Fetal and Neonatal Alloimmune Thrombocytopenia: evidence based screening

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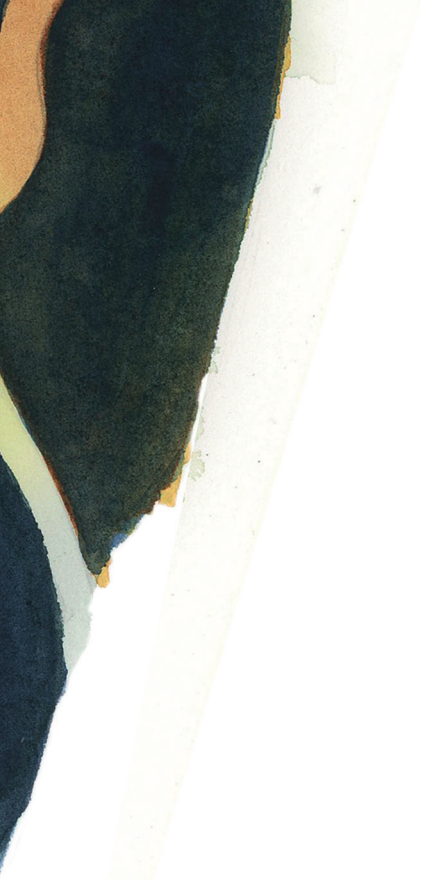

Chapter 6

Treatment and outcomes of fetal/neonatal alloimmune thrombocytopenia: a nationwide cohort study in newly detected cases

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Summary

Fetal/neonatal alloimmune thrombocytopenia (FNAIT) is the most important cause of thrombocytopenia in term-born infants and can cause severe haemorrhages. Postnatal management strategies aim to reduce bleeding tendency by increasing platelet counts, but evidence for the optimal treatment is lacking. In a nationwide cohort, we reviewed postnatal management strategies and outcomes of all newly detected FNAIT, diagnosed and treated in the first week of life ($n = 102$). Postnatal strategies included no treatment ($n = 34$), platelet transfusion (PTx) with compatible ($n = 24$) or random-donor platelets ($n = 16$), or both ($n = 6$), and IVIg (with ($n = 9$) or without PTx ($n = 9$)). In all strategies, a median platelet count $> 50 \times 10^9$/L was reached within four days after birth without the occurrence of new haemorrhages. Highest and fastest increment in platelet count was observed after HPA-compatible PTx, median platelet count 151×10^9/L at five days of age. Treatment with IVIg was associated with the smallest increment in platelet counts, median platelet count 67×10^9/L at day 6. Random-donor PTx were not associated with a higher use of additional transfusions, which suggests that if HPA-compatible platelets are not directly available transfusion with random-donor platelets may be a more appropriate first line therapy in FNAIT.

Introduction

Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is the leading cause of severe thrombocytopenia in term born new-borns.[1] FNAIT is a rare condition that occurs in approximately 1 in 1000 new-borns. Incompatibility in human platelet antigens (HPAs) between mother and fetus may lead to a maternal alloimmune response with formation of maternal IgG class alloantibodies. During pregnancy, there is an active placental IgG transport. Therefore, these alloantibodies will enter the fetal circulation, where they can destruct fetal platelets as well as damage endothelial cells, which can result in bleeding complications.[2,3] The severity of these bleedings can vary, from minor skin manifestations to major organ haemorrhages, of which the most feared complication is an intracranial haemorrhage (ICH) and subsequent neurological sequelae or even mortality.[4,5] The primary goal of treatment of patients with FNAIT is to prevent severe bleeding complications, antenatal as well as postnatal. During the antenatal period, the optimal strategy appears to be weekly maternal infusions with intravenous immunoglobulin (IVIg).[6] After birth, however, no clear consensus exists and currently applied strategies are highly inconsistent and primarily based on expert opinion and clinical experience.[7-9] The two largest cohorts published to date consist of our previous series of 22 cases with known immunisation (anticipated FNAIT) that received antenatal IVIg and an Australian registry based study including 44 cases of confirmed and newly detected FNAIT.[10,11] Thus far, these two studies did not provide comparisons of different treatment strategies for patients with FNAIT. Despite this shortage of evidence, transfusion with HPA-compatible platelets is generally considered the treatment of choice.[12] Small, heterogenic studies implicate that, compared to random-donor PTxs, transfusions with HPA-compatible platelets seem to give a larger increment of platelet count, with a longer sustained effect and therefore fewer transfusions.[11-14] However, in case of emergency, when HPA-compatible platelets are not available, treatment with random-donor platelets has been suggested to be a safe alternative.[15,16] In contrast to the great efficacy of IVIg in antenatal preventive treatment, the role of IVIg in the postnatal management of FNAIT remains unclear.[15,17,18]

Endeavouring to fill the gap in knowledge on postnatal management of FNAIT, we provide the largest cohort analysis reported thus far. While considering the guidelines and clinical features on which the choice for postnatal management is based, we analysed different postnatal management strategies. We set out to describe clinical and laboratory parameters and outcomes of patients with newly detected FNAIT according to whether or not their postnatal treatment comprised either HPA-compatible transfusions, transfusions with random-donor platelets or IVIg.

