Increased Platelet Destruction in Infancy and Childhood

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The number of platelets in the peripheral blood of healthy children, full-term, and premature infants falls into the same range as that of adults. Thrombocytopenia, defined as a platelet count of less than 150,000/mm$^3$ ($<150 \times 10^9$/L), may be due to decreased production, splenic sequestration, or increased platelet destruction. The following is a review of disorders involving the last mechanism, all of which have the common feature of reduced autologous platelet survival. Excluded from current considerations are inherited disorders in which the survival of allogenic platelets is normal and bleeding is mainly due to diminished platelet production, e.g., Wiskott-Aldrich syndrome, or a defect in platelet function, e.g., Bernard-Soulier syndrome.

Destructive thrombocytopenias may be classified on the basis of pathogenesis: these are either immune mediated, nonimmune mediated, or a combination of both. The immune thrombocytopenias may be further divided into disorders of primary type in which there are no identifiable underlying disease processes (e.g., childhood idiopathic thrombocytopenia and neonatal immune thrombocytopenias) and disorders of secondary type in which the thrombocytopenia is associated with an identifiable insult (e.g., secondary autoimmune disorders and drugs). The nonimmune thrombocytopenias include a large group of disorders in which the increased platelet destruction is either surface mediated, e.g., hemolytic-uremic syndrome (HUS), thrombin mediated, e.g., disseminated intravascular coagulation and giant hemangioma, or caused by multiple factors, e.g., necrotizing enterocolitis, hemolytic anemia, exchange transfusion, phototherapy, intrauterine growth retardation, congenital polycythemia, hypoxia, and deficiency of plasma factors. In some disorders, e.g., infection-induced thrombocytopenia, both immune and nonimmune mechanisms have apparently resulted in increased platelet destruction.

Although most forms of thrombocytopenia in children are classifiable as indicated, this is not true for newborn infants. In our own experience and in the relevant literature, 60 to 80% of neonates with thrombocytopenia do not have an identifiable basis for this abnormality. This is a large number of infants considering the fact that up to 50% of babies admitted to neonatal intensive care units have thrombocytopenia.

**IMMUNE-MEDIATED PLATELET DESTRUCTION**

**Immune-Mediated Thrombocytopenia of Primary Type**

Idiopathic Thrombocytopenic Purpura

Idiopathic thrombocytopenic purpura (ITP), the most common form of thrombocytopenia in children, is a diagnosis made by exclusion. In contrast to adults, 70 to 90% of children have the acute form of ITP in which thrombocytopenia may last from 3 days to 6 months with a mean interval to spontaneous recovery of about 1 month, although approximately 4% of children have subsequent relapses. The less frequent chronic form, defined as thrombocytopenia persisting for longer than 6 months, occurs in only 10 to 15% of cases. Large centers have reported a higher incidence of chronic ITP (30%), but this likely represents the referral pattern to tertiary care facilities. This definition of chronic ITP, although widely used, is quite arbitrary and may not be particularly useful. For example, children who have had acute ITP and who have been in remission for up to 6 years may still exhibit a shortened platelet survival.

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more, in our experience, children who have had chronic ITP for months or years may recover spontaneously. This has also been reported in adults.191

Acute ITP in children affects males and females equally and has a peak incidence between 2 and 6 years of age.38,42,143,146,147,247 It occurs predominantly in the winter and spring months.38,42,143,146,147,221,247 and is associated with a preceding viral illness in 50 to 85% of cases. This is usually an upper respiratory tract infection that occurred 1 to 6 weeks earlier.38,42,143,146,147,221,247 The disorder seems to be less common in black children, an observation that does not appear to be due to difficulty in observing purpura in deeply pigmented skin.119,147

In more than 90% of instances, the clinical presentation of acute ITP is that of an abrupt, spontaneous development of petechiae and ecchymoses in an otherwise healthy child. Other forms of bleeding include epistaxis (30%),38,146,147,153 hematuria (5 to 10%),146,147,153 and intracranial hemorrhage (<2%).38,143,146,147,153,221,252 The incidence of bleeding requiring red blood cell transfusion therapy has been reported to be as high as 20%.38

Although blood loss may be severe on occasion, the major life-threatening complication of childhood ITP is intracranial hemorrhage. Woerner et al.252 reviewed the reported cases of intracranial hemorrhage in children with ITP and noted that in 10 of 18 cases, the central nervous system (CNS) bleeding occurred more than 1 month following diagnosis, with one case occurring 5 years later. In addition, six of these patients had platelet counts between 10,000 and 20,000/mm³ and at least four patients were receiving steroid therapy. The latter observations are important, since part of the rationale for treatment with steroids is that patients with severe thrombocytopenia are at greatest risk in the first month after diagnosis. The location of bleeding may be important, with the posterior fossa incurring a particular risk. Patients who received drugs known to inhibit platelet function, such as aspirin and antihistamines, also appeared to be at greater risk of intracranial hemorrhage.

