



CLINICAL HEMOSTASIS REVIEW

An Update on Advances and Issues in Hemostasis

Thrombocytopenia - Common Etiologies and Laboratory Evaluation

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Thrombocytopenia can develop as a result of decreased platelet production, increased destruction of platelets, and alterations in platelet distribution. Both congenital and acquired disorders can contribute to thrombocytopenia although the later is far more commonly found. This issue will discuss the most frequent etiologies of thrombocytopenia and the laboratory assays that can assist in distinguishing the causes of low platelet counts.

Introduction

Platelets are anucleate fragments of megakaryocytes. Platelets have a life span of seven to ten days following a five-day maturation sequence in the bone marrow. Normally, at any given time, approximately one-third of the total number of platelets is sequestered in the spleen. Thrombocytopenia is defined as a platelet count below 150,000/ μ L. However, any rapid decrease in platelet count should be investigated even if the count remains in the normal range of 150,000/ μ L-450,000/ μ L.

Pathophysiology

Individuals with platelet counts between 81,000/ μ L-150,000/ μ L are defined as having mild thrombocytopenia, while counts between 50,000/ μ L-80,000/ μ L are considered moderate thrombocytopenia. Both mild and moderate thrombocytopenia are typically asymptomatic in clinical settings when other hemostatic

abnormalities are absent. Severe thrombocytopenia, platelet counts of less than 50,000/ μ L, can be associated with hemorrhagic diathesis. One of the more frequent findings in individuals with severe thrombocytopenia is petechiae, which may cover large parts of the body.

The urgency of intervention in any given patient is dependent upon the risk posed by the thrombocytopenia. Thrombocytopenia is always the result of an underlying disorder or cause and may be self limiting. In fact, the underlying disorder is often of more significant concern than the thrombocytopenia itself. Often the treatment of the underlying disorder results in resolution of the thrombocytopenia.

Platelet counts less than 10,000/ μ L are associated with spontaneous systemic bleeding, and the possibility for intracranial hemorrhage. Patients with platelet counts between 10,000/ μ L and 50,000/ μ L may experience bleeding after a hemostatic challenge event such as surgery, dental extraction, or

Volume 17, Number 2
February 2003

Objective: The reader will be able to discuss the common etiologies of thrombocytopenia, the laboratory evaluation used to distinguish among these disorders, and the therapies used to manage thrombocytopenia.

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All correspondence should be directed to the attention of the Editor, Clinical Hemostasis Review, 7700 E. Wrightstown Road, Ste. 106, Tucson, AZ 85715.

Subscription Rate: \$65.00/year, 14 issues, prepaid. Outside the USA additional postage is required: Canada \$20.00/year, all other destinations \$50.00/year. Single copies \$7.00. Subscriptions not accompanied by payment will be assessed a billing charge.

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ISSN 0894-1025



physical trauma. The likelihood of spontaneous bleeding is difficult to determine for any given platelet count, because clinical variables such as the co-existence of coagulopathies, presence of drugs that are associated with platelet dysfunction, or other underlying clinical causes can contribute to the risk of hemorrhage.

One caveat in the investigation of thrombocytopenia is warranted. Although infrequent, some patients develop pseudothrombocytopenia, the result of platelet clumping *in vitro* in collection tubes containing EDTA and rarely in the presence of sodium citrate. Although this is an *in vitro* phenomenon only and does not have clinical significance to the patient, in some individuals falsely low platelet counts are reported when samples are kept at room temperature and automatic cell counters enumerate blood counts. Collection of blood by finger stick into ammonium oxalate solution and enumerating platelets by light microscopy may circumvent the EDTA-induced clumping in affected individuals.

Decreased Production

Congenital Causes of Decreased Production

Decreased production of platelets can be the result of a variety of congenital disorders. Decreased platelet production is a frequent finding in Fanconi's syndrome, an autosomal disorder characterized by marrow hypoplasia. Hematological manifestations of Fanconi's anemia typically appear between five and ten years of age. Thrombocytopenia with absent radii (TAR Syndrome) is an autosomal recessive disorder in which hemorrhage may begin at birth and survival is often related to the severity and duration of the thrombocytopenia. Approximately 50% of infants with TAR Syndrome die within the first year of life. Bernard-Soulier syndrome and May-Hegglin anomaly are both congenital disorders characterized by thrombocytopenia with giant platelets evident on peripheral blood smears. About one-third of patients having these disorders are thrombocytopenic. Most patients with these disorders are asymptomatic, although clinically significant bleeding has been reported in both disorders. Thrombocytopenia and markedly decreased mean platelet volume characterize Wiscott-Aldrich syndrome, a rare X-linked disease associated with eczema and recurrent infection due to an immune deficiency.

