

# Should HLA and HPA-matched platelet transfusions for patients with Glanzmann Thrombasthenia or Bernard-Soulier syndrome be standardized care? A Dutch survey and recommendations

Elise J. Huisman<sup>1,2,3</sup>  | Nory Holle<sup>1</sup> | Martin Schipperus<sup>1</sup> |  
Marjon H. Cnossen<sup>2</sup> | Masja de Haas<sup>4,5</sup> | Leendert Porcelijn<sup>4,6</sup> |  
Jaap-Jan Zwaginga<sup>5</sup>

<sup>1</sup>Department of Pediatric Hematology and Oncology, Erasmus MC Sophia Children's Hospital, University Medical Center Rotterdam, Rotterdam, The Netherlands

<sup>2</sup>Department of Medical Affairs, Unit of Transfusion Medicine, Sanquin Blood bank, Amsterdam, The Netherlands

<sup>3</sup>Laboratory of Blood Transfusion, Department of Clinical Chemistry, Erasmus University Medical Center, Rotterdam, The Netherlands

<sup>4</sup>Department of Immunohematology Diagnostics, Sanquin Diagnostic Services and Sanquin Research, Amsterdam, The Netherlands

<sup>5</sup>Department of Hematology, Leiden University Medical Center, Leiden, The Netherlands

<sup>6</sup>Laboratory of Platelet and Leucocyte Serology, Sanquin Diagnostic Services and Sanquin Research, Amsterdam, The Netherlands

## Correspondence

Elise J. Huisman, Department of Pediatric Hematology and Oncology, Erasmus MC Sophia Children's Hospital, University Medical Center Rotterdam, Wytemaweg 80, 3015 CN Rotterdam, The Netherlands.  
Email: [e.j.huisman@erasmusmc.nl](mailto:e.j.huisman@erasmusmc.nl)

## Abstract

**Background:** Glanzmann thrombasthenia (GT) and Bernard-Soulier syndrome (BSS) patients require frequent platelet transfusions and hence have an increased risk for alloimmunization against donor Human Leukocyte Antigens (HLA) when no HLA-matching is performed. Knowing that Human Platelet

**Abbreviations:** ADAMTS-13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; ADR, adverse drug reaction; AE, adverse event; aHUS, atypical hemolytic uremic syndrome; APPT, activated partial thromboplastin time; B19V, parvovirus B19; BSS, Bernard-Soulier Syndrome; cci, corrected count increment; CD, Cluster of Differentiation; COVID-19, coronavirus disease 2019; CPB, cardiopulmonary bypass; CPP, cryo-poor plasma; CRP, cryoprecipitate-reduced plasma; DVT, deep venous thrombosis; FFDP, freeze-dried plasma; FFP, fresh frozen plasma; FNHTR, febrile non-hemolytic transfusion reactions; FNAIT, feto-neonatal allo-immune thrombocytopenia; FP24, plasma frozen within 24 hours of phlebotomy; GI, gastro-intestinal; Glanzmann, Glanzmann Thrombasthenia; GP, glycoprotein; GVHD, graft versus host disease; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; HIV, human immunodeficiency virus; HLA, human leucocyte antigen; HLA<sub>m</sub>, human leucocyte antigen-matches platelets; HUS, hemolytic uremic syndrome; h, hours; HPA, Human Platelet Antigen; ICH, intracranial hemorrhage; IPD, inherited platelet disorder; IU, intra-uterine; IVIG, intravenous immunoglobulins; ICU, intensive care unit; INR, international normalized ratio; MB-FFP, methylene blue-treated fresh frozen plasma; MD, multiple donor; n, number; NA, not applicable; NHTR, non-hemolytic transfusion reaction; NM, not mentioned; NOS, not otherwise specified; OR, odds ratio; PE, pulmonary embolism; PT, prothrombin time; RBC, red blood cell; RCT, randomized controlled trial; S/D, solvent-detergent; SAE, serious adverse event; SARS-CoV2, severe acute respiratory syndrome-related coronavirus-2; TACO, transfusion-associated circulatory overload; TEE, thromboembolic event; TMA, thrombotic microangiopathy; TP, thawed plasma; TPE, therapeutic plasma exchange; TRALI, transfusion-related acute lung injury; TTP, thrombotic thrombocytopenic purpura; UK, United Kingdom; US, United States; UV, ultraviolet; VIPER-OCTA, Vasculopathic Injury and Plasma as Endothelial Rescue-OCTAplusLG; VTE, venous thromboembolism.; PC, (random) platelet concentrate; SDP, single donor platelet transfusion; TRALI, transfusion-related acute lung injury; WB, whole blood transfusion.

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Antigens (HPA) are located on the platelet glycoproteins that can be absent in these patients, preventive HPA-matching may also be considered. Uniform recommendations on this topic lack in transfusion guidelines making standard practice unclear, therefore, we aimed to provide a framework for matched platelet transfusions.

**Study Design and Methods:** We conducted a targeted literature search and a national survey of Dutch (pediatric) hematologists from July to September 2021.

**Results:** We found 20 articles describing platelet transfusion policies in 483 GT-patients and 29 BSS-patients, both adults and children. Twenty surveys were returned for full analysis. All responders treated patients with platelet disorders, including GT ( $n = 36$  reported) and BSS ( $n = 29$  reported). Of respondents, 75% estimated the risk of antibody formation as “likely” for HLA and 65% for HPA. Formation of HLA antibodies was reported in 5 GT and in 5 BSS-patients, including one child. Fifteen respondents gave preventive HLA-matched platelets in elective setting (75%). Three respondents additionally matched for HPA in GT-patients (15%). Main argument for matched platelet transfusions was preventing alloimmunization to safeguard the effectivity of ‘random’ donor-platelets in acute settings.

**Conclusion:** Elective HLA-matching for GT and BSS-patients is already conducted by most Dutch (pediatric) hematologists. HPA-matching is mainly applied when HPA-antibodies are formed. Based on the current literature and the survey, recommendations are proposed.