Physical examination usually reveals only petechiae and ecchymoses. Sixty percent of children have shotty lymphadenopathy147 and in fewer than 10% is the spleen tip palpable.147,153 A prevalence similar to that in normal children.240 Splenomegaly of greater degree does not occur in acute ITP and, if present, this finding should suggest an alternative diagnosis.

Chronic ITP in childhood is similar to the adult entity and cannot be distinguished reliably from acute ITP on the basis of clinical presentation.143,147 It may occur at any age but is more common in older children147,221 and females.38,147,221,247 Although by definition the disorder is persistent, many affected children attain a hemostatic platelet count.119,147 an important consideration when planning specific therapy.

The platelet count is less than 40,000/mm³ in 80% of children with ITP at presentation and the platelet size is increased significantly, the mean platelet diameter being 1.3- to 1.6-fold greater than normal.120,162,177 These are “young” platelets, the presence of which indicates active thrombopoiesis with an increased platelet turnover.75 The total white cell count is usually normal; however, a reactive lymphocytosis is common147 and 20% of children have a mild eosinophilia. Bone marrow examination is undertaken primarily to exclude such disorders as leukemia and hypoplastic anemia. This is essential if steroids are to be used as part of the clinical management. In ITP the bone marrow shows a normal or increased number of megakaryocytes. Morphologic changes, indicating that these are less mature than normal, are fewer nuclear lobes, less cytoplasmic granulation, and a lack of discernable platelet budding:120,162 however, these are not specific features of the condition.

Several investigators have studied both the humoral and cellular immune systems in children with acute and chronic ITP.156,231 The majority of patients exhibited immunologic abnormalities, including autoantibodies and abnormalities in complement, immunoglobulins, or regulatory lymphocytes.156 It is important to measure antinuclear antibody in each patient at presentation and to repeat the measurement in those who follow a chronic course, since systemic lupus erythematosus (SLE) may present with thrombocytopenia. There are no laboratory tests that can accurately predict whether an individual child will have acute or chronic ITP. Chronic ITP has been associated with a low level of immunoglobulin A (IgA)147 less platelet-associated IgG,142 and increased basal thymidine incorporation in lymphocytes.231 When steroids are to be used in the management of a child, it is important to establish that he or she does not have tuberculosis, and to determine if he or she has been exposed recently to the varicella zoster virus.

Historically, ITP was thought to result from a failure of platelet production due to disordered megakaryopoiesis. Harrington and co-workers94 demonstrated that plasma from patients with ITP, when infused into a normal subject, produced severe thrombocytopenia. Only one of these patients was less than 12 years of age. Shulman et al.220 established the immune nature of chronic ITP in adults by demonstrating that the causal circulating plasma factor was IgG.220 Since that time, several investigators have developed assays8,94,100,117 that confirm that 70% of adults with chronic ITP...
have a platelet antibody in their serum. In children, accounts have varied greatly, with 12 to 88% having detectable antibody using these techniques. Recently, several methods for directly measuring platelet-associated IgG\(^1\) and complement have been reported. Using one of these, Lightsey et al.\(^2\) found elevated levels of platelet-associated IgG (PAIgG) in 13 chronic and 7 acute cases of ITP in children. The investigators also noted that the children with chronic ITP had significantly lower levels of PAIgG than did those with acute ITP.\(^3\) In the acute cases, PAIgG returned to normal with spontaneous clinical recovery. It was hypothesized that, in the acute disease, immune complexes form during an antibody response to an infection and bind to the circulating platelets. In chronic ITP, the lesser amounts of IgG bound to platelets may represent antibody directed against a specific platelet antigen.

The site of antibody production in acute ITP in children has not been determined. However, in adults with chronic ITP, the spleen is an important source of platelet-binding IgG.\(^4\) It is interesting to note that this antibody has also been shown to bind to homologous megakaryocytes and it may alter thrombopoiesis.\(^5\) The spleen is a major site of platelet destruction;\(^6\) however, the liver has been implicated as well, particularly in severe cases of platelet destruction;\(^7\) although it is doubtful whether this is accomplished by conventional doses of corticosteroids. Despite the controversy surrounding the administration of steroids, these are relatively safe drugs that are used in more or less selected circumstances, at the discretion of the responsible physician, for children who are thought to be at risk of severe hemorrhage. The usual dose is 2 mg/kg/day in divided doses for a period of 1 to 4 weeks.\(^8\) There is no evidence that long-term steroid therapy is of benefit, and indeed this may cause persistent thrombocytopenia and hypertension, which has been implicated in the pathogenesis of intracranial hemorrhage occurring in patients on corticosteroid therapy.