Acquired Causes of Decreased Production

A number of acquired conditions can decrease the production of platelets, all of which are essentially related to interferences with bone marrow production of the megakaryocytic cell line. Among the most common causes are tumor infiltrations of the bone marrow, radiation exposure of the bone marrow stem cells, or myelosuppressive drug regimens that are frequently prescribed during oncologic therapy. Many of the myelosuppressive agents affect not only platelet cell lines but result in pancytopenia, a pronounced reduction of all cell lines. The most common agents associated with decreased platelet production are shown in Table 1. Cocaine and ethanol use have also been associated with reduced platelet production.

Viral infections can lead to decreased platelet production as the megakaryocyte is a site of viral replication. Mumps, rubella, cytomegalovirus, varicella, Epstein-Barr virus, and parovirus are the viral infections most frequently implicated.

Another viral cause of thrombocytopenia is the human immunodeficiency virus (HIV). Thrombocytopenia has been observed in patients infected with HIV in both autoimmune immunodeficiency syndrome (AIDS) and in patients with asymptomatic HIV infection. A low incidence of thrombocytopenia, generally less than 10%, is reported in HIV infected individuals without the diagnosis of AIDS. However the incidence of thrombocytopenia increases dramatically, up to 30%, in patients with AIDS. Although the majority of HIV-related thrombocytopenias appear to be due to immune destruction of platelets, the mechanism is not well defined at this time.

In individuals with B12 deficiency, platelet production is impaired although the number of megakaryocytes may be increased. Patients generally have normal platelet production two weeks following vitamin repletion. Cyclic thrombocytopenia, a rare disorder, is characterized by periodic fluctuations of platelet counts within a 15-35 day cycle. This disorder is most frequently reported in women and is generally self-limiting although the thrombocytopenia may be severe.

Increased Destruction

Increased platelet destruction may be the result of either immune or non-immune mediated causes. In immune-

- Allopurinol
- Amitriptyline
- Amphotericin B
- Ampicillin
- Antihistamines
- Butabarbital
- Carbamazepin
- Chloramphenicol
- Chloroquine
- Chloramphenicol
- Clindamycin
- Dexamethasone
- Diazepam
- Digoxin
- Ethanol
- Flurocytosine
- Gentamicin
- Heparin
- Hydroxychloroquine
- Neomycin
- Nitrofurantoin
- Pentobarbital
- Phenindione
- Penicillin
- Procainamide
- Quinidine
- Rifampin
- Sulfamethazine
- Sulfathiazole
- Tamoxifen
- Thallium
- Toluene
- Trimethoprim
- Xylene

Table 1. Drugs Associated with Thrombocytopenia

mediated platelet destruction, antibodies attach to the platelet surface, and then phagocytic cells of the reticuloendothelial system prematurely remove the platelet from the circulation. Immune mediated causes of thrombocytopenia include idiopathic thrombocytopenic thrombocytopenia (ITP), drug-induced thrombocytopenia, neonatal alloimmune thrombocytopenia (NAIT), neonatal idiopathic thrombocytopenia, post-transfusion purpura, and thrombocytopenia caused by bacterial infection. Non-immune causes include Disseminated Intravascular Coagulation (DIC), hemolytic uremic syndrome, eclampsia, and thrombotic thrombocytopenic purpura. This article will discuss in further detail the more common causes.

Immune-Mediated Platelet Destruction

Idiopathic thrombocytopenic thrombocytopenia

ITP, also known as autoimmune thrombocytopenic purpura, is generally characterized by a decreased platelet count caused by immune-mediated platelet destruction. The accompanying purpura occur without a detectable cause and the diagnosis of ITP is frequently one of exclusion. Presentation of ITP commonly takes two forms: acute and chronic. Additional diagnostic support can be made when normal or elevated numbers of megakaryocytes are observed in the bone marrow. The immune platelet destruction observed in ITP may be acute and self-limiting, called primary ITP, or may be a result of a variety of disease processes, so named secondary ITP.

