Clinical Management of Bleeding Disorders

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Management of Bleeding Disorders in Children

Catherine S. Manno

Diagnosis and management of congenital and acquired bleeding disorders in children requires not only an understanding of the unique characteristics of pediatric hemostasis but also the natural course of bleeding disorders in children, which may differ substantially from the course observed in adult patients. In this article, three bleeding disorders of great importance to the pediatric hematologist are reviewed: neonatal alloimmune thrombocytopenia (NAIT), hemophilia and immune-mediated thrombocytopenic purpura (ITP). Current aspects of management are outlined. The unique physiology of transplacental transfer of maternally derived anti-platelet antibodies can result in neonatal immune thrombocytopenia, a significant cause of morbidity and mortality from bleeding in affected infants. For patients with hemophilia, approaches to treatment have shifted over the past decade from on-demand therapy to prophylaxis, either primary or secondary, resulting in delay of onset or complete avoidance of hemophilic arthropathy. Hemophilic inhibitors often develop in young children, prompting the need for a thorough understanding of the use of bypassing agents as well as immune tolerance induction in the young child. Finally, although several management strategies for ITP of childhood have been shown to improve the platelet count, side effects associated with corticosteroids, IVIg, anti-D and splenectomy force the practitioner to also consider the option of carefully observing, but not treating, the child with ITP.

The diagnosis and management of children with congenital and acquired bleeding disorders requires knowledge of the normal physiology of pediatric hemostasis and the natural history of coagulation disorders in children compared to adults. The normal range for the newborn prothrombin and partial thromboplastin time extend above those determined for a healthy adult population. Despite this, there is no increased risk of bleeding in a healthy newborn owing in large part to the normally reduced neonatal levels of the naturally occurring anti-coagulants protein C and protein S. Vitamin K-dependent factor levels do not reach the adult range until infants reach six month post-natal age, with the exception of protein C, which takes years longer.1 The normal range for term and premature infants’ platelet counts is the same as the normal range for the adult (150,000-400,000/mm³); less than 1% of term newborns are thrombocytopenic.2 Serious, spontaneous hemorrhage may occur at a higher platelet count in the thrombocytopenic infant, particularly the premature infant, than in an equally thrombocytopenic adult. The risk of intracranial hemorrhage (ICH), particularly intraventricular hemorrhage, is inversely proportional to neonatal gestational age.

Thrombocytopenia due to decreased platelet production may be seen in infants with congenital anomalies or systemic viral infection. Increased platelet destruction in the fetus or infant may be due to disseminated intravascular coagulation, Kassabach-Merritt syndrome, hypersplenism or the transplacental passage of a maternally derived antibody in the context of maternal systemic lupus erythematosus (SLE), maternal immune-mediated thrombocytopenia (ITP), maternal drug use or maternal platelet incompatibility with a paternally derived antigen on the fetal platelet membrane (i.e., neonatal alloimmune thrombocytopenia [NAIT]).

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Neonatal Alloimmune Thrombocytopenia

NAIT is the most common cause of severe neonatal thrombocytopenia with an estimated incidence of 1 in 1000 to 1 in 2000 live births. In affected families, NAIT may occur in the firstborn and the risk of worsening thrombocytopenia increases with each subsequent pregnancy. Prior to birth, as early as 20–24 weeks of gestation, NAIT may cause ICH with the potential for porencephaly or intrauterine death. The risk of clinically significant bleeding in infants with NAIT is higher than in those with similar platelet counts due to maternal ITP or maternal SLE, making the recommendations for intervention more aggressive.

When infantile thrombocytopenia is due to NAIT, the maternal platelet count is normal. Physical findings of the neonate include skin and mucous membrane bleeding with petechiae, ecchymoses and/or cephalohematoma. Laboratory evaluation demonstrates severe thrombocytopenia (<30,000/mm³) with normal white blood count and anemia commensurate with blood loss. Platelet antigens most often associated with NAIT are described in Table 1.

