Fetal and Neonatal Alloimmune Thrombocytopenia: Harvesting the Evidence to Develop a Clinical Approach to Management

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ABSTRACT

Neonatal alloimmune thrombocytopenia (NAIT) is the most common cause of severe thrombocytopenia in an otherwise healthy newborn. The most serious complication is intracranial hemorrhage, which can occur either in the fetus or the newborn. Despite the known serious sequelae, both antenatal management and neonatal treatment modalities are plagued by the lack of gold standard evidence to appropriately direct therapy. Maternal, risk-based therapeutic approaches range from invasive protocols to relatively benign noninvasive strategies to avoid serious procedural complications. Intravenous immunoglobulin (IVIG) with or without steroids and fetal blood sampling constitute the mainstay of antenatal management. Neonatal interventions principally focus on the use of antigen-negative compatible or random donor platelets and IVIG. While awaiting the results of controlled trials, each institution must develop a standardized, collaborative, multidisciplinary approach to the screening, diagnostic evaluation, and management of unexpected and anticipated NAIT based on experience, product availability, and emerging scientific data.

KEYWORDS: Maternal, fetal, neonatal, alloimmune thrombocytopenia, management

Neonatal alloimmune thrombocytopenia (NAIT) is the most common cause of moderately severe thrombocytopenia in an otherwise healthy newborn infant.[1] NAIT results from a platelet antigen incompatibility between the mother and the fetus and is analogous to Rhesus hemolytic disease. Typically, unanticipated NAIT is first diagnosed at or shortly after delivery, with the infant presenting with a platelet count $<50 \times 10^9$/L. For some infants, the thrombocytopenia leads to multiple platelet transfusions, intracranial hemorrhage (ICH) and significant long-term neurological deficits. This article will focus on human platelet alloantigen (HPA)-1a alloimmunization, the pathogenesis and incidence of NAIT, as well as the antenatal and postnatal management of this condition.

MATERIALS AND METHODS

A systematic literature search was utilized to retrieve the studies and articles for this review. An electronic MEDLINE literature search was performed using the following terms: neonatal OR fetomaternal OR newborn

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AND alloimmune thrombocytopenia OR NAIT. The Cochrane Central Register of Controlled Trials (Cochrane Library issue 1, 2010) was searched for controlled studies and the Cochrane Database of Systematic Reviews (Cochrane Library issue 1, 2010) was searched for systematic reviews on the antenatal and postnatal management of NAIT. No language restriction was applied. All identified reports were checked for references to additional studies.

Pathogenesis of NAIT

HPAs are proteins found on the surface of platelets, and the HPA system is used in the nomenclature of platelet antigens. An alloantigen is an antigen that is present in a portion of the population and absent in the rest of that population. There are 24 platelet-specific alloantigens that have been recognized, and they are numbered according to when they were first described.[2] Of the platelet alloantigens, 12 are grouped into *biallelic* systems (HPA-1, -2, -3, -4, -5, -15). The platelet alloantigen is then further defined according to the frequency in which it appears in the population. A high-frequency alloantigen is designated "a" and a low-frequency alloantigen is designated "b."[2] HPA-1a is the most common platelet alloantigen in the Caucasian population and is responsible for ~80% of the cases of NAIT.

NAIT can result when there is an incompatibility between the platelet antigen of the mother and her fetus. Maternal anti-platelet immunoglobulin G (IgG) alloantibodies, produced after exposure to the foreign platelet antigen, cross the placenta and bind to the fetal platelets. Therefore, a mother with HPA-1a-negative platelets who has a fetus with HPA-1-positive platelets becomes sensitized to the HPA-1a-positive platelets and produces anti-HPA-1a, anti-platelet IgG. The antibody-coated platelets pass through the reticuloendothelial system and are rapidly removed from the circulation, resulting in fetal thrombocytopenia. Expression of HPA-1a antigens on fetal platelets has been demonstrated as early as 16 weeks' gestation; however, the first appearance of HPA-1a antibodies may only become evident in the fetus after 20 weeks.[3] The presence of antibodies to the HPA-1a antigen is also strongly associated with the HLA DRB3*0101.[4–9]