In ITP, the binding of antibodies or immune complexes to platelet surfaces causes platelet injury. The antibodies are most commonly directed against the major platelet surface glycoproteins and can be classified as either IgG or IgM.

ITP typically manifests as petechiae, mucousal membrane bleeding, gastrointestinal bleeding, menorrhagia, or rarely, intracranial bleeding. In ITP the platelet count often drops to less than 10,000/ μ L.

Acute ITP generally manifests in children from two to nine years of age. The onset is rapid and often follows a viral infection. For the majority of cases, the abrupt onset of bleeding begins one to three weeks following the infectious disease process. Frequently the infection is a nonspecific viral infection but ITP may accompany rubella, chicken pox, rubeola, or even a live virus vaccination. Unlike chronic ITP, there is no sex predilection and incidence has been suggested to be 4 per 100,000 children. Thrombocytopenia is usually the most severe at presentation and platelet counts below 20,000/ μ L are not uncommon. With or without treatment, greater than 80% of affected children recover with the disorder lasting only two to three weeks. About 10% of affected individuals develop a chronic phase of the disease.

The finding of chronic ITP is reported in two to five persons per 100,000. Chronic ITP is reported more frequently in females than males and usually presents in the third or fourth decade of life. Onset is insidious and a long history of spontaneous bruising, menorrhagia, and epistaxis is not uncommon. Thrombocytopenia is not

as severe as in acute ITP. Platelet destruction occurs due to the binding of the antiplatelet antibody to the platelet surface and subsequent platelet phagocytosis or lysis with or without complement activation. Approximately 20% or less of diagnosed patients undergo spontaneous recovery.

Women with chronic ITP who become pregnant may pass PAIgG antibodies across the placental barrier, passively immunizing the fetus. Low neonatal platelet counts increase the risk of intracranial hemorrhage at birth, making special birthing techniques, such as cesarean section, necessary. Generally, the newborn's platelet count rises to normal within a few weeks following the birth.

Drug-induced thrombocytopenia

Many pharmacologic agents have been reported to induce thrombocytopenia. They can be divided into those that suppress platelet production and those that cause immune-mediated thrombocytopenia.

Drug-induced ITP, while relatively rare, may occur as soon as three to five days after initiation of the drug. Generally, drug-induced purpura occurs most frequently in the elderly due to the fact that they receive more pharmacologic agents than do younger individuals. Quinidine and quinine are the most common drugs associated with drug-induced ITP other than heparin.

Heparin-induced thrombocytopenia (HIT), also known as heparin-associated thrombocytopenia (HAT), is a clinical finding characterized by a decrease in the platelet count by at least 50% following the administration of heparin. HIT is observed in one to five percent of patients receiving standard unfractionated heparin and is seen more often in patients receiving bovine than porcine preparations. HIT may be observed with any route of administration, any dosage regimen, or any heparin type. Two forms of HIT are seen. The most common form, Type I, thought to be caused by a non-immune mechanism, appears as a mild thrombocytopenia one to five days after initiation/exposure to heparin in a patient who has not previously received the drug. Type I HIT is a self-limiting disorder and platelet counts return to normal with or without the cessation of heparin therapy. The second form, Type II, is immune-mediated and can lead to life-threatening complications such as thrombosis. Heparin-induced platelet antibodies are detected with Type II HIT.

The onset of thrombocytopenia in HIT II is typically five to ten days following exposure to heparin. Thrombocytopenia is usually moderate but may be severe. Patients who have been previously exposed and sensitized may have thrombocytopenia and HIT platelet antibodies develop within hours of re-exposure if heparin was administered within the last 100 days. The antibodies responsible for immune-mediated HIT are directed against the heparin-PF₄ complex that normally forms following heparin administration. The thrombosis reported in HIT, Type II, can be venous or arterial with severe and fatal consequences. Not all patients with heparin antibodies will develop clinical manifestations such as thrombosis.

