic potential, ependymomas, medulloblastomas, craniopharyngiomas, and an assortment of less common tumors. If the patient has obstructive hydrocephalus as an initial complication, relief of increased ventricular pressure by shunt or ventriculostomy precedes the cancer surgery. Most primary brain tumors are accessible to the surgeon and can be biopsied or removed. Because of microscopic residual disease and the propensity for most of these to recur, radiation therapy is usually begun when the diagnosis is clarified and the post-operative patient stabilized.

The child with intracranial metastases should be carefully assessed with regard to his prognosis and the accessibility and risks of surgical removal or radiotherapy [243]. Collaboration with the oncologist, neurosurgeon, and radiotherapist is essential to individualize therapy.

Leukemic meningiomatosis, a common complication of the lymphocytic and undifferentiated acute leukemias [240], is diffuse and nonfocal in nature and best treated by intrathecal methotrexate administration. Intrathecal chemotherapy is also the most frequently employed method of preventing leukemic or lymphomatous metastasis to the meninges. Irradiation of the brain may be used with intrathecal drugs. Acute toxicities include chemical meningitis, arachnoiditis, headache, photophobia, and malaise [241,244,245]. A syndrome of "reactive encephalopathy," characterized by somnolence, slowing of electrical activity on EEG, and benign pleocytosis in the CSF, is seen in one-third to one-half of children who have received brain irradiation and is thought to represent transient demyelination [246,247]. Progressive encephalopathy or paraplegia is rare. Chronic, indolent neurotoxicity is more common, however, especially when parenteral and intrathecal methotrexate and cranial irradiation are all used [244]. Deficits include perceptual-motor handicap, seizure disorders, ataxia, and mental retardation [248–252]. Leukoencephalopathy, with or without calcifications in white matter, is the pathologic basis for most chronic neurological disorders in these patients [253–255]. Active meningeal leukemia or lymphomatous infiltration must be excluded before iatrogenic neurotoxicity is implicated.

High doses of radiotherapy to the central nervous system produce a risk of vasculitis, demyelination, or gliosis (scarring) which may mimic stroke, infection, or intracranial tumor [256–258]. Prognosis is uncertain for severe radiation injury; corticosteroid therapy may help [259].

While a drug- or radiation-induced disease is clinically a diagnosis of exclusion and suspicion based upon the constellation of symptoms and signs and the temporal relationships to medications, a brain biopsy may be necessary to define the CNS lesion. If an offending medication is discontinued, the neurological syndrome often improves or resolves.
Occasionally, CNS disease, particularly generalized seizures, is produced by hemorrhage, infection (papovavirus, cryptococcus) [260], hypertension, metabolic disturbances, leukostasis, or thrombosis.

**Leukostasis**

Some types of leukemic cells have a propensity to stick to one another and to the endothelium to cause hyperviscosity, occlude vessels, or prevent transcapillary diffusion. More a characteristic of the acute myelogenous than lymphocytic leukemias, leukostasis is a potential complication of severe leukocytosis and affects mainly the brain and the lung [261,262]. Emergency therapies include leukapheresis [263], exchange transfusion [264], and cranial irradiation [265].

**Disseminated Intravascular Coagulopathy**

Like leukostasis, DIC is a complication of the myelogenous leukemias, especially acute promyelocytic leukemia, although it may also occur in any disseminated cancer [266–268]. Like the metabolic complications of the lymphocytic disease, DIC is a potential life-threatening complication of cellular lysis when the malignant cells are granulocytes rich in lysosomal granules and thromboplastins. Heparinization has been recommended by some as a prophylactic measure in acute promyelocytic leukemia [269,270] and is surely indicated as an adjunct to chemotherapy in the acutely bleeding patient with DIC who does not respond to transfusions of platelets and fresh frozen plasma.

**Overdosage of Chemotherapeutic Drugs**

Although inadvertent drug overdose with chemotherapeutic medications is a rare event when chemotherapy is carefully calculated and supervised, major errors occur which may be life-threatening to the patient.Such errors are usually log increments due to dislocation of the decimal point. Antidotes are rare, with the notable exception of methotrexate, for which folinic acid can be administered to reverse the antifolate block. Folinic acid also may be of benefit in counteracting vincristine [271,272].

The best treatment of severe chemotherapeutic overdose is removal of the medication from the circulation by exchange transfusion or dialysis, if possible, and provision of maximal supportive care to the patient.

**Mediastinal Mass**

The large mediastinal mass producing tracheobronchial compression and acute respiratory embarrassment is an oncologic emergency. Most mediastinal masses are lymphomas and occupy the anterior mediastinal compartment. Hodgkin disease, an indolent malignancy, has a propensity to involve the thymus and mediastinal lymph nodes and may be very large but usually does not cause severe compression of the airway. Conversely, the non-Hodgkin lymphomas grow rapidly, occur more often in preadolescent boys, frequently are associated with malignant effusions, and may compromise ventilation (Fig. 5). The child with severe respiratory embarrassment may not tolerate a surgical biopsy of the tumor nor even a bone marrow biopsy. Emergency maneuvers to reduce the size of the mass include large doses of intravenous corticosteroids and radiotherapy, either of which will decrease lymphomatous masses within 24–48 hours. Maintenance of the airway may require ventilation with an endotracheal tube which reaches the length of the compressed trachea [273].
Infection in the Immunocompromised Host

Bacterial, viral, fungal, and protozoal infections may plague the patient with a compromised immunologic system [274–279].