#### KEYWORDS

antibody formation; antigens, human platelet; Bernard-Soulier syndrome; blood platelet disorders; Glanzmann thrombasthenia; HLA antigens; human antigens, platelet; platelet transfusion

## 1 | INTRODUCTION

Patients with inherited platelet disorders (IPD) require platelet transfusions for the treatment of acute bleeding or for the prevention of major bleeding during surgery and child delivery.<sup>1,2</sup> Repetitive platelet transfusions may lead to alloimmunization against human leucocyte antigens (HLA) or human platelet antigens (HPA). In this regard, IPD-patients with Glanzmann thrombasthenia (GT) and Bernard-Soulier syndrome (BSS) are considered a high-risk group for alloimmunization.<sup>3,4</sup> GT is characterized by either a dysfunctional or (partial) absence of the glycoprotein (GP)-complex IIb/IIIa, also named  $\alpha$ Ib $\beta$ 3 integrin or CD41/CD61.<sup>5,6</sup> This complex is essential in the platelet-fibrinogen binding.<sup>6</sup> BSS is caused by either a dysfunctional or (partial) absent GP-complex Ib/IX/V, also named CD42a/CD42b.<sup>7</sup> This complex is essential for the platelet-von Willebrand factor (VWF) binding. Although hemostatic treatments as tranexamic acid, desmopressin and for GT-patients also recombinant

factor VII exist, platelet transfusions are often inevitable during life.<sup>8</sup> Both GT and BSS are categorized by flowcytometric GP-expression in 3 subtypes: in type 1 glycoproteins are absent or have less than 5% of the normal expression, in type 2 expression is  $\geq 5\%$ –25% of normal range and in type 3 expression is  $\geq 25\%$ –100%; but although sometimes normally expressed, glycoproteins may be dysfunctional in type 2 and 3.

### 1.1 | Risk and incidence of HLA antibodies in GT and BSS

Because platelets carry HLA-class I and HPA, there is a general risk of alloimmunization against non-self (donor) HLA-class I and HPA. The incidence of HLA antibody formation is further modulated by the number of platelet transfusions, remaining leucocytes in the blood products, individual immune characteristics of the receiver and potential antigen mismatch between donor and receiver.<sup>3</sup>

**TABLE 1** HPA antigens located on the platelet glycoproteins that are absent or dysfunctional in Glanzmann Thrombasthenia and Bernard-Soulier syndrome.

Glycoprotein	Platelet disease	HPA-antigen	Original terminology	Antigen frequency*
GPIIIa (CD61)	Glanzmann	HPA-1a	Zw <sup>a</sup> , PI <sup>A1</sup>	98%
		HPA-1b	Zw <sup>b</sup> , PI <sup>A2</sup>	28%
GPIb (CD42b)	BSS	HPA-2a	Ko <sup>b</sup>	99%
		HPA-2b	Ko <sup>a</sup> , Sib <sup>a</sup>	16%
GPIIb (CD41)	Glanzmann	HPA-3a	Bak <sup>a</sup> ,	84%
		HPA-3b	Lek <sup>a</sup> , Bak <sup>b</sup>	63%
GPIIIa	Glanzmann	HPA-4a	Yuk <sup>b</sup> , Pen <sup>a</sup>	100%
		HPA-4b	Yuk <sup>a</sup> , Pen <sup>b</sup>	<1%
GPIIIa	Glanzmann	HPA-6b	Ca <sup>a</sup> , Tu <sup>a</sup>	<1%
GPIIIa	Glanzmann	HPA-7b	Mo <sup>a</sup>	<1%
GPIIIa	Glanzmann	HPA-8b	Sr <sup>a</sup>	<1%
GPIIb	Glanzmann	HPA-9b	Max <sup>a</sup>	<1%
GPIIIa	Glanzmann	HPA-11b	Gro <sup>a</sup>	<1%
		HPA-16b	Duv <sup>a</sup> ,	
		HPA-17b, 19b	Va <sup>a</sup> , Sta	
		HPA-21b, 23b	Nos, Hug	
		HPA-26b, 29b	Sec <sup>a</sup> , Kha <sup>b</sup> Dom <sup>b</sup> , Bl <sup>a</sup>	
		HPA-32b, 33b	Bzh <sup>a</sup> , Efs <sup>a</sup>	
GPIIb	Glanzmann	HPA-20b	Kno	<1%
		HPA-22b, 24b	Sey, Cab2 <sup>a+</sup> Cab3 <sup>a+</sup> , War Lab <sup>a</sup>	
		HPA-27b, 28b		
		HPA-30b		
GPIX (CD42a)	BSS	HPA-31b	Cab4b+	<1%

Abbreviations: BSS, Bernard-Soulier syndrome; CD, cluster of differentiation; Glanzmann, Glanzmann thrombasthenia; GP, glycoprotein; HPA, human platelet antigen.

\*Prevalence measured in cohort with Caucasian ethnicity. For a complete and continuously updated overview we refer to the Human Platelet Antigen Database (<https://versiti.org/products-services/human-platelet-antigen-hpa-database>).