Several factors may influence the severity of the thrombocytopenia; these include: the concentration and subclass of maternal IgG alloantibodies, the density of the "target" antigens on the fetal platelets, the activity of phagocytes in the fetal reticuloendothelial system, and the ability of the fetal bone marrow to compensate for the accelerated destruction of antibody-sensitized platelets.[10]

Ninety-eight percent of Caucasian females have the genotype HPA-1a/1a[7] and approximately 2% are HPA-1a-negative or homozygous HPA-1b/1b. If the mother of an infant with NAIT is HPA-1b/1b the father will either be heterozygous, HPA-1a/1b, or homozygous HPA-1a/1a. If the father has the genotype HPA-1a/1b then 50% of his offspring will be at risk for NAIT and 100% of his offspring will be at risk for NAIT if his genotype is HPA-1a/1a.

Although the pathogenesis of NAIT is similar to Rhesus hemolytic disease of the newborn, in NAIT, the first pregnancy can be affected, and there is a high recurrence risk of fetal/neonatal thrombocytopenia (FNAIT) in future pregnancies.

Incidence

The frequency of HPAs varies across the world. The HPA-1a that predominates in the Caucasian population is rare in the Asian population, where HPA-5b incompatibility is the most common cause of fetomaternal alloimmune thrombocytopenia.[11]

The incidence of HPA-1a-negative mothers can be derived from the large prospective trials. A summary of these trials is shown in Table 1. Ten in 1000 mothers were found to be HPA-1a-negative, 10% were alloimmunized to the HPA-1a antigen, and 40% of these mothers delivered infants with NAIT.[4–9,12–14] The overall incidence of NAIT is 0.7 in 1000 pregnancies.

Thrombocytopenia is defined as a platelet count $<150 \times 10^9$/L. The incidence of thrombocytopenia in large prospective studies of unselected newborns is 0.5 to 0.9%[15–17] and 0.12% will be severely thrombocytopenic with a platelet count of $<50 \times 10^9$/L.[1,16] In NAIT, 50 to 80% will have platelet counts $<50 \times 10^9$/L.[8,16,18] Sensitization to HPA-1a is the most common cause of severe alloimmune thrombocytopenia and is responsible for 75 to 85% of the cases.[10,18,19] Bussel et al[19] reported an initial median platelet count of 18×10^9/L in infants born with an HPA-1a incompatibility as compared with 60×10^9/L with other antigen incompatibilities.

The incidence of an ICH as a result of alloimmunization to the HPA-1a antigen is ~20%.[20] The majority of ICHs occur antenatally (80%), with 14% of these hemorrhages occurring before 20 weeks' gestation and 28% before 30 weeks' gestation.[20]

Clinical Presentation and Predictors of Thrombocytopenia

The diagnosis of NAIT in the firstborn child is usually unexpected by the family and health care providers and is frequently made at birth. The infant can present with petechiae, bruising, and bleeding but will otherwise look well. The treatment of this infant is discussed later in this article. The subsequent pregnancies of this mother can then be closely followed.

Table 1 Prospective Studies of Alloimmunization to HPA-1a Antigen in Nonselected Pregnancies

Authors	Year	Total No. of Women Typed	No. of HPA-1a-Negative Women	No. of Women with anti-HPA-1a/No. Assessed	No. of Cases of NAIT (Platelet count $< 150 \times 10^9$/L)	No. of Cases with Intracranial Hemorrhage
Mueller-Eckhardt et al[12]	1985	1211	26	2/26	2	0
Blanchette et al[4]	1990	5000	81	3/50	1	1
Doughty et al[5]	1995	3473	74	2/71	2*,†	0
Durand-Zaleski et al[6]	1996	2066	52	4/45‡	1	0
Williamson et al[9]	1998	24,417	618	46/387	19§	1
Davoren et al[13]	2003	4090	54	3/34	3	0
Maslanka et al[14]	2003	8013	144	12/122	3‖	1
Turner et al[8]	2005	25,506	546	25/318	8	2
Kjeldsen-Kragh et al[7]	2007	100,448	2111	210/1990	85	2