Platelet transfusions have a very limited role in the management of ITP. The infused platelets are destroyed rapidly and rarely lead to a detectable rise in the platelet count.\(^9\) However, this modality may be helpful in the management of intracranial bleeding.\(^10\) Both plasma and gamma globulin infusions\(^11\) may cause a rise in the platelet count in some individuals with ITP, although the mechanism is unknown. Neither of these maneuvers is recommended as the initial management of a child with acute ITP, but may be useful in some children with the chronic variant. The use of plasmapheresis in children with ITP has been reported and may be temporarily effective.

Of all children with chronic ITP, approximately one-third maintain platelet counts in excess of 50,000/mm\(^3\), have few or no bleeding episodes, and do not require splenectomy.\(^12\) However, others will have clinically significant bleeding and may benefit from removal of the spleen. The decision to perform a splenectomy should be postponed, if possible, until the child is at least 4 years of age.\(^13\) Pneumococcal vaccine should be given and steroids administered perioperatively. Platelets should be available in case of uncontrolled bleeding.\(^14\) Usually the platelet count rises rapidly as soon as the
splanchnic pedicle is clamped. Because of reported failures with the use of pneumococcal vaccine, some centers are using daily oral penicillin prophylaxis as well in a concerted effort to reduce the risk of fatal postsplenectomy infection. The response rate to splenectomy in children with ITP is 55 to 85%, which is similar to that in adults. Another 10 to 20% have a sustained rise in the platelet count to levels at which excessive bleeding does not occur (60,000 to 100,000/mm³). Unfortunately, 10 to 20% derive no benefit from splenectomy. Usually these patients did not respond initially to steroids.

Immunosuppressive agents should be reserved for the few children who have serious bleeding despite all other modes of treatment. The agents that have been used in children are azathioprine, cyclophosphamide, vincristine, and vinblastine. Of these, vincristine and azathioprine have been employed most extensively. Between 50 and 60% of children with chronic ITP respond with a rise in the platelet count, but this is usually short-lived. All of these agents have potentially serious side effects that are of particular importance in young children. Vincristine has been reported to cause platelet dysfunction that, at least theoretically, may predispose to further bleeding.

The management of a thrombocytopenic child who suffers an intracranial hemorrhage has been summarized by Woerner et al. In brief, this includes a computed tomography scan to localize the lesion, supportive measures to control increased intracranial pressure, high-dose steroids (4 mg/kg/day), emergency splenectomy prior to neurosurgical intervention, appropriate neurosurgical intervention if necessary, and platelet transfusions, which should be used if the platelet count does not rise after splenectomy. Fortunately, more than 50% of children who have endured this life-threatening complication have had a favorable outcome.

**Neonatal Immune Thrombocytopenias**

These disorders are conveniently divided into autoimmune and alloimmune variants. The former is a misnomer, since the autoimmune process occurs in the mother and not in the baby, whereas in both variants antiplatelet antibody is delivered transplacentally to the passive fetal recipient and the disorders are therefore self-limiting. Thus, in autoimmune thrombocytopenia of the newborn IgG (subclass 3), from the mother with ITP, crosses the placenta and becomes attached to the infants' platelets. The clinical presentation is usually that of a healthy, full-term infant who develops petechiae and bruising shortly after birth. The maternal history is very important, since there is often evidence of ITP or another autoimmune disorder. Alternative causes of neonatal thrombocytopenia, such as familial disorders, antenatal drug ingestion, or maternal infection, should be excluded. Investigations include a platelet count in both the mother and the newborn infant. The infant is found to be thrombocytopenic and usually, but not invariably, the mother is as well. If the maternal platelet count is normal, the measurement of PAIgG and serum platelet-bindable IgG (S-PBIgG) may be helpful in distinguishing autoimmune from alloimmune thrombocytopenia. In the former, both the infant and mother have an increased PAIgG, whereas in the alloimmune variant the mother does not have an elevated PAIgG but rather S-PBIgG directed against the infant's platelets.

**Neonatal "autoimmune" thrombocytopenia.** The obstetrical management of women who are known to have autoimmune thrombocytopenia is the subject of considerable debate. Of major concern is the risk of intracranial hemorrhage in the infant during vaginal delivery. The frequency of this complication has been reported to range from 0 to 25%, but this is usually short-lived. All of these agents have potentially serious side effects that are of particular importance in young children. Vincristine has been reported to cause platelet dysfunction that, at least theoretically, may predispose to further bleeding. The management of a thrombocytopenic child who suffers an intracranial hemorrhage has been summarized by Woerner et al. In brief, this includes a computed tomography scan to localize the lesion, supportive measures to control increased intracranial pressure, high-dose steroids (4 mg/kg/day), emergency splenectomy prior to neurosurgical intervention, appropriate neurosurgical intervention if necessary, and platelet transfusions, which should be used if the platelet count does not rise after splenectomy. Fortunately, more than 50% of children who have endured this life-threatening complication have had a favorable outcome.