When HLA antibodies are formed, platelet refractoriness and moderate to severe transfusion reactions may occur.<sup>3</sup> No large datasets are currently available on the incidence of HLA alloimmunization in GT or BSS patients. Results from a number of small cohort studies with GT and BSS-patients, demonstrate a broad incidence of HLA antibodies formation of 9%–24%.<sup>1,9–12</sup>

## 1.2 | Risk and incidence of HPA antibodies in GT and BSS

Although 41 HPA antigens are known,<sup>13</sup> five HPA's are regarded as most clinically relevant due to their allele frequencies in Caucasian population, expression levels and immunogenicity: HPA-1a, 1b, 2b, 3a and 5b.<sup>14</sup> Immunization against these antigens and subsequent production of antibodies may lead to platelet transfusion refractoriness, post transfusion purpura and fetoneonatal alloimmune thrombocytopenia.<sup>15</sup> For GT and BSS-patients these may be even more relevant, as these HPA antigens are located

on the glycoprotein-complexes that are largely or completely absent on GT and BSS-platelets.<sup>6,7,13,16,17</sup> (See Table 1) Theoretically, GT and BSS-patients may therefore have a higher risk of HPA antibody formation compared with the general population. In daily practice risk assessment depends on additional factors such as remaining expression of HPA antigens on other tissues than platelets, as is the case if GT is caused by mutations leading to absent expression of GPIIb. In genotypically HPA-1a positive patients, HPA-1a will still be expressed as vitronectin receptor ( $\alpha_v/\beta_3$ ) on endothelium and other blood cells.<sup>2,13,18,19</sup> Reported incidences of HPA antibodies range from 2.5% to 9% in small case-series.<sup>11,20</sup>

## 1.3 | Risk of developing iso-antibodies in GT and BSS

GT and BSS-patients may develop iso-antibodies directed against common epitopes on the GP as well.<sup>21</sup> Such iso-antibodies appear as (pan-)positive results in platelet

antibody tests such as the Monoclonal Antibody-specific Immobilization of Platelet Antigen (MAIPA) with no apparent specificity. All donor platelets will be recognized by these iso-antibodies and no matching strategy can be performed to prevent refractoriness. It is not known if prevention of HLA or HPA antibody formation has a role in prevention of iso-antibodies. But transfusions with HLA and HPA-matched platelets may be useful to prevent HLA and HPA antibody formation. To date, no recommendations is given in the national guidelines in the Netherlands for platelet transfusion management in these patient groups. Therefore we performed a targeted literature search to create an overview of current knowledge. Secondly, we investigated how Dutch hematologists apply HLA and/or HPA-matched platelets in pediatric and adult GT and BSS-patients. We subsequently combined the survey results with current evidence from literature recommending a practical approach.

## 2 | MATERIALS AND METHODS

### 2.1 | Literature search

We conducted a targeted literature search, using the following search terms “Glanzmann, Glanzmann thrombasthenia, Bernard-Soulier syndrome, inherited platelet (function) disorders, congenital platelet (function) disorders, human leucocyte antigen, Human platelet antigen, (platelet) refractoriness” in the PubMed database. Only articles that were available in English as full text and involved GT and BSS-patients were analyzed.

### 2.2 | Data collection

The survey was conducted among (pediatric) hematologists in the Netherlands specialized in the management of IPDs and blood transfusion management. The survey was designed by one investigator (EH) and peer-reviewed in two rounds by two other investigators (JZ and MS). Our survey was forwarded digitally via an online questionnaire ([www.surveymonkey.com](http://www.surveymonkey.com)) program to all seven Dutch Hemophilia Treatment Centers as well as several working parties (WP): WP of the pediatric hematologists of the Dutch Society for Pediatrics (NVK), WP of benign hematologists of the Dutch Society for Transfusion (NVB) and the association of Dutch Hemophilia doctors (NVHB). The survey was completed either by individual practitioners or collectively by cooperating physicians working in the same medical center.

### 2.3 | Data analysis

We have used descriptive statistics for the survey results, using total number and percentage if indicated.

## 3 | RESULTS

### 3.1 | Literature

We found 20 articles describing a total of 483 GT-patients and 29 BSS-patients, both adults and children.<sup>2,10–12,20–35</sup> See Table 2. Two publications focused on pregnant GT and BSS-patients and neonatal outcome.<sup>11,12</sup> Presence of HLA antibodies in eight case-series and one review of  $\geq 5$  patients were reported in 49/265 (18.5%) pediatric and adult GT-patients (range 6.5%–86%),<sup>2,10,11,20–24,30</sup> and in one case-series of 3/18 BSS-patients (17%).<sup>12</sup> It was often not clear if the use of non-leukocyte-reduced platelet transfusions were additional risk factors for the development of HLA antibodies, so this was left out of the overview in Table 2. The impact of the HLA antibodies causing platelet refractoriness and leading to additional treatment was not always reported and ranged from 0 till 33%.<sup>10,22–25,28</sup>

Presence of HPA antibodies in GT-patients were reported in one case-series and one case-report.<sup>2</sup> In the case-series, five out of seven French Gypsy GT-patients had a genetic variant in the ITGA2B gene (coding for integrin  $\alpha 2b$  or CD41).<sup>2</sup> This variant is strongly linked to a homozygous HPA-1bb genotyping. In the one case-report from 1989 a combination of HPA-1a and HPA-1b antibodies were detected in a pregnant GT-patient. However, it is likely that this antibody pattern would currently be classified as iso-antibodies, for discrimination between iso-antibodies and HPA antibodies was not performed or technically not possible then.<sup>11</sup> The other case-series do not mention HPA antibody testing.

Neonatal complications resembling FNAIT were also reported in GT-patients, ranging from postnatal low platelet numbers ( $n = 3$ ) and mild bleedings as mucosal, conjunctival or skin bruises ( $n = 5$ ) till severe gastrointestinal or intracranial bleedings ( $n = 5$ ) and fetal or neonatal death.<sup>10,11,26,28</sup> In BSS-patients reported complications ranged from low postnatal platelet counts ( $n = 7$ ) till severe gastro-intestinal bleedings and intracranial bleeds ( $n = 5$ ) and neonatal death due to bleeding complications ( $n = 4$ ).<sup>12,31,33,34</sup> To note, none of the reports mentioned preventive atraumatic approach during labor nor if GT or BSS was ruled out in the neonate. Maternal iso-antibodies were considered causal for fetal or neonatal bleeding complications in six of the GT-patients and

**TABLE 2** Overview of literature on occurrence of HLA and HPA-antibodies in patients with Glanzmann thrombasthenia and Bernard-Soulier syndrome according to sample size.