Methods

Study design and participants

We performed a nationwide cohort study on all neonates suffering from FNAIT born between 1-1-2006 and 1-1-2017 identified at the Leiden University Medical Centre (LUMC, national reference hospital) as well as at Sanquin Diagnostics, Amsterdam (national reference laboratory), the Netherlands. All cases were confirmed by the presence of specific HPA antibodies of the IgG-class in the maternal serum, directed against fetal/neonatal platelets as confirmed by crossmatch and HPA genotyping. HPA typing of the child was performed by genotyping. We excluded cases with insufficient clinical information, defined as no information on postnatal treatment strategy or course of platelet count. Solely unanticipated cases were included, defined as newly detected cases, diagnosed because of FNAIT related symptoms. To optimally assess the outcome of the postnatal treated we excluded cases that were detected and treated antenatally. We intended to describe the course in platelet counts and bleeding tendency in the first week of life. Ethical approval was provided by the Committee of Medical Ethics at the LUMC (G17·007).

Data Collection

Data were collected at both institutes (LUMC and Sanquin). Laboratory data included type of HPA-alloantibodies, HPA geno-/phenotype of the patients with FNAIT and their parents and the course of platelet count over time. Obstetric data included antenatal therapy (type, dose and duration), obstetric history, gestational age at birth, birth weight, mode of delivery, Apgar score after 5 minutes. Neonatal data comprised bleeding symptoms, postnatal treatment strategy, and the duration of admission. Bleeding symptoms were divided into minor or severe. Severe bleeding was classified as an ICH, an intraventricular haemorrhage (IVH) grade 3-4[19] or other major organ haemorrhage such as a severe pulmonary or gastrointestinal bleeding, requiring a red blood cell transfusion. All other uncomplicated haemorrhages (e.g. skin manifestations, hematomas or grade 1-2 IVH) were classified as minor bleedings. Indications for the measurement of neonatal platelet count were assessed. These indications can be one of the following factors that may be associated with thrombocytopenia as well: proven sepsis defined as a positive blood culture in a neonate with clinical signs of infection, small for gestational age (SGA, defined as a birth weight below the 10th centile), asphyxia, chromosomal abnormalities (trisomy 21) and prematurity. In case of insufficient data, referring hospitals were contacted for additional information. Thrombocytopenia was defined as a platelet count below 150×10^9/L and a severe thrombocytopenia was defined as a platelet count below 50×10^9/L. A platelet count below 20×10^9/L was classified as a very severe thrombocytopenia.

Treatment protocol

Postnatal treatment protocol comprised PTxs whenever the platelet count was below 30 $\times 10^9$/L for all cases treated before 2010 and whenever the platelet count was below 20 $\times 10^9$/L from 2010 onwards in non-bleeding infants. This threshold was 50 $\times 10^9$/L in case of manifest bleeding or need of procedure with a risk of bleeding, and for neonates with a birth weight <1500 g and gestational age < 32 weeks that were clinically ill. Standard dose was 10 – 20ml/kg or 10 – 20 $\times 10^9$/kg. First choice is a with HPA-compatible platelets. In cases of emergency one might resort to a transfusion with random-donor platelets, a product that is, in the Netherlands, composed of material from five donors. An HPA-compatible product is a single donor apheresis product. Both products are comparable in the concentration of platelets, 1.2 $\times 10^9$/mL for the HPA-compatible product and 1.1 $\times 10^9$/mL for the random-donor product. Postnatal IVIg was indicated in case of an insufficient rise in platelet count after two HPA-compatible PTxs (platelet count < 50 $\times 10^9$/L).

Statistical analysis

The incidence of minor or severe bleeding, first and lowest platelet count and clinical course of FNAIT (days to platelet count > 50 $\times 10^9$/L, platelet count > 100 $\times 10^9$/L, discharge) were compared between new-borns receiving different postnatal treatment strategies. Examination of platelet count course for different treatment groups, subgroup analysis of the group of cases caused by HPA-1a alloantibodies and of cases diagnosed the first two days of life were performed as well. These subgroup evaluations were performed in order to display the course of platelet count in a less heterogeneous group. Distributions in categorical variables between groups were compared with Chi-square test or Fisher's exact test, as applicable (Fisher's exact test for observed counts < 10). Comparisons for continuous variables were performed using student's t-test, one-way ANOVA or Mann Whitney U-test, as applicable. Tests were performed using IBM SPSS (version 23.0.0.2) and GraphPad Prism (version 7.02).