The diagnosis of NAIT is generally based on clinical presentation while the purpose of testing is twofold: to confirm the diagnosis in a suspected case and to guide management of future pregnancies of the affected couple and the mother’s family members. Serologic platelet antibody assays (serum mixed with phenotyped, donor type O platelets) can be used to identify platelet-specific alloantibodies in the patient serum and are used to establish platelet alloantigen phenotypes. Flow cytometry, used in conjunction with the monoclonal antibody-specific immobilization of platelet antigen test (MAIPA), will detect weak antibodies or a mixture of antibodies. The most accurate way to perform platelet antigen typing is by using DNA-based platelet typing: this technique not only allows for confirmation of serological typing, but also identifies rare or private antigens and distinguishes heterozygotes from homozygotes at the platelet antigen of interest. Infants with neonatal platelet counts of <50,000/mm³ or with a platelet count <100,000/mm³ with an ICH, a family history of neonatal thrombocytopenia or no obvious cause of neonatal thrombocytopenia should be tested for NAIT. If an infant serum sample cannot be obtained for identification of antibody, maternal and paternal platelet typing should be performed and compared for incompatibility. The importance of sending diagnostic or confirmatory samples to a clinical laboratory with experience cannot be over-emphasized.

The clinical course of NAIT is variable, with the most severely affected experiencing prenatal ICH with resultant porencephaly and/or intrauterine demise. The majority of infants with parenchymal or subdural hemorrhages have a poor prognosis with residual spasticity, hypotonia, cortical blindness, developmental delay, seizures or psychomotor retardation. In nulliparous females, the presenting features of NAIT may be ICH or hydrocephalus observed on a screening prenatal ultrasound. In the context of an anticipated recurrence, fetal blood samples taken at 20 weeks gestation allow for analysis of fetal platelet antigen typing and fetal platelet count. If the fetus is affected, treatment with intravenous immunoglobulin (IVIg) in a dose of 1-2 g/kg is administered to the mother on a weekly or bi-weekly basis. Follow-up fetal blood sampling is performed at 24 weeks gestation to assess response to the immunomodulatory therapy. If the platelet count remains low despite treatment with IVIg, corticosteroids may be administered to the mother. At the time of delivery, if the response to IVIg or corticosteroids has been inadequate and the infant’s platelet count is <50,000/mm³, consideration should be given to intrauterine platelet transfusion prior to vaginal delivery or delivery via C-section.

Infants born with thrombocytopenia (<30,000/mm³) due to NAIT require rapid pharmacological or transfusion intervention since the platelet count is likely to fall further even though the source of antibody disappears when the umbilical cord is cut. In the face of active, life-threatening bleeding (e.g., an evolving ICH or gastrointestinal bleeding), platelet transfusion with random donor platelets should be given while awaiting a platelet unit from an antigen-negative donor or from the infant’s mother, who is by definition, antigen-negative. If maternal platelets are transfused, they must be washed to remove the corresponding antibody and also irradiated. Today, many blood centers have developed a registry of committed donors whose platelet antigen type is known. If there is no active bleeding, treatment with IVIg is appropriate with the goal of raising the platelet count at least above 50,000/mm³. All infants with NAIT should be evaluated with CT or ultrasound of the brain to evaluate for ICH. Close follow-up of platelet count is recommended for the first month of life, until the platelet count normalizes, at which time recurrence of thrombocytopenia is unlikely.

Table 1. Platelet antigens most often associated with neonatal alloimmune thrombocytopenia (NAIT).