Post-transfusion purpura

In both post-transfusion purpura (PTP) and NAIT alloimmune PAIg antibodies arise when there is an antigenic challenge to an individual who lacks specific platelet antigens. About 80% of PAIg antibodies are anti-PLA¹ HPA-1a. The rest are antibodies to Baka HPA-3a, Pen^aHPA-4a, and PL^{A2}HPA-1b. In PTP, donor platelets induce the PAIg antibody response. The antibody subsequently destroys both donor and recipient platelets. PTP causes severe thrombocytopenia seven to ten days following re-exposure to the offending platelet antigen in a patient with a history of transfusion or pregnancy. The antibody, triggered by the transfused foreign antigen, reacts with the patient's antigen-negative platelets, causing a severe, often life-threatening thrombocytopenia, risk of intracranial hemorrhage is high. The mechanism for the recipient platelet destruction is not understood.

Neonatal autoimmune thrombocytopenia

In NAIT, maternal PAIg antibodies form in response to fetal platelet antigens absent from the maternal platelets. These platelet antibodies cross the placental barrier coating the fetal platelets causing immune destruction of the baby's platelets. Thrombocytopenia develops in a manner similar to the development of Rh disease of the newborn. Unlike Rh disease, NAIT may occur with the first pregnancy. The incidence in the general population is 1 in every 5000 deliveries. Similar to ITP, low neonatal platelet counts increase the risk of intracranial hemorrhage during birth making c-section delivery a necessity. The platelet count generally rises to within normal a few weeks after delivery.

Symptoms may manifest up to 12 hours after delivery.

Nonimmune-Mediated Platelet Destruction

Bacterial infection

Bacterial infection is a frequent cause of isolated thrombocytopenia in hospitalized patients. Usually thrombocytopenia in this setting is moderate but may become severe. The thrombocytopenia is most often resolved following successful treatment of the underlying infection. Some viral infections have been associated with a transient thrombocytopenia even without treatment.

Disseminated intravascular coagulation

The syndrome of DIC can readily consume platelets and lead to moderate or mild thrombocytopenia in about 80% -90% of affected individuals. DIC is a manifestation of underlying disorders which include obstetrical complications, transfusion reactions, trauma, vascular disease, primary fibrinolysis, liver disease, shock, microangiopathic disorders, envenomation, tissue injury, carcinoma, and infection. In DIC, platelet numbers fall in conjunction with other clotting factors, decreasing as they are consumed in the clotting process. Review of the peripheral blood smears can generally confirm the thrombocytopenia and accompanying red blood cell fragments found in DIC.

Thrombotic thrombocytopenic purpura

Thrombotic thrombocytopenic purpura (TTP) is a complex syndrome characterized by hemolysis, thrombocytopenia, and microthrombotic lesions. The etiology is not well understood although approximately 40% of patients with TTP have experienced a prodromal viral infection. The syndrome, found most often in females, usually presents in the fourth decade of life with petechiae and ecchymosis. Other bleeding may occur but is usually insignificant. The platelet count varies from day to day and unlike DIC, other hemostatic assays are usually normal. If left untreated the mortality rate is considerably high.

Hemolytic uremic syndrome

Hemolytic uremic syndrome (HUS) normally affects infants from four to twelve months of age but adult HUS has also been reported. Clinically, HUS resembles TTP, although the vascular lesions are generally localized. The optimal therapy for HUS is not well defined although hemodialysis is often indicated.

Other Clinical Conditions Associated with Thrombocytopenia

Abnormal Distribution of Platelets

Splenomegaly

Splenomegaly, associated with a variety of disorders, is accompanied by increased splenic pooling of the platelets leading to thrombocytopenia despite normal platelet production. Treatment is usually directed at resolving the underlying cause of the splenomegaly. Thrombocytopenia is generally not severe and platelet counts below 20,000/ μ L are rare, as is any bleeding manifestation. Typically, the platelet count is 60,000/ μ L-100,000/ μ L, and splenectomy is not often warranted.

Dilution

Transfusion of large volumes of blood products may result in thrombocytopenia as a result of dilution. Over time, stored platelet products lose their functionality and viability and this can also contribute to the problem as well. Dilutional thrombocytopenia is frequently observed during or shortly after surgery, especially when large volumes of plasma expanders have been utilized. Essentially all patients undergoing surgical procedures will experience a drop in platelet count, although the platelet count usually resumes its normal level or elevates above normal post surgically.

Thrombocytopenia in Pregnancy

Thrombocytopenia in pregnancy, typically occurring between 24 weeks of gestation and delivery, is associated with a decrease in the platelet count of approximately 11%. Approximately 5% -10% of pregnancies are affected, and in some cases the fetus may suffer consequences as well. The etiology is uncertain although increased consumption and diminished megakaryocytopoiesis have been proposed.