Journal	Patient and disease characteristics		Risk factors for antibody formation			Reported incidences in exposed group			Clinical outcome		
	IPD type	Number (n); sample size (% female)	Category by subtype (n) <sup>a</sup>	Reported pregnancies (n)	Platelet transfusion product/LR	Platelet transfusion frequency	HLA antibodies, n (%)	HPA antibodies, n (%)	Iso-antibodies, n (%) <sup>b</sup>	Platelet refractoriness, n (%)	Neonatal outcome
<i>Case-series Glanzmann thrombasthenia</i>											
Zoiz (2019) <sup>21</sup> <i>GT registry</i>	GT	131 children (46%)	Type I: 35 Type II: 13 Type III: 3 Variant: 3 Unknown: 80	NA (child)	Platelets NOS, LR NM	NM	3/46 (6.5%) <sup>a</sup>	NM	20/46 (44%)	1/3 (33%)	NA
Poon (2015) <sup>22</sup> <i>GT registry</i>	GT	96 adults and children (54%)	Type I: 48 Type II: 6 Type III: 1 Unknown: 41	NM	Platelets NOS, LR NM	NM	16/96 (17%)	NM	35/96 (37%)	23/96 (24%)	NM
Poon (2004) <sup>23</sup> <i>Survey</i>	GT	59 adults (59%)	Type I: 39 Type II: 7 Type III: 3 Unknown: 10	NM	Platelets NOS, LR NM	NM	13/54 (24%) <sup>b</sup>	NM	21/54 (39%)	17/59 (29%)	NM
Siddiq (2011) <sup>11</sup> <i>Review</i>	GT	35; adult (100%)	Unknown	40	SDP n = 6, HLA <sup>a</sup> n = 7, Platelets NOS n = 27, WB n = 1, LR NM	Table 1: 1- ≥ 120 in n = 38; n = 1 history NM, n = 1 not given	8/35 (23%)	1/40 (2.5%, HPA-1a & HPA-1b) <sup>y</sup>	9/35 (26%)	NM	IWIG in 3 pregnancies, Plasma-exchange in 2 pregnancies, n = 6 healthy neonates, n = 4 IU deaths due to ICH, n = 1 IU death after amniocentesis, n = 1 conjunctival bleeding, n = 3 FNAIT, n = 1 marked bruises
Fiore (2012) <sup>20</sup>	GT	24; adults and children (58%)	Type I: 16 (Manouche) Type I: 5 Type II: 2 Variant: 1	3	Platelets NOS, LR NM	NM	NM	NM	Manouche: 13/16 (81%) Other: 2/8 (25%)	NM	NM
Santoro (2010) <sup>10</sup>	GT	17; adults (53%)	Type I: 14 Type III: 3	7	Platelet concentrate MD, LR NM	Table 1: 4-335 units (n = 14, n = 2 not given)	3/14 (219%)	NM	2/14 (14%) <sup>b</sup>	0/4 (0%)	n = 5 live births, n = 1 voluntary abortion, n = 1 early abortion at 13 weeks, no bleeding complications.
Fiore (2021) <sup>2</sup>	GT	7; adults and children (100%)	Type I: 6 (Manouche) Type I: 1 (other)	0	Platelets NOS, LR NM	NM (n = 6, 1 unknown)	1/7 (14.3%)	5/7 anti-HPA-1a (71%)	7/7 (100%)	NM	NA

TABLE 2 (Continued)

Journal	Patient and disease characteristics		Risk factors for antibody formation		Reported incidences in exposed group			Clinical outcome				
	IPD type	Number (n); sample size (% female)	Category by subtype (n) <sup>a</sup>	Reported pregnancies (n)	Platelet transfusion product/LR	Platelet transfusion frequency	HLA antibodies, n (%)	HPA antibodies, n (%)	Iso-antibodies, n (%) <sup>b</sup>	Platelet refractoriness, n (%)	Neonatal outcome	
Friend (2020) <sup>24</sup>	GT	2; children (50%)	Unknown	NA (child)	Platelets NOS, LR NM	NM (n = 2)	0/1 (0%)	NM	0/1 (0%)	0/1 (0%) <sup>d</sup>	NA	
<i>Case-reports Glanzmann thrombasthenia</i>												
Soni (2019) <sup>25</sup>	GT	1; adult woman	Type I: 1	1	1 unit SDP; others LR NM	≥8 units	NM	NM <sup>f</sup>	1 (100%)	0/1 (0%)	n = 1 IU death due to ICH	
Cid (2017) <sup>26</sup>	GT	1; adult woman	Unknown	0	Platelets NOS, LR NM	NM	1/1 (100%)	NM	1/1 (100%)	NM	NA; hysterectomy due to heavy menstrual bleeding at age of 20 years	
Léticée (2005) <sup>27</sup>	GT	1; adult woman	Type I: 1	2	Platelets NOS, LR NM	NM	1/1 (100%)	NM	1/1 (100%)	0/1 (0%) <sup>e</sup>	1st pregnancy early abortion, 2nd pregnancy IU death due to ICH	
Ito (1991) <sup>28</sup>	GT	1; adult woman	Unknown	1	WB and HLA <sub>m</sub> , LR NM	≥15 units	1/1 (100%)	NM	1/1 (100%)	0/1 (100%)	n = 1 healthy neonate born after antibody removal therapy	
<i>Case-series combined Glanzmann thrombasthenia and Bernard-Soulier syndrome</i>												
Gabe (2022) <sup>19</sup>	GT	11; adults (82%)	Type I: 6	3	Platelet concentrate (MD)	3–521 units	1/11 (9%)	1/11 (9%)	1/11 (9%) <sup>e</sup>	NM, but 3 transfusion reactions (TRALI, allergy, NHTR)	NM	
	BSS	4; adults (100%)	Variant: 3 Unknown: 2 Unknown: 4	0	LR applied	0–28 units	1/4 (25%)	NM	0/3 (0%)	NM, but 3 transfusion reactions (NHTR)	NA	
Almeida (2003) <sup>29</sup>	GT	5; children (%)	Type I: 4	NA (child)	Unknown, LR NM	1–4 (n = 3), 0 units	4/5 (80%) <sup>f</sup>	0/5	0/3 (0%)	NM, but 3 transfusion reactions (NHTR)	NA	
	BSS	1; child (%)	Type III: 1 Unknown: 1	NA (child)			1/1 (100%)	0/1			NA	
<i>Case-series Bernard-Soulier syndrome</i>												
Petitsidis (2010) <sup>12</sup>	BSS	18; adult (100%)	Unknown	30	HLA <sub>m</sub> n = 1, SPD n = 1, Platelets NOS n = 10, Blood NOS n = 1, LR NM <sup>k</sup>	NM	3/10 (30%)	NM	7/10 (70%)	NM	IVIG in 5 pregnancies, n = 1 IU death due to GI-bleeding; 1 neonatal death <6 h due to ICH, n = 4 neonates with FNAIT, n = 18 neonates with normal platelet counts	
<i>Systematic review</i>												