<table>
<thead>
<tr>
<th>Platelet Antigen</th>
<th>Alternative Name</th>
<th>Gene Frequency</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPA-1a</td>
<td>P&lt;sup&gt;a&lt;/sup&gt;, Zw&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.85</td>
<td>Responsible for 75% of clinically significant NAIT in Caucasian population&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>HPA-3a</td>
<td>Bak&lt;sup&gt;a&lt;/sup&gt;, Lek&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.63</td>
<td>Clinically significant NAIT in Caucasian population&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td>HPA-4a</td>
<td>Pen&lt;sup&gt;a&lt;/sup&gt;, Yku&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.99</td>
<td>Severe disease in Asian population, rarely Caucasian&lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
<tr>
<td>HPA-5a</td>
<td>Br&lt;sup&gt;b&lt;/sup&gt;, Hc&lt;sup&gt;b&lt;/sup&gt;, Zav&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.89</td>
<td>Causes mild NAIT in Caucasian population&lt;sup&gt;4,5&lt;/sup&gt;</td>
</tr>
<tr>
<td>HPA-5b</td>
<td>Br&lt;sup&gt;b&lt;/sup&gt;, Hc&lt;sup&gt;b&lt;/sup&gt;, Zav&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.10</td>
<td>In Caucasian population&lt;sup&gt;6&lt;/sup&gt;</td>
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Hemophilia

Hemophilia A and B are X-linked bleeding disorders with no racial predilection. Hemophilia A (factor [F.] VIII deficiency), with an incidence of 1 in 5000 live male births,\(^{15}\) is four times more common than hemophilia B (F. IX deficiency). About 70% of babies born with hemophilia have a positive family history. Patients with severe hemophilia have < 1% functional factor activity. When the diagnosis is not suspected based on a positive family history, affected children present with bleeding at circumcision, bleeding following intramuscular immunization, excessive bruising, or rarely with ICH. The most common cause of morbidity in severe hemophilia is bleeding into closed joint spaces (hemarthrosis), while the most common cause of mortality is ICH.

In the context of hemophilia, molecular genetic testing can be used for several purposes: (1) to confirm a diagnosis suggested by low circulating F. VIII levels, (2) to determine whether female relatives of hemophilia patients are carriers or (3) for prenatal diagnosis. Genetic testing and counseling should be offered to potential female carriers of hemophilia, that is, female relatives of either obligate carriers or hemophilic males. This should occur before conception in order to fully outline the clinical course in affected individuals, the potential for prenatal diagnosis and options for current or future pregnancies.\(^{15}\) Daughters of men with hemophilia are by definition obligate carriers and thereby do not require genetic testing. DNA analysis is revealing in 90% of cases of severe hemophilia. Prenatal diagnosis can also be made through the analysis of fetal blood samples for F. VIII or F. IX activity. These samples cannot be obtained until approximately 16 weeks gestation, and contamination of the fetal blood samples with amniotic fluid may give a false negative result.

Molecular diagnostic testing for hemophilia A

More than 800 F8 mutations have been reported in the Human Gene Mutation Database (Cardiff) (http://uwcmml1s.uwcm.ac.uk/uwcm/mg/search/119124.html). Molecular analysis of DNA derived from chorionic villus sampling can be performed in the 11th-12th gestational week and is the most reliable method for prenatal identification of a causative mutation. The approach to genetic diagnosis of severe hemophilia A starts with evaluation for the F8 intron 22 –A gene inversion using Southern blot analysis. Forty-five percent of cases of severe hemophilia A cases are a result of this gene inversion, which prevents amplification of the RNA message across the boundary between exon 22 and 23.\(^{14,15}\) If Southern blot analysis is not revealing, direct sequence analysis of all 26 exons and flanking sequences is performed for detection of point mutations, either missense or nonsense (62%), splice junction changes (6%), large deletions (10%), small deletions (14%), and small insertions (4%) (data from Human Gene Mutation Database, Cardiff). If sequence analysis does not uncover a mutation, an inversion of intron 1 has been demonstrated to be responsible for 1%-2% of cases.\(^{16}\)

Analyses in a single laboratory, the Genetic Diagnostic Laboratory at the University of Pennsylvania, on 89 individuals with F. VIII deficiency demonstrated that 80 (90%) had a mutation in the coding sequence of F. VIII:C.\(^{17}\) Seven of 9 mutation-negative individuals who had severe disease did not reveal any mutation in the coding sequence or the rearrangement in intron-22 but had mutations in non-coding sequences, demonstrating that other loci can act as modifiers of the hemophilic phenotype. Analysis of these mutations is not currently part of routine screening of the F. VIII gene. If the causative mutation in an affected family member has been previously identified, screening for that mutation can usually be accomplished in 2-3 weeks.