Results

During the 11-years study period, a total of 139 new-borns with newly detected FNAIT were identified, of which 31 cases had to be excluded, due to loss to follow-up, after transfer to an unknown hospital, or insufficient clinical information (Figure 6.1). Of the remaining 108 cases, six were excluded for analysis of postnatal treatment due to antenatal IVIg treatment for an ICH detected during pregnancy, which left 102 newly detected cases eligible for inclusion.

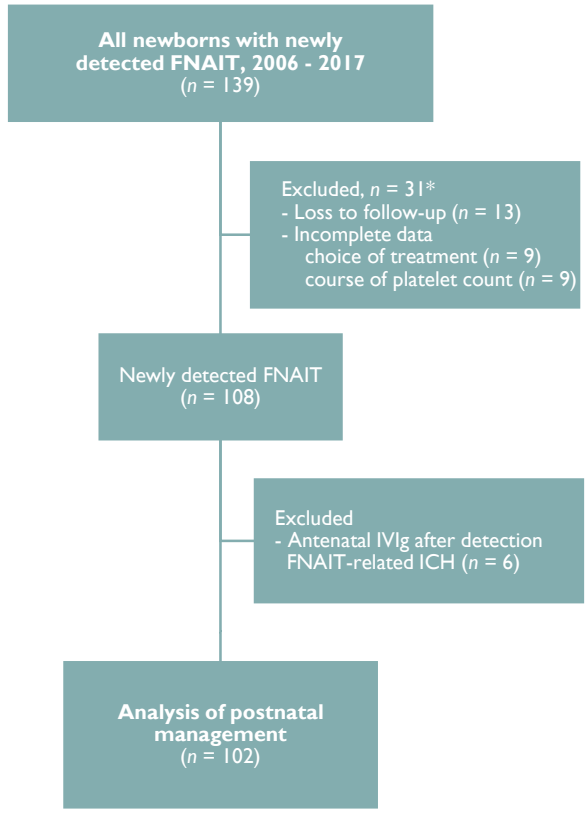

Figure 6.1 – Flowchart and description of study population

** Excluded cases did not differ from the included cases for HPA-type or, when known, the severity of the disease.*

FNAIT, fetal and neonatal alloimmune thrombocytopenia; ICH, intracranial haemorrhage; IVIg, intravenous immunoglobulin.

Demographic and clinical characteristics

Involved antibodies were directed against HPA-1a (*n* = 78), HPA-5b (*n* = 19), HPA-15a (*n* = 2), HPA-6 (*n* = 1) and in two cases alloantibodies directed against a newly detected private antigen, located on glycoprotein complex Ia/IIa (Table 6.I). Cases were detected because of bleeding symptoms (in 68/102 (67%) of all cases, or 64/98 (65%) of all living new-borns) or because of platelet count measurement as part of the work-up for prematurity (9/98, 9%), suspicion of an infection (9/98, 9%), asphyxia (2/98, 2%), small for gestational age (SGA, 6/98, 6%), trisomy 21 (1/98, 1%), chance finding due to hypoglycaemia or hyperbilirubinaemia (6/98, 6%), or because of suspicion of neonatal anaemia after large intrapartum haemorrhage of 3L (1/98, 1%). The proportion of new-borns that were SGA was higher than expected, 22% (22/98) versus 10% in general population. In six new-borns diagnostic work-up for FNAIT was performed because of the SGA and in the remaining 16 new-borns that were SGA, FNAIT was diagnosed because of bleeding symptoms.

Table 6.1 – Demographics and clinical characteristics

Antibodies directed against, *n* (%)	
HPA-1a	78 (77)
HPA-5b	19 (19)
Other*	5 (4)
Gravidity, median (range)	2 (1-5)
GA at birth†, in weeks, median (range)	38+3 (30+1-41+4)
Birthweight†, in grams, mean (SD)	2960 (733)
Small for gestational age†, *n* (%)	22 (22)
Apgar < 7 at 5 minutes†, *n* (%)	5 (5)
Infection†, n (%)	6 (6)
Minor bleeding, n (%)	65 (64)
Severe bleeding, n (%)	8 (8)
of which resulted in mortality	*4 (50)*
Platelet count†, $\times 10^9$/L, median (range)	
nadir platelet count	17 (3-91)
< 50	89 (91)
< 30	70 (82)
< 20	57 (58)
Postnatal treatment†, n (%)	64 (65)

* HPA-15a ($n = 2$); HPA-6 ($n = 1$) and private antigen ($n = 2$).

† 4 cases of intrauterine death excluded.

A total of 14 severe haemorrhages had occurred (Figure 6.1, Table 6.I). Six of these haemorrhages concerned antenatally detected ICHs that subsequently received antenatal IVIg and therefore had to be excluded from analysis of postnatal treatment. Of the eight included severe haemorrhages, four led to decease of the fetus; one infant died in utero because of a severe ICH detected at 29 weeks' gestation, a second infant died in utero due to a severe gastro-intestinal bleeding and in two cases with a severe ICH, the pregnancy was terminated at 19 and 22 weeks' gestation, respectively. In the four surviving children, the severe haemorrhages comprised three ICHs and one pulmonary bleeding, that were detected in the first days of life.