*Twins.
†One mother treated with IVIG. Platelet count prior to delivery 210×10^9/L.
‡One mother treated with IVIG. Platelet count at birth 207×10^9/L. One mother treated with corticosteroids (two mothers did not consent to fetal blood sampling).
§Excludes one in utero death.
‖One case treated with intrauterine platelet transfusions, one case treated with intrauterine platelet transfusions and IVIG. Platelet count at birth 237×10^9/L. ICH occurred despite intrauterine transfusions.
HPA, human platelet alloantigen; ICH, intracranial hemorrhage; IVIG, intravenous immunoglobulin; NAIT, neonatal alloimmune thrombocytopenia.

In a recent prospective study, Killie et al[21] demonstrated a strong correlation between maternal antibody levels and the platelet count of the neonate. Maternal anti-HPA-1a antibody levels above 3.0 IU/mL at 22 and 34 weeks' gestation were good predictors of the degree of thrombocytopenia in the neonate both in the first and subsequent pregnancies with a clinical sensitivity of 93% and specificity of 63%.[22]

The best noninvasive predictor of the severity of thrombocytopenia and related ICH in future pregnancies with HPA-1a alloimmunization is the presence of an in utero ICH in the sibling.[19] The rate of recurrence of an ICH in a sibling of an infant with NAIT and ICH is 72% with fetal deaths not included in the analysis and 79% when fetal deaths were included.[23] Unfortunately, there are no other noninvasive surrogate measures to determine the severity of thrombocytopenia in fetuses whose sibling did not have an ICH.

The risk of having an alloimmunized fetus can be guided by the presence of HLA DRB3*0101, which is linked to HPA-1a and has a positive predictive value of 35% and a negative predictive value of 99.6%.[9] However, this investigation is limited to women who have had a previously affected fetus.

Antenatal Management

Routine screening to identify fetuses at risk for hemolytic disease of the newborn is well established. A similar screening program of all pregnant women to identify those fetuses at risk for NAIT is not routinely performed. The lack of a standardized approach to the antenatal management of these pregnancies has impacted the adoption of a universal screening program.[24] A typical screening and intervention program encompasses HPA-1a typing of all pregnant women antenatally and screening HPA-1a-negative individuals for anti-HPA-1a antibodies at ~22 and 34 weeks' gestation. Immunized women are offered delivery by cesarean section 2 to 4 weeks prior to term, and infants with severe thrombocytopenia (platelet count $<35{,}000 \times 10^9$/L) are immediately treated with reserved, donor platelets, which are compatible in >95% of all cases, to reduce the severity of complications[25] (Fig. 1). Discussion is ongoing on the cost-effectiveness of implementing such programs and whether the short- and long-term outcomes will be favorable as reported by Kjeldsen-Kragh in Norway.[6–8,26,27] The cost of a screening program for primigravida women to prevent one case of death/disability was estimated at $1,876,656 in 2005.[8] More recently, a cost-utility analyses by Killie et al[27] and Kjeldsen-Kragh et al[25] showed that antenatal screening would reduce health care costs by almost €1.7 million, would generate between 210 and 230 additional quality-adjusted life-years, and is being considered for adoption as part of the antenatal program in Norway.