1. Elective Caesarian section for all pregnant women with a history of autoimmune thrombocytopenia. This approach is based on the report of a neonatal mortality rate of 25% following vaginal delivery. Of major concern is the risk of intracranial hemorrhage in the infant during vaginal delivery. The frequency of this complication has been reported to range from 0 to 25%, but this is usually short-lived. All of these agents have potentially serious side effects that are of particular importance in young children. Vincristine has been reported to cause platelet dysfunction that, at least theoretically, may predispose to further bleeding. The management of a thrombocytopenic child who suffers an intracranial hemorrhage has been summarized by Woerner et al. In brief, this includes a computed tomography scan to localize the lesion, supportive measures to control increased intracranial pressure, high-dose steroids (4 mg/kg/day), emergency splenectomy prior to neurosurgical intervention, appropriate neurosurgical intervention if necessary, and platelet transfusions, which should be used if the platelet count does not rise after splenectomy. Fortunately, more than 50% of children who have endured this life-threatening complication have had a favorable outcome.

2. Elective Caesarian section only for mothers with platelet counts less than 100,000/mm³. A policy arising from the reported association between the mother's platelet count at delivery and the platelet count in the infant. However, in a more recent study, Scott et al. found no correlation between maternal and fetal platelet counts in 113 pairs of mothers and infants. A policy arising from the reported association between the mother's platelet count at delivery and the platelet count in the infant. However, in a more recent study, Scott et al. found no correlation between maternal and fetal platelet counts in 113 pairs of mothers and infants.

3. Elective Caesarian section reserved for all women who have had a splenectomy. A policy arising from the reported association between the mother's platelet count at delivery and the platelet count in the infant. However, in a more recent study, Scott et al. found no correlation between maternal and fetal platelet counts in 113 pairs of mothers and infants.
This form of management is based on an observation in 1950 that death was more likely to occur in infants whose mothers had undergone splenectomy.²⁰⁰

There is no good evidence that any of these three approaches is efficacious. The following two observations, however; appear to be promising:

1. Caesarian section if the fetal scalp venous platelet count obtained early in labor is less than 50,000/mm³. Using this novel technique, Scott et al.²¹² avoided Caesarian section in 9 of 12 women who had ITP. The lowest platelet count in the infants was 72,000/mm³. In contrast, three infants were delivered by Caesarian section and all had platelet counts less than 20,000/mm³. This approach should be used only in centers that have experience with the sampling technique, for fetal scalp venous blood samples clot readily and may give falsely low platelet counts.

2. Karpatkin et al.¹¹⁸ advocate the administration of steroids to the mother for 10 to 14 days prior to vaginal delivery. In a controlled series, 12 mothers received steroids and seven did not. The mean platelet count in the infants of the steroid-treated mothers was 151,000/mm³ (range 65,000 to 399,000), whereas in the infants of untreated mothers it was 42,000/mm³ (range 12,000 to 112,000).

After birth, the offspring of a mother with ITP should have a platelet count measured every 6 to 8 hours initially. If it is below 80,000 or falling precipitously, corticosteroid therapy should be instituted. In our experience this is usually effective in preventing or controlling hemorrhage, but, if serious bleeding occurs or the platelet count falls below 10,000/mm³, infusion of platelet concentrates from random donors or exchange transfusion with fresh blood may be effective in the short term. Splenectomy is contraindicated due to the risk of subsequent serious infection and the self-limiting nature of the disorder. Vincristine²¹⁴ has been used, but should only be considered when all other measures have failed. Thrombocytopenia may persist for 4 to 8 weeks.

Neonatal alloimmune thrombocytopenia. The thrombocytopenia results from active immunization of the mother by paternal antigens on the platelets of her fetus. The pathogenesis is analogous to that of Rh hemolytic disease of the newborn but, in contrast to Rh disease, first-born infants are often affected.¹¹⁸ Although thrombocytopenia may be severe, the maternal platelet count is always normal. In 50 to 75% the maternal antibody is directed against the platelet-specific antigen PL,A¹,₂¹⁸,²⁴⁴ which is not present on the mother's platelets. Since this is a public antigen (only 2% are PL,A¹ negative), the disorder is uncommon, affecting only 1 to 2/10,000 live births.¹⁸⁸,²¹⁸ Other antibodies to platelet-specific antigens which have been implicated are anti-Dujo,¹⁷³ anti PLE₂²¹⁸ and anti Bak.²⁴⁵ Anti-HLA antibodies have also been detected but the significance of this finding is uncertain.²⁴⁵ Identification of platelet-specific antibodies in maternal serum is often difficult, for these do not cause platelet agglutination and seldom bind complement.²¹⁸ In a comparison of several methods for detecting antibody in alloimmune thrombocytopenia, von dem Borne et al.²⁴³ found that immunofluorescence of paraformaldehyde-fixed platelets in suspension gave the best results.²³⁷-²³⁹ The radioactive indirect antiglobulin test developed by Soulier and co-workers²²⁴ has also been valuable. We have used the measurement of PAIgG and S-PBILgG to distinguish this disorder from autoimmune thrombocytopenia.¹²⁷

The optimal obstetric management of women who have had previous babies with alloimmune thrombocytopenia is uncertain.⁷,⁷⁴,¹⁸⁸,¹⁸⁹,²²² Of primary concern is that 10 to 14% of such infants have suffered an intracranial hemorrhage.¹⁸⁹,²²² In at least four instances, this event has occurred in utero.¹¹²,²⁵⁵ On the basis of a 75% recurrence rate in second pregnancies, most investigators advocate elective Caesarian section. The possible benefit of antenatal steroid therapy has not been evaluated.