A total of 98 live new-borns with newly detected FNAIT remained. Of these, 34 new-borns received no treatment, 55 new-borns received one or more PTx and nine new-borns received only postnatal IVIg treatment (Table 6.2).

Course of platelet counts

As expected, the median of the first platelet count was higher in new-borns who were not treated compared to treated infants; 34×10^9/L versus 14×10^9/L (Table 6.2). Individual first and lowest platelet counts per treatment strategy are displayed in figure S1. Figure 6.2 depicts

the courses of platelet counts for the different treatment strategies. The corresponding values of the median platelet count, the interquartile range per treatment group and the number of cases contributing to the cohort per day are provided by supplemental table S6.I. In all children, irrespective of the postnatal treatment strategy, a median platelet counts above 50×10^9/L was reached within four days after birth (Figure 6.2A). Cases of FNAIT caused by HPA-1a or cases diagnosed in the first two days of life showed similar patterns of recovery of platelet count as compared to the whole group (Figure 6.2B and 6.2C versus figure 6.2A).

Table 6.2 – Distribution and effect of postnatal treatment

		No treatment	**Only compatible PTx**	**Only random PTx**	**Compatible after random PTx**	**PTx + IVIg**	**Only IVIg**
		n = 34	*n* = 24	*n* = 16	*n* = 6	*n* = 9	*n* = 9
First platelet count, $\times 10^9$/L median (range)		34 (14-128)	13 (4-61)	23 (3-56)	7 (3-12)	8 (4-15)	9 (6-39)
No clinical bleeding, *n* (%)		22 (65)	5 (21)	6 (38)	1 (17)	1 (11)	0
>1 PTx, *n* (%)		-	3 (13)	2 (13)	6 (100)	6 (67)	-
Platelet count above	***Days after diagnosis****						
20×10^9/L	1, *n* (%)	33 (97)	21 (88)	13 (81)	5 (83)	7 (78)	5 (56)
	2, *n* (%)	34 (100)	24 (100)	15 (94)	6 (100)	9 (100)	7 (78)
	3, *n* (%)	34 (100)	24 (100)	15 (94)	6 (100)	9 (100)	8 (89)
50×10^9/L	1, *n* (%)	14 (41)	16 (83)	10 (63)	2 (33)	2 (22)	3 (33)
	2, *n* (%)	21 (62)	20 (83)	14 (88)	5 (83)	4 (44)	3 (33)
	3, *n* (%)	23 (68)	21 (88)	14 (88)	6 (100)	5 (56)	4 (44)

PTx, platelet transfusion; IVIg, intravenous immunoglobulin.

*Day after diagnosis of thrombocytopenia, after which no drop below the given threshold of platelet count.

Transfusion with random-donor platelets, compared to HPA-compatible platelets, gave comparable amounts of new-borns that reached the transfusion threshold of 20×10^9/L or a platelet count of 50×10^9/L in the first days after diagnosis and treatment (Table 6.2). At three days after diagnosis of thrombocytopenia, treatment with PTx and IVIg or IVIg only had the lowest proportion of new-borns with a platelet count > 50×10^9/L (56% and 44%, respectively).

A total of 46 newborns were treated with (one or more) PTxs, solely. Of these, the first transfusion was with HPA-compatible platelets in 24 cases and with random-donor platelets in 22 cases (Table 6.3). After an HPA-compatible transfusion, three cases received one or more additional transfusions and eight cases received another PTx after a random transfusion (Supplemental S6.2). Of these 11 additional transfusions, four were adequately administered because of a drop

in platelet count below 30 × 10^9/L after the first transfusion. This included 2/24 initial HPA-compatible transfusions (8%) and 2/22 initial random-donor PTxs (9%). In the remaining seven cases the additional transfusion was administered almost simultaneously with the first PTx (*n* = 2, HPA-compatible directly after a random transfusion) or despite a platelet count above 30 × 10^9/L was already reached (*n* = 5).

Table 6.3 – Cases treated with one or more platelet transfusions

	First transfusion Compatible, *n* = 24		**First transfusion Random, *n* = 22**	
	Received 1 PTx *n* = 21	Received >1 PTx *n* = 3	Received 1 PTx *n* = 14	Received >1 PTx *n* = 8
First platelet count, × 10^9/L, median (range)	13 (4-61)	10 (8-58)	23 (3-56)	9 (3-24)
No clinical bleeding, *n* (%)	5 (24)	0	5 (36)	3 (38)
Day first PTx, median (range)	1 (1-4)	1	2 (1-52)	1 (1-4)
Dropped to platelet count < 30 × 10^9/L after first PTx, n (%)	-	2 (8)	-	2 (9)
Dropped to platelet count < 20 × 10^9/L after first PTx, *n* (%)	-	0	-	1 (5)

PTx, platelet transfusion.