Bacterial sepsis in the face of profound neutropenia is the most common acute and fulminant infectious complication in the child with cancer [280–282]. The severely neutropenic individual with a total granulocyte count < 200/mm³ is subject to the development of septicemia from enteric or hospital-acquired bacteria.

While extreme isolation in self-contained, sterile units or laminar air-flow rooms may be available at some institutions, most pediatric intensive care units practice simple isolation techniques to minimize hospital-acquired infections [283–285]. Separation of the patient in a private room and rigorous attention to hand washing by examiners, particularly physicians, are reasonable safeguards. Rectal manipulations should be avoided, since perirectal abscesses may be created by small mucosal tears [286]. Stool softeners should be given to the constipated child.

The severely neutropenic child with fever deserves immediate and aggressive antibiotic therapy [287,288]. The absence of neutrophils minimizes certain signs of inflammation—redness, abscess formation, and radiologic pulmonary infiltrates. However, neutrophils are not necessary for the expression of fever and local pain. Therefore, temperature elevations are a reliable guide to the severity of the infection, and local pain, meningismus, and peritonitis are reliable in their presence or absence. Cultures of the throat, blood, and urine are mandatory in these individuals. Cultures of the CSF should be restricted to those with meningeal signs of central nervous system disturbance.

Intravenous broad-spectrum antibiotics should be begun promptly [289]. The choice of antibiotics depends upon the specific organisms in the institution. In general, the most common offending organisms in the neutropenic patient with cancer are staphylococcus [290], pseudomonas, and other enteric organisms. A documented septicemia, abscess, cellulitis, or pneumonia without prompt improvement on antibiotic therapy is an indication for granulocyte transfusions. Supportive
measures used for any child with septicemia are appropriate for use in the potentially curable child with cancer.

_Pneumonia_, particularly interstitial pneumonitis, can be a rapidly progressive cause of pulmonary failure in the immunocompromised host and poses a diagnostic dilemma for the physician [291]. Interstitial pneumonitis in these patients can be caused by _Pneumocystis carinii_ (Fig. 6) [292,293], viruses, gram-negative bacteria, fungi, some neoplastic processes (leukemia, histiocytosis), fibrotic reactions to radiotherapy, or desquamation or fibrosis from some chemotherapeutic drugs [294,295]. With the advent of trimethoprim-sulfamethoxazole and the discovery that most _Pneumocystis_ infections are cured by them [296], one avenue of therapy in the child with mild or moderate pneumonitis is a trial of trimethoprim-sulfamethoxazole, with careful evaluation of lung function (Fig. 7). An accurate

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**FIG. 6.** Interstitial pneumonitis caused by _Pneumocystis carinii_ in an adolescent with acute lymphocytic leukemia.

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**FIG. 7.** Interstitial pneumonitis in the immunocompromised host: Suggested management.
diagnostic procedure is usually required, however, in the patient with flagrant interstitial disease who requires mechanical ventilation or whose disease is rapidly advancing. The method of diagnosis varies; needle aspirate of the lung, endotracheal or gastric aspirate, or bronchoscopy brushings may show pneumocysts with Giemsa or silver stains. Open, thoracoscopic, or possibly transbronchial lung biopsy is more reliable and is preferred if gastric washings are negative for the organism. A lung biopsy also provides sufficient tissue for culture and histologic demonstration of fungal or bacterial invasion.

Viral infections carry an increased risk of complicated illness in the immunosuppressed child, particularly one whose therapy is continuous or comprises multiple drugs or whose underlying disease is a neoplasm of the immune system, such as acute lymphocytic leukemia or Hodgkin disease.

Varicella-zoster infections, particularly chickenpox, are of particular concern \[297,298\]. A protracted, more severe course is usual in the immunosuppressed patient. About one-fourth of children with varicella develop pneumonia, and about one-fourth of these patients die \[298\]. Other deaths are due largely to superimposed bacterial infection with septicemia. Mortality rates among all compromised children with primary varicella average 7 percent and rise if the underlying disease is active or if recent chemotherapy has included highly immunosuppressive drugs, such as corticosteroids or l-asparaginase.

Of the newer antiviral compounds, three—vidarabine (ara-A, adenine arabinoside), acyclovir, and alpha interferon—have decreased mortality and serious morbidity of varicella \[299–303\]. Treatment is certainly warranted for patients with nonhealing lesions or pneumonia from primary varicella and for disseminated zoster, and may be indicated for all primary varicella in an immunocompromised host \[304,305\]. Primary infection can be prevented or modified with immune globulin, immune plasma, immune transfer factor, or vaccination with attenuated live virus \[306–309\].

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