Molecular diagnostic testing for hemophilia B

The F. IX gene is also located on the X chromosome. Unlike severe hemophilia A, there is no single mutation responsible for a large number of cases of hemophilia B. While severe disease is caused by gross gene alterations, frameshift or splice junction changes or nonsense/missense mutations, mild and moderate disease is usually caused by missense mutations. Genetic analysis of the F. IX gene is accomplished via direct sequence analysis, which can identify more than 99% of causative mutations found in the promotor, coding sequences or splice sites of the gene.

Clinical management and outcomes in hemophilia

Over the past 20 years, the combination of routine, comprehensive medical care, safe factor concentrates and aggressive disease-specific education has allowed the current younger generation of hemophilia patients to grow into adulthood with excellent joint function, the potential for full-time employment and a relatively normal life-style. Concentrates are prescribed on an on-demand or prophylactic schedule, depending on the individual patient’s bleeding pattern and the philosophy of the treating physician. The Medical and Scientific Advisory Council (MASAC) of the National Hemophilia Foundation, recommends that recombinant factors should be the treatment of choice for individuals with hemophilia A and hemophilia B (www.hemophilia.org/research/masc/masac106.htm).

Joint disease is the major morbidity to be prevented in severe hemophilia. Standardized tools that categorize the degree of arthropathy traditionally relied on plain X-ray changes. The Arnold-Hilgartner scale describes pathology in a single joint.\(^{18}\) The Pettersson score also describes a radiological classification but requires assessment of 8 characteristics of the 12 large joints.\(^{19}\) The individual and population benefits of treatment programs aimed at preserving joint function can be compared through the use of these tools. More recently magnetic resonance imaging (MRI) of hemophilic joints has allowed for earlier detection of synovial hypertrophy than can be detected on physical examination or plain X-ray. An international group has published
two MRI scales, compatible with each other, to help make MRI joint assessment uniform and to facilitate international comparison of joint health.20

On-demand factor concentrate infusions (i.e., the infusion of concentrate at the time of a bleeding episode and prior to surgery or dental procedure) are appropriate for severe hemophilia patients with a ‘mild phenotype’ (approximately 15% of patients with <1% F. VIII or F. IX), characterized by rare hemarthroses or other spontaneous bleeding episodes. When applied to the appropriate patient, the on-demand approach is less expensive and less invasive than prophylaxis but associated with the same excellent outcome. A prospective randomized pediatric prophylaxis study is currently under analysis that will determine the role of “aggressive on demand” therapy compared to standard prophylaxis in joint disease progression.

Primary prophylaxis involves routine administration of F. VIII concentrates (3 times per week or every other day) or F. IX concentrates (2 times per week) starting early in life for prevention of joint bleeding and progression to chronic joint disease. Secondary prophylaxis involves the routine infusion of factor concentrate after a bleeding episode with the goal of halting the progression of joint disease. Many prophylaxis regimens begin with the goal of maintaining a trough factor level of ~1%. Although secondary prophylaxis does not reverse chronic joint disease and is associated with an increased risk of arthropathy compared with primary prophylaxis, it does reduce the frequency of bleeding, days lost from school and days of hospitalization.