Following delivery, the treatment of choice for the infant affected by alloimmune thrombocytopenia is an infusion of washed maternal platelet concentrates,²¹⁵ since the mother's platelets lack the target antigen. If the diagnosis is suspected, platelet concentrates can be prepared prior to delivery.¹²⁷ Thrombocytopenia may persist for 1 to 8 weeks and maternal platelet infusions may have to be repeated until the infant's platelet count has stabilized at a safe level (>50,000/mm³). Other forms of therapy have been used without consistent success. These include administration of steroids to the baby, infusion of platelets from random donors, and exchange transfusion. Splenectomy is clearly contraindicated.

Immune-Mediated Thrombocytopenia of Secondary Type

Autoimmune Disorders

Immune-mediated thrombocytopenia is a feature of several autoimmune disorders that occur in children as well as in adults. Temporary thrombocytopenia may also occur in the newborn infant of a mother affected by hyperthyroidism or SLE.¹⁸²,²¹³
Hyperthyroidism in adults is sometimes complicated by thrombocytopenia.\textsuperscript{138} Congenital thyrotoxicosis presents with hepatosplenomegaly and thrombocytopenia.\textsuperscript{64,254} Recently, an infant with congenital thyrotoxicosis at our institution had an elevated cytopenia.\textsuperscript{138} The platelet count was decreased, and the infant responded poorly to infusions of random donor platelets, suggesting that the pathogenesis of thrombocytopenia was immune-mediated platelet destruction. There are also case reports of SLE in the mother causing thrombocytopenia in the infant.\textsuperscript{182,213} In one case, platelet agglutination was demonstrated in the mother and the infant.\textsuperscript{182} Administration of steroids to the infant may ameliorate neonatal thrombocytopenia of this type.\textsuperscript{213}

**Drug-Induced Platelet Destruction**

A major difficulty in evaluating the reports of suspected drug-induced, destructive thrombocytopenia is that the evidence is often circumstantial. However, there are well-documented cases of immune-mediated thrombocytopenia associated with the administration of drugs to infants and children.\textsuperscript{19,57,117,151,171} These are relatively infrequent by comparison with the adult experience, probably reflecting the lesser exposure of children to the causal agents, comprehensive lists of which are available in other reviews.\textsuperscript{91,166} In children, anticonvulsants\textsuperscript{19,143,171,204} and antibiotics\textsuperscript{143} are most commonly implicated. Of the anticonvulsants, valproic acid, a relatively new agent, has been reported to cause an immune-mediated thrombocytopenia that may be dose related in some patients.\textsuperscript{204} In our own experience with 45 children receiving this drug, reduction in the platelet count appeared to be immune mediated, as demonstrated by elevated PAIgG determinations,\textsuperscript{19,171} but the pathogenesis was far from clear, since the thrombocytopenia resolved despite continuing drug administration. Evidently the mechanisms involved are more complex than was previously realized.\textsuperscript{19}

In almost all cases the antibody that is held to be responsible is an IgG, although IgM has been implicated on occasion.\textsuperscript{23,61,204} There are at least two mechanisms by which the drug-antibody-platelet interaction can occur. The drug or drug metabolite\textsuperscript{62} may interact with a plasma protein ("carrier molecule") and evoke an antibody response that is directed against the drug-carrier complex. The resulting antigen-antibody complex then attaches to the platelet nonspecifically, presumably via the Fc receptor; or the drug or its metabolite may attach directly to the platelet surface, the antibody then combining with the drug-platelet complex.\textsuperscript{219} In either event, the antibody-coated platelets are then removed from the circulation by the reticuloendothelial system. Several methods are available for detecting the presence of specific drug-dependent platelet antibodies. These include complement fixation,\textsuperscript{103,217} "immunoinjury" techniques,\textsuperscript{117,217} and platelet agglutination.\textsuperscript{217} Such methods are preferable to those that measure platelet-bound antibody, since the former can be performed in the presence or absence of the suspected drug. However, Kelton et al.\textsuperscript{128} have used a combination of PAIgG and S-PBlgG determinations to demonstrate the increased binding of IgG to platelets, both in vivo and in vitro, in patients with drug-induced thrombocytopenia.