A mother with an identified personal or family history of NAIT allows health care professionals to provide close surveillance and early antenatal management during the pregnancy. A maternal sister who has had a pregnancy that has been complicated by NAIT should alert the physician to proceed with platelet antigen typing in her sibling's pregnancy. New cases of NAIT, with a negative family history, are unlikely to be recognized prior to delivery. If an in utero ICH or its sequelae such as cysts, leukomalacia, or hydrocephalus is identified, then NAIT should be strongly considered as the precipitating cause. If FNAIT is suspected, then identification of the maternal HPA antibody and serological platelet phenotyping/genotyping of the parents for a

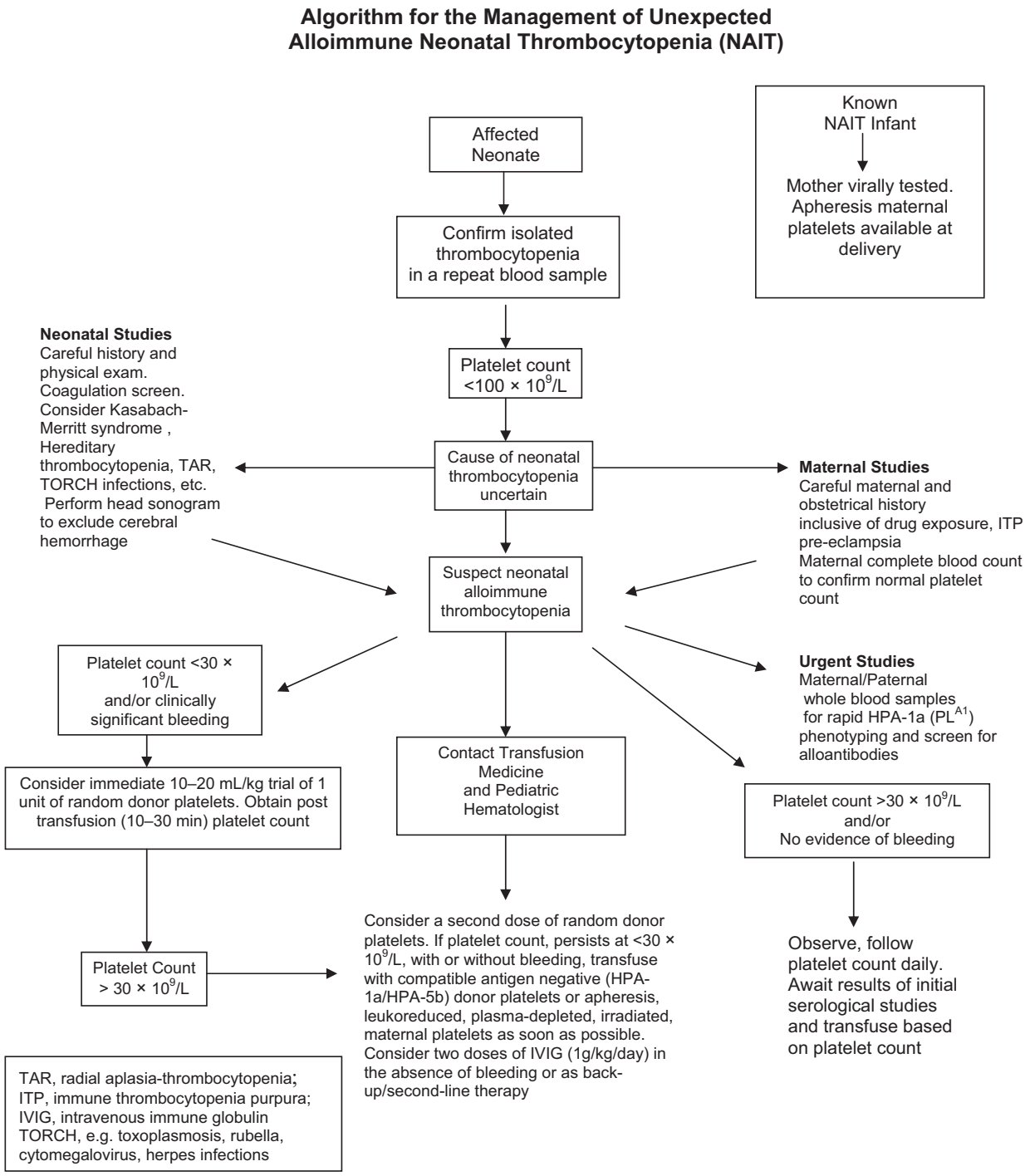

Figure 1 Algorithm for the management of unexpected alloimmune neonatal thrombocytopenia (NAIT). (Adapted from Blanchette VS, Johnson J, Rand M. The management of alloimmune neonatal thrombocytopenia. Baillière's Clin Haematol 2000;13:365–390, with permission from Elsevier.)