The precise time to begin prophylaxis is controversial. The effect of postponing secondary prophylaxis in a cohort of severe hemophilia patients born between 1965 and 1985 showed that for every year that prophylaxis was postponed after the first joint bleed, the orthopedic joint score was increased by 8%. This effect was independent of age at first joint bleed and dose of prophylaxis used.21

One widely accepted guideline for successful prophylaxis is to prescribe a dose and interval that allows the trough level prior to the next infusion to be ≥1%, therefore converting severe hemophilia to moderate hemophilia (1%-5% baseline factor levels). An alternate approach is to adjust the dose and dosing interval based on an individual child’s bleeding pattern. When the frequency of joint bleeds and orthopedic joint scores were evaluated in 121 patients with severe hemophilia who had started prophylactic treatments at least weekly prior to age 10 years, a significant reduction in the overall number of joint bleeds per year was observed after shortening the interval between infusions from 1 per week to 2 (hemophilia B) or 3 (hemophilia A).22 Later age at start of prophylaxis was found to be an independent predictor for the development of arthropathy but dose and infusion interval were not. These authors of this study reiterate the importance of early initiation of prophylaxis but recommend that treatment schedules and doses be individualized in response to a particular patient’s bleeding pattern because of the wide variability of individual bleeding patterns.22

For patients with chronic hypertrophic synovitis, pain and deformity may be disabling. Removal of the diseased synovium to reduce or eliminate recurrent bleeding can be accomplished by arthroscopic surgery or radionuclide synovectomy (RS). Arthroscopic synovectomy controls recurrent hemarthroses and slows the progression of joint disease with less post-operative bleeding, infection and time to recovery than observed with the open procedures.20 More procedures have been performed on knees than any other joint.

RS involves injection of a radioisotope (usually phosphorus-32) into the joint space. RS is less expensive than arthroscopic synovectomy owing to a shorter rehabilitation period and lesser requirement for factor replacement. Because the risk of bleeding is less than with surgical procedures, RS has been preferred in many centers for patients with high titer hemophilic inhibitors who have intractable joint disease. Concern has arisen recently following the report of a second case of acute lymphoblastic leukemia within one year of RS in boys with hemophilia.27 Although cause and effect has not been established between RS and ALL in patients with hemophilia, the potential of a link between the two cannot be dismissed. Prudence in recommending RS is reasonable while more data are collected on this low incidence but potentially life-threatening association. The MASAC has published guidelines for clinicians who are considering referring hemophilia patients for RS, outlining the details of the two leukemia cases, information for informed consent and mechanisms for reporting new cases.28

Inhibitory antibodies (usually IgG4 antibodies that neutralize the procoagulant activity of F. VIII or F. IX) develop in approximately 25% of patients with severe hemophilia A and 3%-5% of patients with hemophilia B following exposure to factor concentrates. In a group of severe hemophilia A pediatric patients from Germany, followed from 1976 to 1991, time to inhibitor formation after first exposure to factor concentrate was a median of 11.5 exposure days, making recognition and management of new inhibitors a pediatric problem in the majority of patients.29 Inhibitors are classified as low titer (<5 Bethesda units [BU]) or high titer (>5 BU). Many low titer inhibitors may disappear with time and patients may not require specific eradication therapy. Patients with high titer inhibitors may present with lack of clinical response to previously effective factor concentrate infusion during a bleeding episode. Patients with high titer inhibitors do not stop bleeding when infused with factor concentrates and also demonstrate anamnesis with resultant rise in inhibitor titers following exposure to factor. Routine screening for the presence of inhibitors, using the Bethesda assay, should be part of routine screening in the clinic and may be the first clue to its development. Bleeding episodes require treatment with bypass agents, either recombinant F. VIIa (NovoSeven®, NovoNordisk A/S, Denmark) or FEIBA VH, a plasma-de-
rived, activated prothrombin complex concentrate (Baxter Healthcare Corporation, Westlake Village, CA), but success is judged by clinical improvement alone since laboratory testing does not correlate with hemostasis. Recommended dosing for rVIIa in inhibitor patients who are experiencing a bleeding episode or prior to an invasive procedure is 90 µg/kg, every 2 hours until bleeding manifestations improve.30 FEIBA VH is given at a dose of 75 IU/kg every 12 hours with the same recommendation, to repeat doses until clinical improvement is observed. A head to head comparison of the safety or efficacy of these two agents in the context of hemophilic inhibitors has not yet been completed. Eradication of inhibitors with immune tolerance induction is costly and intensive. Routine high-dose infusion of the factor to which the antibody is made is successful in long-term eradication of high titer inhibitors in approximately 70% of patients. Parameters associated with success include peak historical titer, inhibitor titer at the start of immune tolerance of < 10 BU, initiation of the tolerance program in relation to inhibitor development (earlier being related to increased success), and genetic defect causing the hemophilia.31 Others regimen variables are currently being investigated in the International, Randomized, Controlled Trial of Immune-Tolerance Induction. There are also suggestions that F. VIII inhibitors, F. VIII concentrates that contain von Willebrand factor may increase the success of tolerance induction better that ultrapure recombinant F. VIII (rFVII) concentrates. Several registries documenting international experience with tolerance induction have allowed for better understanding of this difficult management issue.31