Reports of drugs being given antenatally to the mother, and purportedly causing thrombocytopenia in the newborn infant, are seldom well documented. An exception is the case of quinine-induced thrombocytopenia in a mother and infant, in both of whom platelet agglutinins were demonstrated.\textsuperscript{151} Other drugs that have been implicated are tolbutamide,\textsuperscript{207} hydralazine,\textsuperscript{251} and the thiazide diuretics.\textsuperscript{201} In these instances the pathogenetic mechanism has not been clearly defined, and the association may well be circumstantial. Certainly the role of thiazides is highly controversial.\textsuperscript{110,165,201} In the original report by Rodriguez et al.,\textsuperscript{201} three of seven cases were siblings and in one of these pregnancies it was not known whether the mother was receiving thiazide therapy. Such circumstances are more suggestive of an autoimmune or alloimmune process than drug-related thrombocytopenia. Another infant was found to be thrombocytopenic only after suffering a severe apneic episode associated with a grand mal seizure. Since this original report, other investigators have been unable to find an association between maternal thiazide ingestion and thrombocytopenia in the infant.\textsuperscript{110,165} Thus, although drug-related and immune-mediated thrombocytopenia has occurred in infancy, it is a rare event.\textsuperscript{188} Fatal intracranial hemorrhage resulting from drug-induced thrombocytopenia has been reported in adults,\textsuperscript{56} but not in children. Withdrawal of the offending agent is the treatment of choice and results in a rise in the platelet count usually within a few days.

**Nonimmune-Mediated Platelet Destruction**

**Surface-Mediated Platelet Destruction**

**Hemolytic-Uremic Syndrome**

Hemolytic anemia, acute renal failure, and thrombocytopenia constitute the triad described by Gasser et al.\textsuperscript{76} in 1955 as HUS. Since then, there have been numerous case reports and reviews of the
subject. The disorder has a peak incidence in early childhood, usually before the age of 4 years, involving males and females equally. Typically, affected infants and children have been previously healthy, except for a preceding mild infection that is usually manifested as non-specific gastroenteritis or occasionally involvement of the upper respiratory tract. One to 10 days later, pallor, purpura, and oliguria become evident. Melena, hematemesis, and neurologic manifestations occur less frequently. Lethargy, pallor, hepatosplenomegaly, purpura (30 to 40%), and hypertension (50%) are the dominant physical findings. The relationship between HUS and thrombotic thrombocytopenic purpura (TTP) is considered elsewhere in this issue. Although TTP is principally a disorder of adult life, it has been reported in infants and older children. In HUS the hemoglobin concentration ranges from 3 to 10 gm/dl and the blood smear reveals evidence of red cell fragmentation. Reticulocyte and total leukocyte counts are often elevated. The direct antiglobulin test is usually negative, and the red blood cell enzyme defects have not been demonstrated. Other laboratory evaluations reveal an elevated blood urea nitrogen and serum creatinine, an abnormal urinalysis (proteinuria, hematuria, casts). Thrombocytopenia is present in virtually all cases, but it is usually mild or moderate in degree. There is general agreement that the severity of the renal involvement dictates the ultimate outcome, with prolonged anuria and persistent hypertension being associated with a poor prognosis. Although in earlier series a mortality rate as high as 40% was reported, improved management of acute renal failure has lowered this to 5 to 10%. Long-term problems may result from chronic renal failure, hypertension, neurologic deficits, and recurrence of the disorder.

Several factors have been implicated in the etiology of HUS, including familial and genetic predisposition, pregnancy, viruses, bacteria, drugs, and contaminated apple juice. In the latter series, a cohort of 14 children presented within a 10-day period with a wide clinical spectrum of disease, i.e., from severe CNS involvement to only minor renal abnormalities. All of these children had ingested fresh apple cider manufactured locally in a single batch, suggesting that a contaminating organism or toxin was responsible.

It is very likely that diverse insults lead to a common renal injury. The pathology of the lesions in the kidneys has been reviewed extensively. In brief, the most consistent feature is thickening of the glomerular capillary walls due to an accumulation of periodic acid-Schoff (PAS) positive material in the subendothelial space. Thrombi are seen less frequently. Mechanisms that have been proposed to explain the thrombocytopenia are disseminated intravascular coagulation (DIC), adhesion of platelets to the damaged glomerular capillary wall, platelet aggregation in the kidneys as a result of local intravascular coagulation, and intrarenal platelet injury with subsequent sequestration in the reticuloendothelial system. Although abnormalities of plasma clotting factors have been reported, these values are usually normal, indicating that DIC is not an important mechanism leading to thrombocytopenia in this disorder. Furthermore, although labeled platelets do have a shortened half-life, external counting over the kidneys has failed to demonstrate significant renal pooling. Thus, the most plausible mechanism is platelet injury inflicted by fibrin strands in the renal microcirculation.

The care of children with HUS has been reviewed exhaustively in recent articles in which the energetic management of acute renal failure, with the early use of dialysis, is emphasized. Any role for steroids, fibrinolytic agents, anticoagulants, aspirin, or dipyridamole is debatable, and the use of these agents is probably not indicated.