potential platelet incompatibility is essential to confirm the diagnosis. Commercial enzyme-linked immunosorbent antibody kits (Pak-Plus or Pak12, GTI Diagnostics, Waukesha, WI) are now available for initial screens followed by the monoclonal antibody-specific immobilization of platelet antigens assay and radioimmunoprecipitation assay (RIP) for further antibody testing.[28,29] The RIP assay is able to identify all platelet glycoproteins including previously uncharacterized antigen targets, but its use is limited by cost, the need for specialized expertise, and the use of radioisotopes.[29] Amniocentesis can be employed for fetal-maternal antigen testing if the father is heterozygous or in the case of doubtful paternity.

The goal of antenatal therapy is to reduce the severity of thrombocytopenia and thereby reduce the complications of ICH, long-term disability, and death.

Options for therapy include in utero transfusions of antigen compatible platelets, intravenous immunoglobulin (IVIG), and systemic corticosteroids. Studies on which to base therapy are mainly observational because of the low incidence of alloimmunization to the HPA-1a antigen and NAIT in the general population.

In utero platelet-compatible transfusions have been shown to effectively increase the fetal platelet count,[30–33] but weekly transfusions are necessary because of the short half-life of platelets, and there are significant risks to the procedure. In a retrospective review of 12 pregnancies and 84 platelet transfusions, Overton et al[31] reported the procedure-related fetal loss to be 1.2% (1/84) per procedure and 8.3% (1/12) per pregnancy. This was consistent with the experience of other centers. There were two deaths reported in the study; one was directly related to the procedure after the needle dislodged from the placental cord insertion site, and the other occurred 1 week following a successful in utero platelet transfusion. Neither of the two deaths was related to ICH.

Quantification of the fetal platelet count, to evaluate effectiveness of treatment, can be done by cordocentesis, but this carries a risk of complications that include bleeding, infection, thrombosis, preterm delivery, and death.[30,31,34–36] A 2003 review by Radder et al[23] estimated the total complication rate for cordocentesis for NAIT to be 2.8%.

IVIG and IVIG in combination with a corticosteroid have been used for several years as a preventive strategy in the management of FNAIT. Immunoglobulins play a major role in host defense include antigen binding and a variety of effector functions such as complement activation, complement binding, and binding to Fc receptors.[37] However, their action in FNAIT has not been clearly delineated. Importantly, there is considerable intra- and interpopulation variation in the pharmacokinetics of IVIG.[38] There have been no randomized control trials (RCTs) evaluating the efficacy of IVIG or steroids alone versus no treatment in alloimmune thrombocytopenia. Trials of this nature would be unethical because of the known risk of ICH with this condition. However, many observational reports comparing two different treatment modalities have been executed. Rayment et al,[11] in a Cochrane systematic review, summarized the results of 26 observational studies on the maternal administration of corticosteroids and IVIG in pregnancies with fetomaternal alloimmune thrombocytopenia. The results of these studies are unclear with regard to the prevention of an ICH, particularly in the most severely affected fetuses. Three RCTs have examined the role of IVIG with or without steroids.[39–41] Table 2 shows the outcomes of these trials. Bussel et al[39] did not demonstrate any difference in the fetal platelet count between IVIG and IVIG with steroids. Moreover, Berkowitz et al[40]

Table 2 Randomized Controlled Trials of Intravenous immunoglobulin (IVIG) with or without Steroids in Pregnancies with Alloimmune Thrombocytopenia