Prevention of inhibitor formation is an area of great interest. Some investigators believe that early exposure to F. VIII may be associated with an increased risk of inhibitor formation. In an attempt to eliminate exposure to F. VIII early in life, Canadian investigators treated bleeding episodes in infants with rVIIa until age 2 years and then reverted to treatment with rFVIII. The rate of inhibitor formation in the boys who had received rVIIa exclusively was comparable to the group that received rFVIII.32 Reliable venous access is important for the success of prescribed prophylaxis regimens as well as for immune tolerance induction in patients. Central venous access devices may be indicated to reduce anxiety associated with repeated, unsuccessful attempts and to be certain that factor is administered as scheduled. Single lumen catheters are preferred for the delivery of coagulation factor concentrates. The risk of catheter-related infection is higher in patients with hemophilia than in other patient populations due to the residual blood left at the injection site following concentrate infusion. The most common causative organisms are gram-positive Staphylococcus epidermidis and S. aureus. Gram-negative causes include Pseudomonas and Enterobacter cloacae ssp.23 Reported rates of catheter-related infection in hemophilia vary widely; a recent meta-analysis calculated a pooled incidence of infection of 0.66 per 1000 central venous access device (CVAD) days (CI: 0.44–0.97 per 1000 CVAD days).24 This analysis also showed the overall risk of infection with CVAD was 40.0%. The infection risk in inhibitor patients is higher still perhaps due to the increased number of times ports are accessed during immune tolerance induction. An alternative method to consider for routine access into the venous system, particularly for children and those with inhibitors, is the creation of arterio-venous (A-V) fistulae.25

**Immune-Mediated Thrombocytopenic Purpura**

Nearly half of the cases of immune-mediated thrombocytopenic purpura (ITP) seen each year are in children, typically at ages 3-6 and 11-14 years. The classical presentation includes a previously well child with sudden onset of excessive bruising, petechiae or mucous membrane bleeding 1-2 weeks after a viral infection or an immunization. The physical examination is significant for lack of adenopathy of hepatosplenomegaly. The CBC demonstrates isolated (and often profound) thrombocytopenia, although some children may be anemic due to blood loss and approximately 10% of children have transient absolute neutropenia. Screening to rule out systemic lupus erythematosus, Evans syndrome, human immunodeficiency virus (HIV) infection or other causes of immune-mediated thrombocytopenia may be indicated.