### Thrombin-Mediated Platelet Destruction

#### Disseminated Intravascular Coagulation

Although DIC is an infrequent event in childhood, it occurs in up to 10% of sick infants admitted to a neonatal intensive care unit. The precipitating disorders include obstetrical complications, asphyxia, infection, hypothermia, necrotizing enterocolitis (NEC), severe hemolytic anemia, vascular lesions, and neoplasia. In a series of infants with severe birth asphyxia and cardiovascular collapse at our institution, 40% developed hypofibrinogenemia, and two-thirds of these were thrombocytopenic. However, the remainder of the infants who did not develop DIC were at no greater risk than other infants of developing thrombocytopenia. This suggests that DIC is an important mechanism by which asphyxia causes thrombocytopenia in the newborn.

The laboratory diagnosis of DIC in children is the same as in adults. In the neonate, it is essential to compare the results with age-related values. Prolongation of the prothrombin time and partial thromboplastin time is not very helpful, but the thrombin clotting time as a screening test, the fibrinogen concentration, and platelet count are very useful in deciding whether DIC exists.
wise, assays of Factors V and VIII, which are normally in the adult range, are commonly reduced when DIC is present.

The most effective treatment for DIC, in both infants and older children, is correction of the underlying disease process. Unless this is accomplished, DIC will usually persist and the outcome is often fatal. Heparin has not been of value in managing DIC in childhood and rather may cause further bleeding. Unless there is evidence of widespread thrombosis, we do not recommend the use of heparin. In our experience replacement of the underlying disorder.

**Giant Hemangioma**

Giant hemangiomas may cause consumptive coagulopathy with hypofibrinogenemia, thrombocytopenia, and resulting generalized purpura (Kasabach-Merritt syndrome). The vascular tumor is present at birth, may occur anywhere on the body, and is usually large and solitary. Approximately 50% of affected infants experience systemic bleeding during the first month of life. It is believed that platelets are destroyed or sequestered within the tumor, regression of which may occur spontaneously or following the use of steroids or radiation therapy. Surgical excision has also been effective. Hemangiomas of the placenta have caused self-limiting destructive thrombocytopenia at birth.

**Nonimmune-Mediated Thrombocytopenia from Other Causes**

**Necrotizing Enterocolitis**

NEC presents in the premature infant with bloody stools, vomiting of bile-stained gastric residue, and abdominal distension. Intramural gas is usually demonstrable radiographically, and the diagnosis is confirmed by histologic examination of the bowel either at autopsy or following surgical resection. The hematologic parameters of 44 infants with NEC were studied at our institution. In 85% of these infants there was gastrointestinal bleeding and 47% were thrombocytopenic, including all of those who died (25%). DIC was present in only 22% of those with thrombocytopenia, suggesting that alternative mechanisms were responsible for the reduction in the platelet count in most instances. Other investigators have reported similar results. Additional features in some of these infants were polycythemia, infection, and hypoxia, all of which may contribute to thrombocytopenia, as may local consumption of platelets in the necrotic bowel wall.

**Hemolytic Anemia and Exchange Transfusions**

Thrombocytopenia may occur in infants with erythroblastosis fetalis. The mechanism is undefined, but the possibilities include hypersplenism, DIC, and platelet destruction secondary to interaction with procoagulant products of red blood cell lysis. Exchange transfusions in these infants and in others are known to result in thrombocytopenia. This is secondary to dilution by nonviable platelets in stored blood, removal of viable platelets during the process of volume exchange, and a limited ability of the bone marrow to compensate for such an acute deficit.

**Phototherapy**

Phototherapy, a common form of treatment for hyperbilirubinemia in the newborn, has been demonstrated to cause a mild thrombocytopenia. In a rabbit model, phototherapy shortened the platelet survival, suggesting that increased destruction was taking place. In vitro experiments have been performed in which platelets were exposed to a broad spectrum blue fluorescent light, with a resulting decrease in aggregation, reduction of glycogen granules and organelles, and loss of definition of the external membranes.

**Intrauterine Growth Retardation and Congenital Polycythemia**

Intrauterine growth retarded infants, without other problems, often have a mild degree of thrombocytopenia. Postulated mechanisms include consumption in an infarcted placenta, chronic hypoxia, and DIC.

The association of congenital polycythemia and thrombocytopenia has been described frequently. The mechanism has not been determined, but it has been proposed that the increased platelet consumption is induced by the blood hyperviscosity, an hypothesis supported by observations in children having polycythemia secondary to cyanotic congenital heart disease.

**Congenital heart disease.** Children with cyanotic congenital heart disease frequently have thrombocytopenia when the hemoglobin concentration is greater than 17 gm/dl. Platelet kinetic studies have revealed a reduction in the platelet lifespan, but DIC does not appear to be the pathogenetic mechanism responsible.
Hypoxia

Hypoxia, a common insult in the newborn period, has been shown to cause a severe and persistent thrombocytopenia in mice. Possible mechanisms are a decreased rate of platelet production or a structural or metabolic defect in the platelets leading to increased destruction. Whether this is an important phenomenon in human neonates has not been determined.