Author	Year	Time Frame	Sample Size	Intervention	Nonresponders (*n*)	Mean Change in Platelet Count Between First and Second Samples (10^9/L)		Intracranial Hemorrhage
Bussel et al[39]	1996	1990–1993	54	IVIG	12	37,400		0
				IVIG + dexamethasone	(Groups combined)	33,900		0
Berkowitz et al[40]	2006	1994–2001	79	High risk*:				
				IVIG	16	17,300		1
				IVIG + prednisone	7	67,100		0
				Standard risk†				
				IVIG	10	30,600		2‡
				Prednisone	12	25,700		
						Platelet Count at 32 wk ($n < 30 \times 10^9$/L)	**Platelet Count at Birth ($n < 50 \times 10^9$/L)**	
Berkowitz et al[41]	2007	2001–2006	73	IVIG		9	5	1§
				IVIG + prednisone		5	4	1§

*High-risk—sibling with an ICH during the peripartum period or initial fetal platelet count $< 20 \times 10^9$/L.
†Standard risk—no sibling with an ICH, initial fetal platelet count 20–100×10^9/L.
‡Distribution between groups unclear.
§Cases not treatment failures.
ICH, intracranial hemorrhage; IVIG, intravenous immunoglobulin.

were also not able to demonstrate a difference in standard risk pregnancies but did demonstrate that IVIG and prednisone was more effective in raising the fetal platelet count in high-risk pregnancies. The Berkowitz et al[41] trial in 2007 showed good outcomes and comparable results between the IVIG and the IVIG/prednisone group in standard-risk pregnancies. In this study, fetal blood sampling, to evaluate effectiveness of therapy, was performed at 32 weeks' gestational age.

The adverse effects of IVIG use in maternal alloimmune thrombocytopenia are uncommon. Moderate to severe fatigue has been reported, and in only 1 out of 200 cases IVIG therapy was discontinued due to a rash.[41] More adverse effects have been reported with prednisone and include gestational diabetes, fluid retention, mood swings, insomnia, and jitteriness.[41] Bussel et al[39] reported two cases of oligohydramnios in women who had received dexamethasone. In one case, the mother received three times the dose of dexamethasone; however, the oligohydramnios resolved following discontinuation of the steroid.

Mode of Delivery

There is no clear evidence on the mode of delivery for fetomaternal alloimmune thrombocytopenia, and cesarean section is performed for either maternal obstetric indications or the planned delivery of known high-risk cases. Van den Akker et al[42] reported on 32 pregnancies affected by fetomaternal alloimmune thrombocytopenia; all mothers had delivered a previous sibling with NAIT but no ICH. Twenty-three infants were delivered vaginally, 3 of whom had severe thrombocytopenia. No infant had an ICH.

In summary, the antenatal management of pregnancies complicated by alloimmunization can be guided by an algorithmic, risk-based approach.[34,35,40,41] Fetuses at highest risk are those who have a sibling who suffered an in utero ICH. There is an increasing trend to utilize noninvasive protocols in the management of alloimmune thrombocytopenia because of significant procedural complications following confirmatory and follow-up fetal blood sampling. Prospective, comparative studies indicate that the noninvasive approach may be both safe and effective, but the evidence remains inconclusive because of small sample sizes.[34,35,40,41] In practice, IVIG (1g/kg) administered weekly from 24 weeks' gestation onward is the most common noninvasive protocol utilized. The management of all alloimmunized pregnancies should occur in a tertiary care center with immediate access to neonatal services. Treatment modalities available include in utero platelet antigen-compatible transfusions, maternal IVIG, and systemic steroids either singly or as combined therapy depending on the presence or absence of an ICH in a previous sibling.[35,40–42] In the absence of placebo-controlled trials, the use of IVIG or steroids independently, in the antenatal period, stems from RCTs evaluating these therapies alone versus an alternative combined therapeutic intervention, which demonstrated safety of these maneuvers. Cordocentesis should be reserved for the experienced practitioner and to evaluate effectiveness of therapy.