(Continues)

TABLE 2 (Continued)

Journal	Patient and disease characteristics		Risk factors for antibody formation		Reported incidences in exposed group			Clinical outcome				
	IPD type	Number (n); sample size (% female)	Category by subtype (n) <sup>a</sup>	Reported pregnancies (n)	Platelet transfusion product/LR	Platelet transfusion frequency	HLA antibodies, n (%)		HPA antibodies, n (%)	Iso-antibodies, n (%) <sup>b</sup>	Platelet refractoriness, n (%)	Neonatal outcome
Uofila (2008) <sup>30</sup>	BSS	2; adult (100%)	Unknown	6	Unknown, LR NM	NM	1/2 (50%)	NM in n = 1, excluded in the other	1/2 (50%)	NM	IVIG 1 ×/week in both pregnancies; n = 3 neonates of 1st pregnant woman had normal neonatal platelet counts, n = 3 neonates of 2nd pregnant woman had FNAIT and bleeding NOS	
<i>Case-reports Bernard-Soulier syndrome</i>												
Pascual (2011) <sup>34</sup>	BSS	1; adult woman	Unknown	2	HLAm, LR assumed	NM	1/1 (100%)	NM	0/1 (0%)	1 (100%)	n = 2 neonates with normal platelet counts	
Sandrock (2010) <sup>31</sup>	BSS	1; adult man	Type 1: 1	NA (male)	Unknown, LR NM	NM	1/1 (100%)	NM	NM	NM	NA	
Fujimori (1999) <sup>32</sup>	BSS	1; adult woman	Unknown	NM	Unknown, LR NM	NM	NM	NM	1/1 (100%)	NM	n = 1 neonatal death 6 h after delivery due to ICH and FNAIT	
Peng (1991) <sup>33</sup>	BSS	1; adult woman	Unknown	4	Unknown, LR NM	NM	NM	NM	1/1 (100%)	NM	1st neonate healthy, 2nd neonate IU death due to GI-bleeding and FNAIT, 3rd FNAIT, 4th, normal platelet count after weekly IVIG in 4th pregnancy	

Abbreviations: BSS, Bernard-Soulier syndrome; FNAIT, fetoneonatal allo-immune thrombocytopenia; GI, gastro-intestinal; GT, Glanzmann thrombasthenia; ICH, intracranial hemorrhage; h, hours; HLA, Human leucocyte antigen; HLAm, Human leucocyte antigen-matches platelets; IU, intra-uterine; IPD, Inherited Platelet Disorder; IVIG, intravenous immunoglobulins; k, peitsidis; MD, multiple donor; n, number; NA, not applicable; NHTR, Non-hemolytic transfusion reaction; NM, not mentioned; NOS, not otherwise specified; PC, (random) platelet concentrate; SDP, single donor platelets; TRALI, transfusion-related acute lung injury; WB, whole blood transfusion.

<sup>a</sup>Type 1 is defined as <5% glycoprotein expression compared to wild type, type 2 as 5%–25% versus wild-type, type III as 25%–100% versus wild-type, also called variant.

<sup>b</sup>Anti-αIIbβ3 for GT patients; anti-GPIIb/IX for BSS-patients.

<sup>c</sup>Platelet transfusions were avoided because of iso-antibody presence, no refractoriness reported in early years.

<sup>d</sup>Not mentioned in the second case.

<sup>e</sup>Mentioned as HPA-antibody in the article, but later described as anti-αIIbβ3.

<sup>f</sup>7 children were included, but one patient had a storage pool defect and is excluded in this table. In the article 6/7 including the patient with SDP had developed HLA antibodies after transfusion.

<sup>g</sup>International registry in Asia, Africa, Europe and North America. In 25 children antibodies were reported but only in 3 patients this was determined as HLA-antibodies with refractoriness in 1/3. Therefore, we have only included this number in the table.

<sup>h</sup>HLA antibody tests were not known in all included patients.

<sup>i</sup>anti-PLA is the former name of anti-HPA-1.

<sup>j</sup>Incompatibility of HPA-15 between parents was shown, but presence of anti-HPA-15b was not examined.