A retrospective study of 72 patients who had follow-up of at least 6 months showed that 75% had a durable spontaneous remission of ITP within 6 months. In a multivariate analysis, low admission mean platelet volume (< 8 fL), a history of a viral prodrome and low admission platelet count (< 10,000/mm³) correlated with remission.33 The insidious onset of bruising with less severe thrombocytopenia and diagnosis at ages 10-18 years are more likely associated with a chronic clinical course.34 A recent Dutch study found a low frequency of Fc gamma receptor 2B (FCGR2B)-2321/T genotype in patients with acute disease,35 compared to chronic ITP, suggesting that alterations in apoptotic signaling and B cell survival may play a role in the production of platelet autoantibodies.36

Therapeutic options to increase the platelet count and, by proxy, reduce bleeding manifestations in acute ITP include corticosteroids, IVIg and anti-D (Win-Rho). Bone marrow aspiration has been routinely performed in the past when corticosteroids were the preferred pharmacological treatment for acute ITP, in order to eliminate the possibility of acute lymphoblastic leukemia. Today, with the ready availability of newer immune-mediated treatments, the diagnostic bone marrow examination is reserved for only the most ambiguous presentations of ITP. When compared with placebo, corticosteroid administration is associated with an earlier rise in platelet count than seen when no therapy is administered.37 However, the side effects of weight gain, sleep disturbance, hypertension and hyperglycemia require careful monitoring (although short courses utilized in childhood ITP are not commonly associated with these symp-
tons). For patients with acute ITP, a short course of high-dose corticosteroids, using either an oral or intravenous preparation, results in a clinically significant increment in platelet count with cessation of bleeding, without excessive steroid side effects. High-dose steroid courses have not been demonstrated to cure childhood ITP.

The benefit of IVIg has been demonstrated in several prospective studies over the past two decades. A Canadian trial with four treatment arms compared two IVIg regimens (0.8 g/kg once, 1.0 g/kg on 2 successive days) with oral prednisone (4 mg/kg/day for 7 days with a 2-week taper) and anti-D (25 µg/kg for 2 days). The low-dose IVIg was shown to be as effective as the higher dose. When the clinical endpoint of number of days with platelet count < 20,000/mm³ was considered, the IVIg options were found to be more effective than anti-D. The effect of IVIg on the platelet count lasts between 2 and 6 weeks. The major disadvantages include high cost and infusion-related side effects such as rigor, chills and aseptic meningitis.

Although the effect of anti-D on platelet count is generally not as long-lived as that of IVIg, many practitioners prefer its ease of administration (IV push). A retrospective analysis by Tarantino et al comparing the use of 45-50 µg/kg with IVIg (0.8-1.0 g/kg) concluded that 50 µg/kg of anti-D for initial treatment of ITP compared favorably with IVIg. Anti-D must be used in Rh(D) positive patients who have not undergone splenectomy. Adverse events include headache, nausea, chills and fever. Sixteen percent of adult patients treated with anti-D developed hemolysis with a mean hemoglobin drop of 0.8 g/dL + 1.5, 7 days after treatment.

There is an emerging experience with anti-CD20 (rituximab) in the treatment of acute and chronic ITP. An early, encouraging case report was of an infant with severe, life-threatening ITP who had a sustained response after receiving anti CD20. More recently, the effect of 375 mg/m² of rituximab in 4 weekly doses in 24 patients aged 2-19 years with chronic ITP was reported to induce a complete response in more than half of the patients, and the response lasted 4-30 months. The results of a multicenter study of rituximab in ITP will be published soon. Splenectomy is recommended for acute or chronic ITP associated with significant hemorrhage when other therapies have had no significant benefit or are overly toxic. The acute risks include portal vein thrombosis, bleeding, and the longer-term risk for overwhelming sepsis. The clinician must carefully assess the patient’s potential for eventual recovery without surgery especially in chronic, mild-moderate pediatric ITP. Splenectomy is usually performed by laparoscopy during a relatively short hospital stay. A review of 38 elective splenectomies performed at a single institution over a 35-year period showed that 76% had a normal platelet count a median of 2.1 years after surgery.

References