Deficient Plasma Factors

Thrombocytopenia, which is corrected by infusions of plasma, has been reported in both infants and older children. Platelet survival is shortened and a hemolytic anemia may be present as well. In our experience with such a patient, temporary remission has been achieved repeatedly with fresh frozen plasma and infusions of cryoprecipitate but not with albumin. The basic abnormality remains undefined.

Hypersplenism

Hypersplenism occurs in numerous diseases in children, and thrombocytopenia is a well-known complication. The degree of thrombocytopenia is usually mild (50,000 to 100,000/mm³) and exhibits an inverse correlation with the size of the spleen. The use of labeled platelets has demonstrated clearly that splenic “pooling” is responsible for the reduction in the circulating platelet count. Normally, one-third of the total platelet mass is located in the spleen, but in hypersplenic patients up to 90% is contained in this organ. The half-life of the labeled platelets is only minimally decreased, indicating that these are only sequestered in the spleen and not destroyed there prematurely.

COMBINED IMMUNE- AND NONIMMUNE-MEDIATED PLATELET DESTRUCTION

Infection-Induced Platelet Destruction

Thrombocytopenia has been documented frequently in infants and children who are acutely infected with a variety of microorganisms. Bacterial and viral infections have been studied in greatest detail. In neonates and older children with proved bacterial infections, thrombocytopenia occurs in 60%. This is similar to the frequency reported in adults. Although 25 to 60% of such children have some evidence of DIC, in at least 40% this is not the explanation for the thrombocytopenia. Indeed there is experimental evidence to support other pathogenetic mechanisms, such as endothelial damage by bacteria or bacterial products leading to platelet adhesion and aggregation, and immune-mediated thrombocytopenia. Kelton et al. have reported that PAIgG is increased in adult patients with documented sepsis, and Tate and his co-workers made an identical observation in eight of nine infants with bacterial infections.

A low platelet count has been reported in association with a wide variety of viral infections in children. Experimental studies indicated that several mechanisms may be involved. These include DIC, virus-induced lysis of red blood cells with the release of procoagulant materials, endothelial damage with increased platelet consumption, platelet phagocytosis of virus particles, loss of sialic acid from the platelet membrane due to the action of viral neuraminidases, intravascular platelet aggregation, immune-mediated platelet destruction, and impaired platelet production. In clinical studies, direct invasion of the megakaryocytes with virus, has been reported. Immune-mediated platelet destruction is likely to be an important mechanism, as suggested by the association of a preceding viral infection in the majority of children with acute ITP and the high level of PAIgG in six of eight infants with documented viral infections. In the latter series, four infants had CMV, two had enteroviral infections, one had herpes simplex virus, and one had an echovirus. Thrombocytopenia due to rubella infection has been studied in some detail. In congenital rubella, 86% of infants have thrombocytopenia, with a majority having counts between 20,000 and 60,000/mm³. Serious hemorrhage occurs rarely, and the thrombocytopenia resolves usually by 4 to 8 weeks of age. A decrease in the number of megakaryocytes has been reported in bone marrow aspirates from these infants, but, given the difficulty of obtaining reasonable specimens in the newborn period, it is difficult to interpret this information reliably. Platelet kinetics and platelet-related antibodies have not been measured in these infants. Rubella-induced thrombocytopenia in older children is thought to be immune mediated.

The management of infants and older children with thrombocytopenia, which is secondary to infections, will depend on the severity and pathogenesis of the reduction in the platelet count. In the majority of children the thrombocytopenia is mild and no specific treatment for the thrombocytopenia is necessary. For the few in whom intervention is...
required, infusion of random donor platelets and the administration of corticosteroids have been of benefit in selected cases.172,253

**COMMENT**

Although numerous defined pathologic processes contribute to increased platelet destruction in infancy and childhood, the mechanism responsible for thrombocytopenia may be unclear or multifactorial. Thus, in a recent prospective study of all infants admitted to a neonatal intensive care unit, approximately 10% of whom were appreciably thrombocytopenic (<100,000/mm$^3$) in the first few days of life, no cause for the low platelet count could be identified in the great majority.26 In this age group in particular, much remains to be learned of the factors that influence platelet turnover and the pathologic events that may lead to exaggerated platelet destruction.

**REFERENCES**


129. Kelton JG: Personal communication.


175. Moulinier J: New observations on the platelet group DUZO.
INCREASED PLATELET DESTRUCTION IN INFANCY AND CHILDHOOD—ANDREW, BARR 261


225. Steele BT, N Murphy, GS Arbus, CP Rance: An outbreak of hemolytic uremic syndrome associated with ingestion of fresh apple juice (cider). Submitted for publication.