<sup>k</sup>Some women received both HLA-matched en platelets n.o.s or SDP and platelets n.o.s. Also, no information on platelet product selection was given on historically transfused women.

in 10 of the BSS-patients of whom the pregnancy was complicated with FNAIT.<sup>10-12,21,26,28,29,31,33,34</sup> Two pregnant GT-patients received weekly IVIG and in one GT-patient plasma-exchanges were performed.<sup>11,31,36</sup> Coexistence of maternal HPA antibodies was often unknown. Healthy neonates and normal neonatal platelets were seen as well ( $n = 3$  in GT,  $n = 18$  in BSS).<sup>10-12,31,34</sup>

## 3.2 | Survey results

### 3.2.1 | General demographics of survey respondents

Twenty surveys were fully completed and used for analysis. All respondents treated patients with IPDs: 50% had 1–10 patients with any type of IPD in follow-up ( $n = 10$ ), 35% had 10–25 patients ( $n = 7$ ) and 15% had >25 patients with IPD ( $n = 3$ ). Of the IPD-patients, GT- and BSS-patients were treated in some but not all centers (range 0–4 GT-patients per center and 0–2 BSS-patients per center). Overall, 36 GT and 29 BSS-patients were reported. Determination of incidence is not possible due to possible overlap in reported patients and the absence of specific patient characteristics.

### 3.2.2 | HLA and HPA antibody screening and formation

Most respondents estimated the risk on HLA or HPA antibody formation as likely (estimated risk for development of HLA antibodies in GT and BSS-patients was 75%; and 60% for HPA, see Figure 1A,B). This high-risk estimation was reflected in current practice: to prevent alloimmunization in GT and BSS-patients, 15 respondents routinely gave HLA-matched platelets in elective setting (15/20, 75%). Three of these respondents also preventively matched for HPA (3/20, 15%). The other five (5/20) did not give HLA-matched platelet transfusions when no HLA antibodies were formed or signs of clinical refractoriness present.

Preventive matching did not lead to a regular screening for the formation of HLA or HPA antibodies during follow-up in all centers. If surveillance was part of routine medical care, HLA antibody screening was most frequently performed in patients with GT ( $n = 13/20$ , 65% at least once) and less frequently in BSS-patients ( $n = 7$ ; 35%). For HPA antibody screening, this was 35% in GT ( $n = 7$ ), and rarely done in BSS ( $n = 3$ , 15%). See Figure 1C. Positive test results on HLA antibody-formation were reported equally in 5 GT and in 5 BSS patients. For BSS, one pediatric hematologist added as a

note that HLA antibodies were confirmed in one 12 year old child who had received 3 units of non-leucocyte depleted platelet transfusions in Iraq. HPA antibodies were found less frequent: four times in GT patients, and two times in BSS patients. One pediatric hematologist added as a note that HPA antibodies were found in a 14 year old child who had received 14 units of 5-donor concentrated platelets before the age of 13, indicating that HPA antibodies can occur at younger age. Negative test results were found as well: 5 times respondents mentioned that they had tested their GT-patients and found no HLA antibodies, and 5 times as well no HLA antibodies were found in BSS-patients. See Figure 1D. Determination of incidence is not possible due to low number and possible overlap in reported patients. The presence of iso-antibodies has not been surveyed, because no transfusion strategy can be performed to prevent or overcome iso-antibodies.

### 3.2.3 | Motivations for HLA and HPA antibody testing and preventive matched platelet transfusions

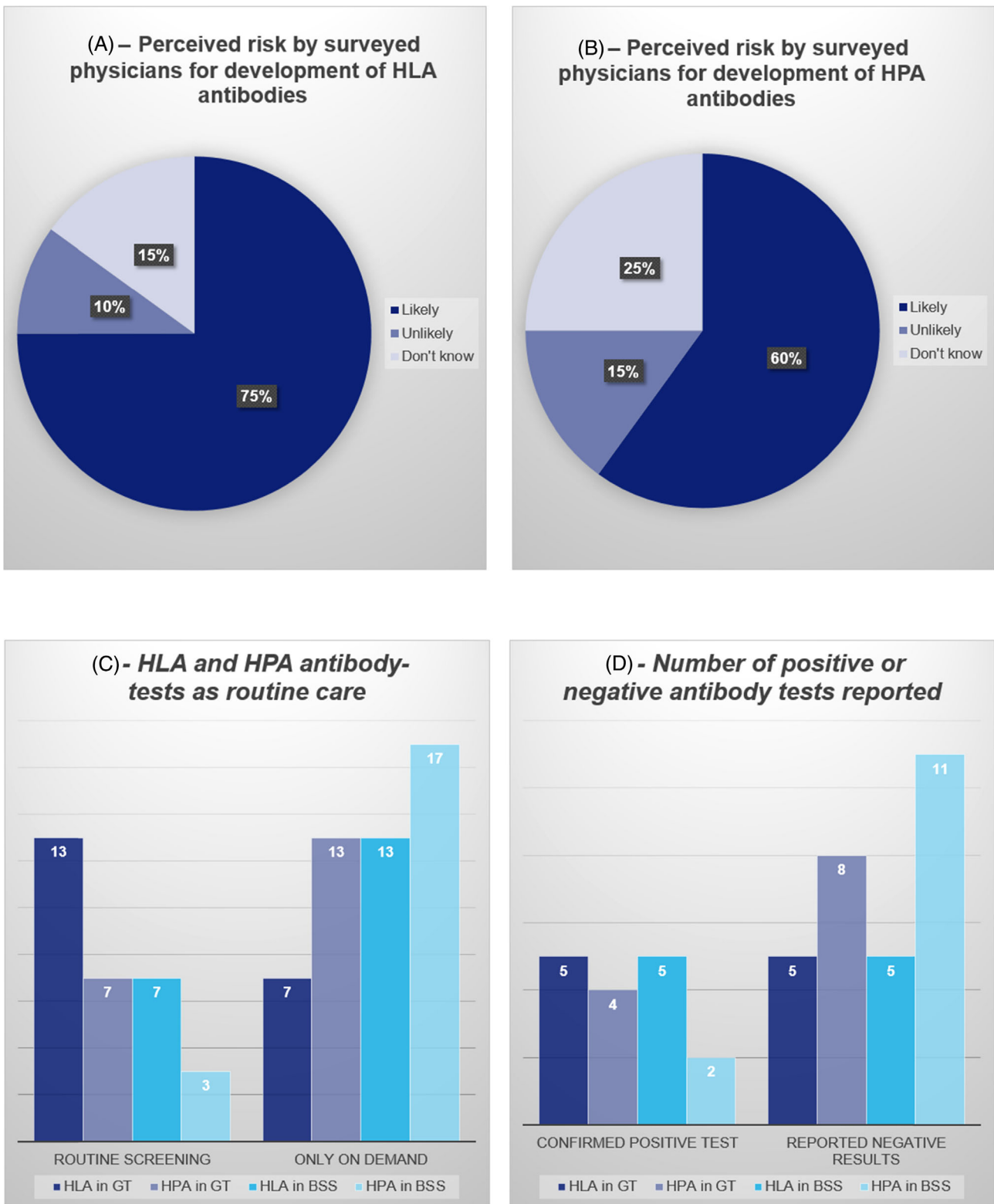
If performed, reasons for testing HLA and HPA antibodies varied from routine screening during follow-up ( $n = 11$ ), routine screening for scheduled platelet transfusion in ( $n = 7$ ) or clinical platelet refractoriness ( $n = 7$ ). Transfusion reactions or pregnancy were not reported as reason.