Eight neonates with a nadir platelet count of 30 × 10^9/L or higher, above transfusion threshold in guidelines, received postnatal therapy (Figure 6.3). Four of these cases presented with minor bleeding (platelet counts 30, 35, 35 and 38 × 10^9/L, respectively). The remaining four cases were without clinical bleeding, though showed additional complications. One neonate was premature (gestational age 30^{+1}; platelet count 41 × 10^9/L), one was both premature (gestational age 32^{+6}) and SGA (platelet count 33 × 10^9/L), one other suffered from asphyxia (Apgar 2/2/5; platelet count 30 × 10^9/L) and the last was diagnosed with a transposition of the great arteries (platelet count 30 × 10^9/L). In seven of these eight cases, a random-donor PTx was administered and one case was treated with an additional HPA-compatible PTx.

Clinical presentation and choice of postnatal treatment

Neonates suffering from FNAIT with clinical bleeding were treated more frequent than asymptomatic new-borns (Figure 6.3). One case (HPA-5b) with an ICH received no treatment, because the nadir platelet count was 75 × 10^9/L. Despite very severe thrombocytopenia (platelet count < 20 × 10^9/L), seven new-borns did not receive any form of postnatal therapy (Figure 6.3). Of these cases, two had no signs of bleeding, and were detected because of a suspicion of infection one with FNAIT caused by HPA-1a and one by HPA-5b (both platelet count 17 × 10^9/L). Another two cases presented with skin bleeding; one with alloantibodies against HPA-1a and

one with anti-HPA-15a (both platelet count 14 × 10^9/L). In the last three cases, two caused by anti-HPA5b, the other by anti-HPA-1a, no signs of bleeding were found, but one child suffered from sepsis, one was diagnosed with trisomy 21 and one was small for gestational age (platelet count 15, 15 and 17 × 10^9/L, respectively). In six of these seven cases, a rapid increase of platelet count was seen, with a platelet count well above 20 × 10^9/L within one day.

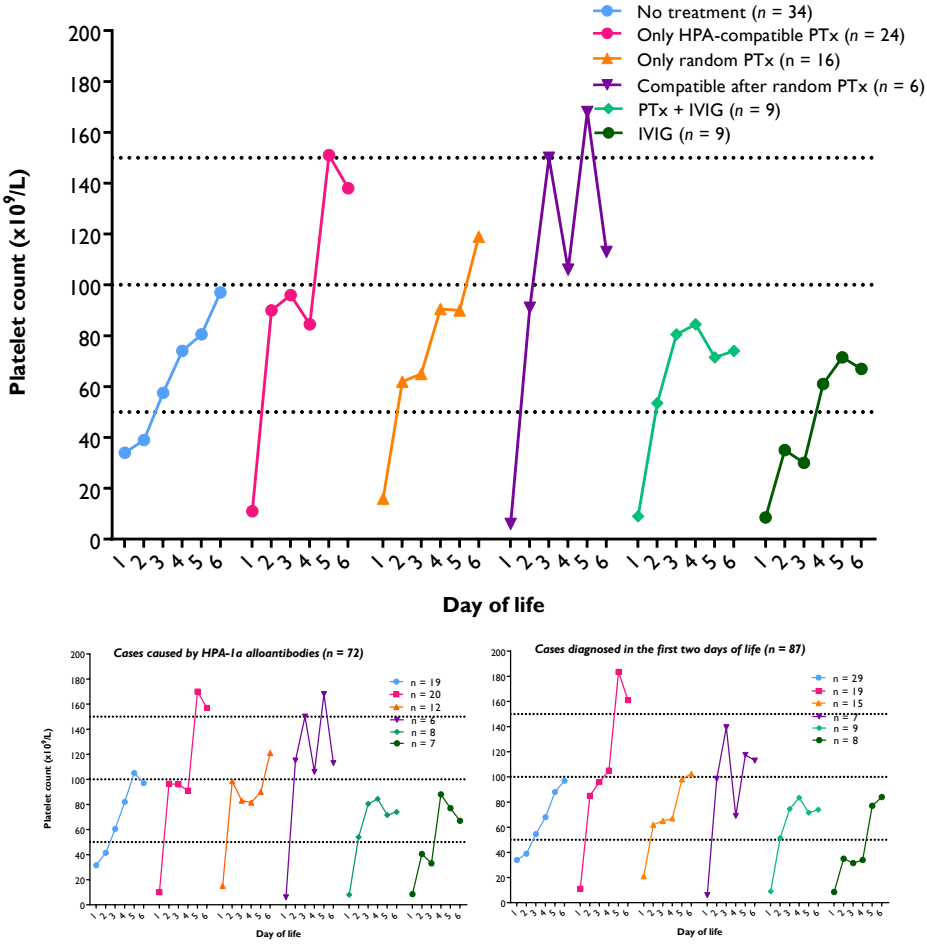

Figure 6.2 – Course of platelet count per postnatal treatment strategy

A. All live born neonates, *n* = 98. **B**. Only cases caused by HPA-1a, *n* = 71. **C**. Only cases diagnosed in the first two days of life.