Postnatal Management

There is no universal consensus on the treatment threshold for neonates presenting with NAIT at birth. A survey of Canadian and German neonatologists addresses this issue: 60% of Canadian neonatologists would commence treatment of preterm infants with a platelet count of 30 to 50×10^9/L, whereas only 32% of the German neonatologists would start treatment at this level and 25% would use a threshold of 10 to 20×10^9/L. In term infants, 6% of Canadian neonatologists and 16% of German neonatologists use a transfusion threshold level between 5 and 10×10^9/L.[43]

Different transfusion thresholds appear throughout the literature, but they are not based on high-quality trials. A transfusion threshold of $<20 \times 10^9$/L or clinical bleeding has been proposed by Ouwehand et al[44] and a threshold of $<30 \times 10^9$/L has been suggested by Blanchette et al[10] and Arnold et al.[29] Overall, a platelet count of $<30 \times 10^9$/L is generally accepted as a clinical trigger for therapeutic intervention. Bussel et al[45] also suggested that the platelet count be kept above 100×10^9/L initially, if there was evidence of clinical bleeding, such as an intraventricular hemorrhage, and the platelet count should then be maintained at $>50 \times 10^9$/L for 1 to 2 weeks.

Several therapies are available for the clinician to treat the infant born with NAIT. However, as many of these infants present unexpectedly, at the time of delivery or shortly thereafter, the most recommended treatment option may not be readily available. An algorithm for the management of the unanticipated infant with NAIT is shown in Fig. 1.

Transfusion with matched antigen-negative platelet concentrates is the treatment of choice for an infant presenting with NAIT. HPA-1a- and HPA-5b-negative platelets are compatible in 95% of cases presenting with NAIT and produce higher increments in platelet counts with longer survival.[44,46] However, few hospitals and national blood transfusion services have a registry of typed donors and stock such platelets for immediate transfusion.[43] Compounding this issue is that physicians are often unaware that this treatment modality is available in their institutions.[43]

Apheresis, leukoreduced, plasma-depleted, irradiated, or washed maternal platelets is an alternative therapy. This strategy is of value for cases diagnosed in

utero, as there is time to prepare the platelets prior to delivery. Platelet preparation takes time, as viral testing is mandatory prior to transfusion. Other treatment options are preferred for the unexpected severely thrombocytopenic infant.

Transfusion of random donor platelets has been shown to offer some benefit to infants with NAIT.[47,48] However, although highly effective in some cases, this treatment modality should be used only to temporize the situation until compatible platelets are available.[49,50]

High-dose IVIG (400 mg/kg day over 5 days) has been shown to be effective in infants with NAIT in a small number of case reports.[51–53] Ballin et al[54] reported success with a dose of 1 g/kg/d for 2 consecutive days, and Linder et al[55] reported a beneficial effect of a single dose of IVIG (1 g/kg/d) in four infants with a fifth infant requiring a second dose. These authors reported no adverse effects. Although some centers advocate the use of IVIG combined with either random donor or matched platelets, the efficacy of this strategy has not been evaluated prospectively.

CONCLUSION

The potentially devastating sequelae of alloimmune thrombocytopenia necessitate a rapid response from the health care team in regard to diagnosis and treatment. In the absence of large-scale, randomized controlled trials, there continues to be disparity among health care providers regarding the optimum management of FNAIT and NAIT. The risks and benefits of both maternal and fetal interventions need to be carefully weighed based on experience within institutions and evidence from current scientific literature. The diagnosis and care of the infant requires a coordinated, collaborative effort between obstetrics, neonatology, hematology, and transfusion medicine. Local, consensus protocols should be established to guide consistency in the treatment of NAIT. The infant born outside of a tertiary-level hospital with NAIT should be immediately transfused with random donor platelets, if severe thrombocytopenia exists or bleeding is evident, and promptly transferred to a tertiary level neonatal intensive care unit for further management.

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