Motivations to transfuse or not to transfuse HLA and/or HPA-matched platelets in GT and BSS-patients were very heterozygous (Table 3). In general, the reasons for preventive HLA-matching resulted from the expectation that GT and BSS were more likely to develop HLA more than HPA antibodies ( $n = 16$ ). This was supported by the wish to preserve the use of ready-available random platelet transfusions, for example, in case an acute bleeding would occur ( $n = 10$ ). This motivation was explained in more detail by the argument that there are not many alternative treatments, other than recombinant FVII for GT-patients ( $n = 1$ ).

Availability of HLA and/or HPA-matched platelets takes approximately 48 hours between donation and transfusion in The Netherlands. In case of emergency, this time is not available.

The motivations to refrain from transfusing HLA or HPA-matched platelets were variable and less supportive for the preventive use of HPA-matching than for HLA-matching. The main argument against HLA and HPA-matching was the absence of clear incidence numbers in adults and children ( $n = 5$ ). Furthermore, to match for HLA was considered less urgent in the era of universal





**FIGURE 1** Risk assessment by surveyed physicians for HLA or HPA antibody development in Glanzmann thrombasthenia and Bernard Soulier syndrome. Total number of responders  $n = 20$ . BSS, Bernard-Soulier syndrome; GT, Glanzmann thrombasthenia; HLA, human leucocyte antigen; HPA, human platelet antigen. [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

leukocyte filtration ( $n = 2$ ). Two respondents remarked that matching for HPA did not prevent the development of iso-antibodies which they considered a more serious

risk than HLA antibody formation. Finally, not all physicians were aware of the possibility to transfuse combined HLA and HPA-matched platelets, but in The

**TABLE 3** Pros and cons with regard to HLA matched platelets in Glanzmann thrombasthenia and Bernard-Soulier syndrome as formulated by Dutch (pediatric) hematologists.

In favor of preventive HLA matching	Against preventive HLA matching
Prevention of HLA antibody formation because I consider this group a high-risk group for developing HLA antibodies due to frequent platelet transfusions ( <i>n</i> = 16)	There is no or only sparse data on the incidence of HLA antibodies, proving that alloimmunization for HLA is higher in Glanzmann or BSS patients ( <i>n</i> = 1)
Prevention of HLA antibody formation in elective settings leaves the possibility to use random concentrated platelet transfusion units in acute settings ( <i>n</i> = 10)	HLA matching is not suitable in acute settings ( <i>n</i> = 1)
Prevention of HLA antibody formation in order to preserve HLA matched platelet transfusions for treatment, because there are no/few other treatment options for IPD-patients ( <i>n</i> = 1)	My personal experience is that the risk for HLA alloimmunization is low, as I have still to observe a positive HLA antibody test in Glanzmann or BSS patient ( <i>n</i> = 1)
	I consider the risk to be low after universal leukodepletion ( <i>n</i> = 2)
	There is insufficient data on the incidence of HLA alloimmunization in children ( <i>n</i> = 1)
	Potentially children are less at risk for formation of HLA antibodies, therefore this is less relevant for young children ( <i>n</i> = 1)
	Matching for HLA or HPA does not solve the formation of complete GPIIB/IIIA-antibodies in Glanzmann patients ( <i>n</i> = 1)
	It is not recommended in the national transfusion guidelines ( <i>n</i> = 2)
	Creates a precedential space for other IPDs ( <i>n</i> = 1)
In favor of preventive HPA matching	Against preventive HPA matching
Same arguments as HLA ( <i>n</i> = 2)	I consider the chance of HPA antibody formation considerably lower than

(Continues)

**TABLE 3** (Continued)

In favor of preventive HPA matching	Against preventive HPA matching
	HLA antibody formation ( <i>n</i> = 6)
I have one adolescent patients with Glanzmann who did develop a HPA antibody at young age, but I do not know if this is an exception or the patient is high-risk due to her disease	I consider the risk for HPA antibody formation low, as I have never encountered a positive HPA antibody test in this group of patients ( <i>n</i> = 1)
	Incidence numbers of HPA antibody formation are not available in the literature ( <i>n</i> = 2)
	Personally i have a lack of knowledge on the topic ( <i>n</i> = 5)
	It is not recommended in the national transfusion guidelines ( <i>n</i> = 5)
	It is not possible to match on HLA and HPA at the same time; if indicated I prefer HLA matching ( <i>n</i> = 1)

Abbreviations: BSS, Bernard-Soulier syndrome; Glanzmann, Glanzmann thrombasthenia; GP, glycoprotein; HLA, human leucocyte antigen; HPA, human platelet antigen; IPD, inherited platelet defects; *n*, number.

Netherlands, donors can be selected based on both HLA and HPA antigens.