In the majority of affected pregnancies, the thrombocytopenia is mild, an incidental finding that requires no further investigation either for the pregnant woman or fetus. The next most common cause of thrombocytopenia in pregnancy is associated with hypertensive disorders, primarily pre-eclampsia. ITP is the third most common cause of thrombocytopenia during pregnancy. Pregnant women with a history of chronic ITP or those who presently have ITP have an increased risk of delivering an infant with thrombocytopenia. In neonatal alloimmune thrombocytopenia, the

maternal platelet count generally does not correlate well with the neonate's count. Approximately 50% of mothers with platelet counts below 100,000/ μ L will give birth to infants with decreased platelet counts.

Laboratory

Platelet Count

In most laboratory settings, automated cell counters perform the platelet count. The peripheral blood smear is then used to confirm the findings of the automated instrument. Increased platelet destruction and consumption are reflected on the peripheral smear by large platelet size, indicating a young age platelet population indicative of increased megakaryocyte production in the bone marrow. The complete investigation of thrombocytopenia may require a bone marrow evaluation to observe the megakaryocyte count as well as the presence of other cell lines. The finding of cell fragments on a peripheral smear indicates the possible presence of DIC.

Bleeding Time

The bleeding time is a complex test, subject to a number of variables, since its performance is operator dependent. A prolonged bleeding time in a patient with a normal platelet count suggests possible platelet dysfunction. This test is of limited value in the thrombocytopenic patient. Furthermore, test results are ambiguous because of the poor correlation with bleeding risk in patients, low reproducibility, unsuitability for serial testing, and limited sensitivity. Although, this assay is not performed as frequently as in the past, some institutions still rely on its results in the evaluation of platelet disorders.

HIT Assays

HIT antibody is measured using either a functional assay such as Serotonin C-14 Release Assay (SRA) or immunologically using an enzyme immunoassay (Elisa). Current recommendations are to perform both assays for confirmation of HIT, as neither assay correlates 100% with the clinical picture and both assays produce false positive and negative test results.

In the SRA assay, washed donor platelets are tagged with radioactive Serotonin C-14. The patient's serum sample is first heat inactivated to remove residual thrombin that would cause thrombin-induced aggregation. The heat-inactivated serum is then added alone and with low dose and high dose heparin concentrations to donor platelet suspensions in microtiter wells.

After incubation and centrifugation, the samples are tested for release of the Serotonin C-14. A release of C-14 in the low dose heparin test only is indicative of heparin-induced antibodies.

In the Elisa assay, the patient serum sample is added to a microwell coated with platelet factor 4 complexed to heparin or to another linear polyanionic compound such as polyvinyl sulfonate (PVS), and if present, heparin-induced platelet antibody binds to the complex coating the well. Production of a chromophore is a direct function of the concentration of heparin-induced platelet antibody present in the test sample.

Assays for Immune Thrombocytopenia

The laboratory assays for immune-mediated thrombocytopenia include the platelet antigen test, the direct platelet antibody tests, the platelet specific antibody test, and the platelet antibody screen test. These assays and their expected results will be discussed in the May 2003 issue of Clinical Hemostasis Review.

Therapy

Patients with thrombocytopenia should take precautions to reduce risk of serious hemorrhage. Thrombocytopenic patients should avoid unnecessary trauma, including invasive diagnostic procedures, and discontinue all non-essential medications that impair platelet function.

The etiology of the thrombocytopenia is important in determining whether to utilize platelet transfusions and the presence of thrombocytopenia does not in and of itself make platelet transfusion essential. Generally, disorders associated with decreased production of platelets benefit from platelet transfusion therapy, while those related to increased destruction of platelets will not. In patients with life-threatening hemorrhage, immediate transfusion of platelets is employed and a transient increase of the platelet count can be observed before immune destruction of the transfused platelets occurs.

Platelet Transfusions

Indications

Platelet transfusions are administered primarily to control or prevent bleeding in patients with low platelet counts or diminished platelet function. Prophylactic platelet transfusion may be indicated for patients with severe thrombocytopenia. In late 1997, The Royal College of

Physicians of Edinburgh held a consensus conference regarding platelet transfusion practices. This conference adopted a threshold platelet count of 10,000/ μ L as a safe lower limit for the prescription of platelet transfusion in stable patients. This platelet threshold has been associated with a 20% incidence of significant bleeding. This recommendation does not include patients with fever, infection, rapidly decreasing platelet counts, and those undergoing invasive surgical procedures. For individuals with underlying complications, the recommended therapeutic threshold is 20,000/ μ L.