In addition, nine new-borns with platelet counts between 20 × 10^9/L and 30 × 10^9/L did not receive postnatal treatment. Of these, eight were caused by HPA-1a and one by HPA-15a. Five children presented with skin bleeding, two children were premature and the other three were a chance finding of thrombocytopenia.

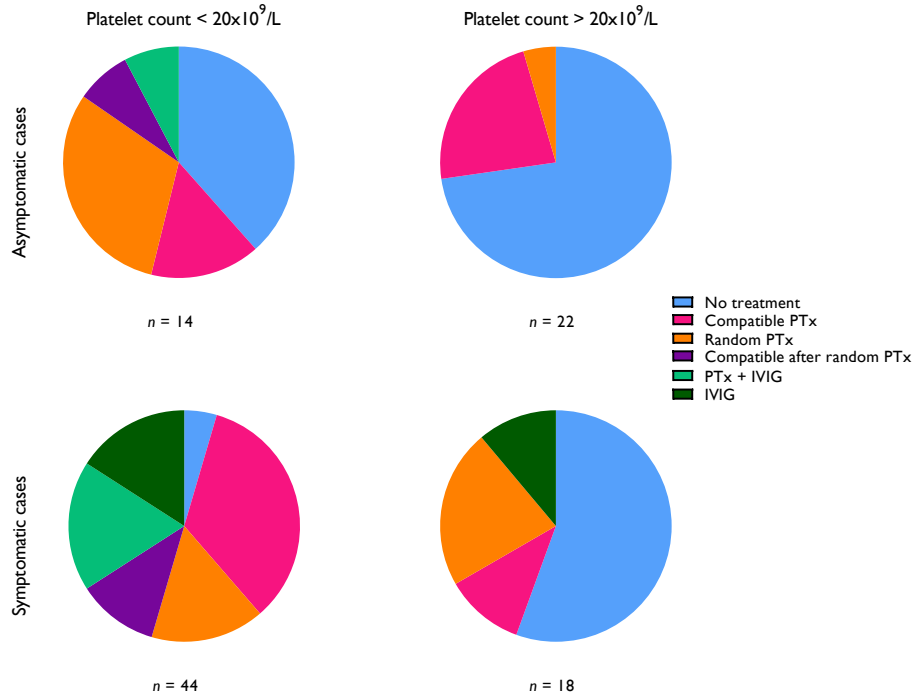

Figure 6.3 – Treatment choice based on platelet count and clinical outcome

A. Asymptomatic cases (without clinical bleeding). **B**. Symptomatic cases (with minor or severe bleeding).

Treatment with IVIg before 2010 in 7/30 (23%) and from 2010 in 2/68 (3%).

Discussion

This study represents the largest cohort of patients with FNAIT with recorded postnatal treatment strategies. Over the 11-years inclusion period, we collected data of 102 cases with newly detected FNAIT. These cases concerned children with newly detected FNAIT, in which a diagnostic FNAIT work-up was performed because of either an unexpected bleeding or severe thrombocytopenia. Despite national guidelines on the postnatal management of these children, a variety of strategies were applied in numerous combinations; transfusions with HPA-compatible platelets, random-donor platelets and IVIg administration. Overall, patients' outcomes were favourable, independent of postnatal treatment strategies. A median platelet count > 50×10^9/L was reached within four days after birth in every treatment group and none of the children showed new haemorrhages. This is in line with previous observations, that severe postnatal bleeding in FNAIT rarely occurs.[20] As expected first and nadir platelet count were important indicators of the administration of postnatal therapy.

Interpretation of these results should be done with care and caution, due to the observational nature of this study, the missing data, confounding by indication and selection bias. Next to the knowledge of existing guidelines and experience of the physician, the choice for a specific treatment is influenced by the overall clinical presentation and severity of the disease. This severity, however, is amongst others determined by our primary outcome measure, the (course of) platelet count. In order to assess and reduce the risk of bias towards less severe cases, the results were displayed for separate subpopulations as well, for example HPA-1a-mediated FNAIT or early diagnoses, presumably more severe cases, in the first two days of life. Also, it should be taken into consideration that the ultimate goal of treatment in FNAIT is to prevent (severe) bleeding, which in clinical practice is usually objectified by aiming for a platelet count above a certain level (20 or 30×10^9/L).