Variables that may influence the decision to transfuse platelets include; the expected duration of the thrombocytopenia, the competency of the hemostatic mechanism with regard to any concomitant coagulopathies, bleeding occurrence or risk of bleeding, presence of pharmacologic agents that can interfere with platelet function, and hazards of transfusion.

Dosing and response

Appropriate platelet dosing has become more important as the clinical applications for platelet component therapy increase. Although there is no standard platelet dose currently used in medical practice, clinicians often order platelet concentrates in an amount of six or fewer units. The desired platelet count and clinical manifestations may be used to determine the dosage of platelets transfused. Stored platelets are expected to survive *in vivo*, once transfused for seven days. However, in thrombocytopenic patients, the platelet survival time may be compromised due to increased consumption or destruction of transfused platelets and platelets may be required every two to four days.

ABO-compatible platelet transfusions are preferable to avoid passive administration of ABO-incompatible plasma. When this is not possible, platelets can be washed to diminish the plasma content of the transfusion. For individuals with alloimmunethrombocytopenia, human platelet antigen (HPA) matched-products are the most successful transfusion components when required.

The term platelet refractoriness is used for patients that consistently fail to respond to platelet transfusions. Platelet refractoriness can be the result of the quality of the platelet transfusion product, as well as immune and non-immune causes. Platelet transfusion response can be poor in platelet concentrates that have been stored for five

days, despite careful collection methods. Non-immune causes of platelet refractoriness include febrile reactions, splenomegaly, or DIC. Immune causes of platelet refractoriness include the presence of leukocytes in donor platelets, HLA antibodies, platelet-specific antibodies, autoimmune processes, and drug-dependent antibodies. Patients with HLA class I alloantibodies become refractory to additional platelet concentrate transfusions and may subsequently require HLA-matched platelets to prevent hemorrhage.

Some disorders require repeat platelet transfusions until the underlying problem is corrected. Severe thrombocytopenia secondary to an immune thrombocytopenic syndrome, such as that associated with autoimmune disease, rarely responds well to platelet transfusion since the mechanism that caused the initial platelet destruction results in destruction of the transfused platelets as well.

ITP

Because many patients with acute ITP spontaneously recover and/or exhibit relatively mild symptoms, therapy for these patients often requires only close observation. More intensive therapies are initiated when serious manifestations of the disease occur.

Several treatment modalities for ITP patients at high risk for bleeding or those with imminent invasive procedures exist. Usually these treatments are used in a progressive manner after a patient has failed other therapeutic regimens. For patients requiring long-term management of chronic ITP, corticosteroids are frequently used. Patients with ITP that fail to respond to treatment with other agents may be candidates for splenectomy. Splenectomy is considered an effective treatment for ITP and 50%-80% of patients reach long-term remission after surgery. In acute ITP, if the platelet count is less than 20,000/ μ L, or if there is evidence of bleeding, physicians often prescribe oral prednisone or other immunosuppressive drugs. The platelet counts should begin to return to normal after 2-3 weeks. In chronic ITP, if the platelet count is less than 20,000/ μ L, or if there is evidence of bleeding, physicians often prescribe oral prednisone or other immunosuppressive drugs. Splenectomy may be attempted in patients who fail to respond to steroids. In pregnancy, the mother may be given prednisone to maintain platelet counts greater than 50,000/ μ L. Neonatal platelet counts can be taken from the cord or scalp vein at

the time of labor. To prevent intracranial hemorrhage, an atraumatic delivery method such as cesarean section should be considered.

NAIT (NATP)

Intrauterine diagnosis is recommended if NAIT is suspected, and if it is confirmed, early cesarean section is often recommended. The newborn may receive washed maternal platelets or antigen negative platelets.

PTP

Immune suppression or plasmapheresis may halt the immune destruction of patient platelets. Patients should not receive further platelet concentrates if at all possible.

Multi-Transfused Patients Refractory to Platelet Therapy

Platelet refractoriness may be prevented by using single donor apheresis platelets, leukocyte-poor blood products, UV-irradiated donor platelets, and cross-match compatible platelet concentrates. ▲