Consistent with international series, transfusion with HPA-compatible platelets was associated with the fastest and highest increment in platelet counts in our cohort.[11,12] Despite a possible shorter half-life and less pronounced increment, a median rise of platelet count over 100×10^9/L after six days was achieved in cases treated with only random-donor transfusions, as well. Between the group of cases treated with HPA-compatible or that treated with random-donor PTxs only, there was no significant difference in the amount of children reaching a platelet count of 20×10^9/L or 50×10^9/L within the first days of life. In our cohort, transfusion with random-donor platelets did not seem to lead to a higher need for additional transfusions, in terms of a drop in platelet count below 20×10^9/L or 30×10^9/L. Smaller observational studies have reported on the effect of random-donor platelets in FNAIT before. Kiefel and colleagues[16] reported a rise in platelet count of $> 80 \times 10^9$/L after treatment with one or two transfusions in ten newborns and Backchoul and colleagues[15], demonstrated a platelet count above 30×10^9/L for longer than 24 hours after one random-donor PTx in 5 out of 7 cases compared to 2 out of 4 cases treated with HPA-compatible platelets. It can be taken into account that our group of 16 treated cases with only random-donor PTxs included four children with anti-HPA-5b mediated FNAIT, for whom the five-donor product might have partially contained compatible platelets, since an estimated 81·3% of donors is HPA-5b negative.[21]

Postnatal treatment with IVIg seemed to be the least effective in our cohort. These results are in line with previously reported data.[22-24] Besides two case reports, Mueller-Eckhart and colleagues[22] demonstrated an increase of 30×10^9/L after 3-5 days in 10 out of 13 children treated with IVIg. Likewise, in the nine cases in our cohort treated with IVIg only, a platelet count above 50×10^9/L was reached after 5-6 days versus 2-3 days in new-borns treated with random-donor platelets or HPA-compatible platelets, thus leading to a longer admission. So, treatment with IVIg only might not a preferable postnatal treatment strategy.

We observed a large proportion of new-borns that were SGA in our cohort, 22/98 (22%). This may be partly due to a detection bias, whereas SGA can be the cause for measuring the neonatal platelet count. However, this was the case for only six of the 22 children that were SGA. Additionally, it has been suggested that interaction of anti-HPA-1a with trophoblast cells, which also express the HPA-1a epitope, affect normal placental development.[25,26]

All postnatal treatment strategies resulted in an increase in median platelet counts and no new haemorrhages occurred. Or, inversely, one could state that a safe platelet count will be reached regardless of the specific strategy applied and that it is all just natural course. This might especially be displayed by the gradual rise in platelet count in the group of new-borns that did not receive any postnatal treatment. The natural course of FNAIT, however, cannot be predicted and extrapolated from the untreated children in our cohort, due to their likely less severe disease. Also previous studies that identified the risk of FNAIT upon screening for HPA-1a negativity in pregnancy were not able to describe the natural course of disease, due to the taken interventions to minimize the risk of perinatal bleeding.[20,27]

In our cohort 16 new-borns with severe thrombocytopenia ($< 30 \times 10^9$/L, of which seven $< 20 \times 10^9$/L) did not receive a PTx or other treatment. In all cases, platelet counts increased spontaneously above the transfusion threshold within two days and no new haemorrhages were detected. In this regard, our data confirm that the transfusion threshold of 20×10^9/L was not associated with an increased risk of bleeding.

Overall, our data suggest that a transfusion with HPA-compatible platelets induces the fastest and highest increment in platelet count. In the Netherlands, HPA-1a and 5b-negative donor platelets are directly available from shelf in two blood bank distribution centers, which facilitates our quick administration of HPA-compatible transfusions. Further, our data illustrates that a transfusion with random-donor platelets may also lead to sufficient rise in platelet counts (well above transfusion triggers of 20 or 30×10^9/L), without an increase in the need for additional transfusions or the occurrence of new haemorrhages. A randomized study comparing bleeding tendency and rise of platelet counts upon transfusions with random-donor platelets or HPA-compatible platelets in homogenous treatment groups would provide more insight for optimal postnatal management of FNAIT.

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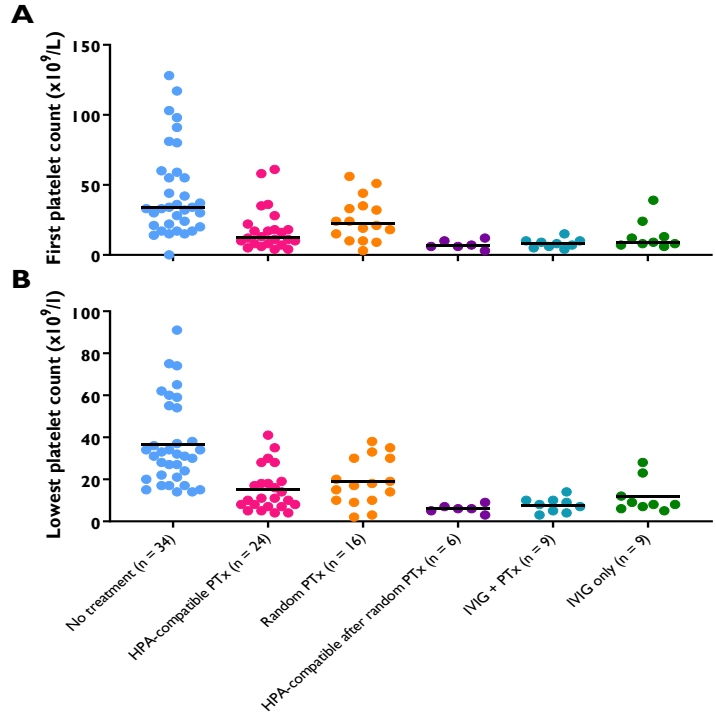
Supplemental material

Supplemental table S6.I – Course of median platelet count and interquartile range per postnatal treatment strategy

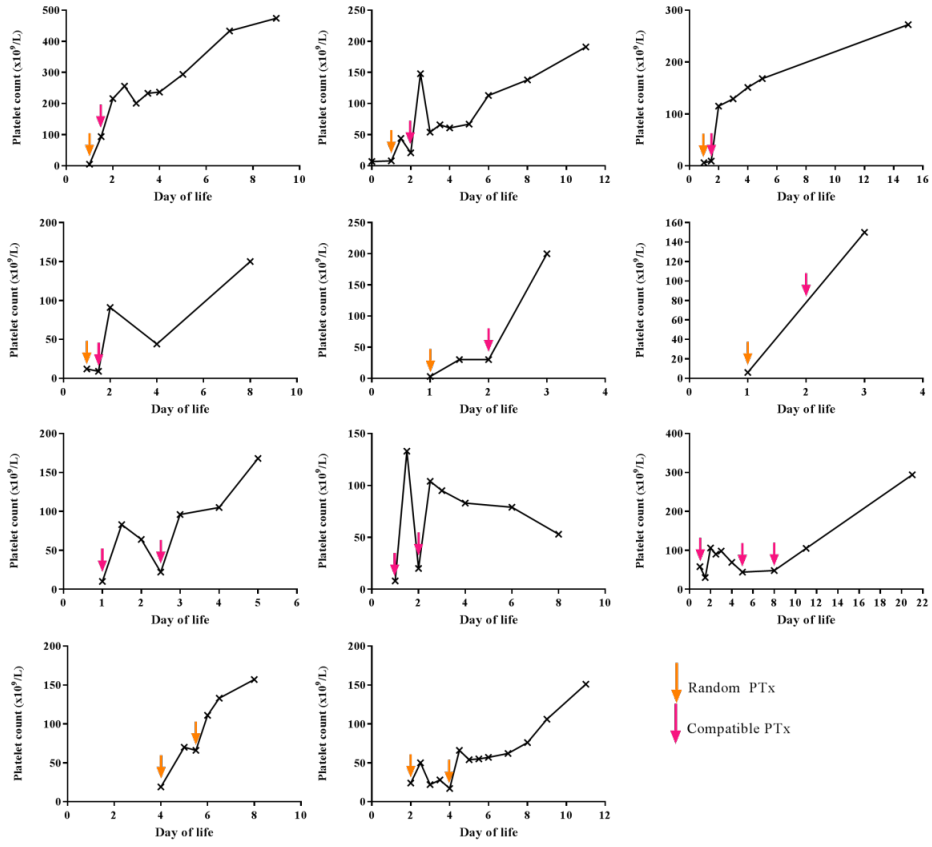
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
No treatment	34 (22 – 80)	39 (35-72)	58 (38-80)	74 (44-94)	81 (34-110)	97 (55-165)
Number of cases	*23*	*29*	*31*	*31*	*34*	*34*
Compatible PTx	11 (8-19)	90 (67-104)	96 (62-132)	85 (43-167)	151 (44-222)	138 (79-178)
Number of cases	*20*	*21*	*23*	*24*	*24*	*24*
Random PTx	16 (10-34)	62 (31-108)	65 (30-144)	91 (59-111)	90 (66-100)	119 (55-128)
Number of cases	*10*	*14*	*15*	*16*	*16*	*16*
Compatible after random PTx	6 (5-8)	91 (26-166)	150 (98-201)	106 (48-216)	168 (67-168)	113
Number of cases	*6*	*6*	*6*	*6*	*6*	*6*
PTx + IVIg	9 (6-12)	54 (43-83)	79 (35-91)	94 (66-108)	72 (53-119)	74 (63-178)
Number of cases	*9*	*9*	*9*	*9*	*9*	*9*
IVIg only	9 (7-21)	35 (15-63)	30 (13-48)	61 (27-117)	72 (52-211)	67 (37-67)
Number of cases	*8*	*8*	*9*	*9*	*9*	*9*

IVIg, intravenous immunoglobulins; PTx, platelet transfusion.



Supplemental figure S6.1 – Individual first and lowest platelet counts per postnatal treatment strategy

A. First platelet count. **B.** Lowest platelet count.



Supplemental figure S6.2 – Course of platelet count of cases receiving > 1 platelet transfusion