### 3.2.4 | Use of corrected count increment in GT and BSS

When HLA or HPA matched platelets are transfused, the Dutch transfusion guidelines advise to measure the corrected count increment (cci) as a measure for effect or refractoriness in thrombocytopenic patients. BSS-patients show mildly decreased till severely decreased platelet counts, but GT-patients often have a normal platelet count. We therefore investigated whether the GT and BSS-patients were tested for platelet refractoriness using cci: this was routinely done by *n* = 16 as “a standard procedure to evaluate effect (*n* = 13),” or as “a quality requirement after HLA or HPA matched platelets (*n* = 3).” The arguments not to use the cci routinely were: “only useful in patients with severe thrombocytopenia (*n* = 1),” and “only used when there are clinical signs of refractoriness (*n* = 3).”

### 3.2.5 | HLA matching in other IPDs than GT or BSS

In addition to the specific treatment strategies in GT and BSS-patients, we surveyed the use of preventive HLA and HPA-matching in other IPDs than GT or BSS. The other IPD forms were not specified by the respondents. Most physicians did not match for HLA in other IPDs (13/20, 65%), but seven respondents mentioned to give all IPD patients HLA and/or HPA matched platelets. Several reasons were mentioned: transfusion-dependent IPDs ( $n = 3$ ), other IPDs not classified ( $n = 3$ ), routine practice, because all IPDs follow the same care pathway as GT-patients ( $n = 1$ ).

## 4 | DISCUSSION

### 4.1 | Conclusions

In current guidelines, recommendations for HLA-matching are based on only three small cohort studies in GT patients reporting the occurrence of HLA antibody formation.<sup>10,21,37</sup> Unfortunately, these studies do not provide sufficient insight in the effectiveness of prophylactic transfusion strategies with HLA-matched products.<sup>38</sup> In absence of high-quality evidence on prophylaxis while facing the practical and therapeutic dilemmas of HLA antibodies when formed, some treatment guidelines<sup>8,9,19,38–41</sup> or national transfusion guidelines have implemented prophylactic matching.<sup>42,43</sup> But some national transfusion guidelines do not, as is the case in the Dutch International Federation of Medical Specialists (IFMS) guideline,<sup>44</sup> the Joint UK<sup>45</sup> or Canadian guidelines on transfusions.<sup>46</sup> Recently published cohort-studies confirm that 14%–30% of GT and BSS-patients will develop HLA antibodies, some already in childhood (reported incidence of 7%).<sup>2,10–12,20,22–24,30</sup> This life-long incidence is higher for male GT and BSS-patients than the population-risk, but approaches incidences in post-pregnant healthy women, as HLA antibody formation occurs in 7% of healthy non-transfused male donors (95% CI 6.3–7.8),<sup>47,48</sup> and in 24%–33% of healthy female donors after pregnancy.<sup>47,49</sup> The impact of the developed HLA antibodies, however, in patients with a platelet disorder is clearly much higher than for healthy persons in the general population, as the chance to receive a platelet transfusion as prophylaxis or during severe bleeding is much higher for GT and BT-patients. Not to notice the lack of alternative treatment options to prevent or treat serious bleeding. This makes preventive HLA-matching an desirable strategy in GT and BSS-patients. This impact is reflected in our survey results, showing that the

formation of platelet antibodies is estimated as a likely risk by a large proportion of respondents leading to preventive matching for HLA antigens in elective setting. This consensus is not unanimous for all Dutch hematologists, because of the absence of true incidence numbers in thorough, prospective trial results leaving the risk assessment incomplete. Although true incidence numbers can also not be deducted from our survey, we can conclude that despite universal leukocyte reduction in our country HLA antibodies still may occur in GT and BS-patients, leaving this issue relevant.

Preventive HPA matching is not advised in current guidelines and, as the survey shows, less frequently applied by Dutch (pediatric) hematologists. True incidence numbers cannot be presented from current case-series, nor deducted from our survey. It was mentioned only once in the survey to occur in an adolescent with GT. In general, it remains unclear if this is the result of a lower true incidence, difficulty in screening when collateral iso-antibodies are present or less intense surveillance. All we can conclude is that HPA antibody formation may occur and in risk groups such as pregnant GT and BSS-patients can lead to extra treatment due to the risk of platelet refractoriness and neonatal complications as major bleedings resembling FNAIT.<sup>11,12</sup> Because serological tests in GT-patients can be incongruent to HPA genotype, genotyping HPA-antigens should preferentially be performed.<sup>2,16,50</sup>

The occurrence of iso-antibodies and their pathogenicity has not been studied in our survey, but our literature review has demonstrated that it will be of importance to investigate the existence of iso-antibodies, because they may lead to platelet transfusion refractoriness and in pregnant GT or BSS-patients are associated with fetal and neonatal complications. Although not advised in a recent guideline on managing pregnancy in GT-patients,<sup>51</sup> we consider it of importance to screen at least all GT and BSS-patients with frequent platelet transfusions and female GT and BSS-patients. Besides maternal and perinatal care in pregnant women with GT and BSS, we conclude that neonatal care needs special attention, as is demonstrated by the case-series and cases described in Table 2.

### 4.2 | Recommendations

Combining the results of the current body of evidence with the survey, we propose the following recommendations (See Figure 2):

*Recommendations on screening in GT and BSS-patients*



**FIGURE 2** Flowchart of HLA or HPA platelet matching in patients with Glanzmann thrombasthenia and Bernard-Soulier syndrome. Abbreviations: BSS, Bernard-Soulier syndrome; CD, cluster of differentiation; cci, corrected count increment; FNAIT, feto-neonatal allo-immune thrombocytopenia; GP, glycoprotein; GT, Glanzmann thrombasthenia; HLA, human leucocyte antigen; HPA, human platelet antigen. [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

- Perform HLA class I antigen typing in all patients, children and adults. Preferably at diagnosis, but certainly when platelet refractoriness occurs or HLA class I antibodies have been detected;
- Screen at least once for the occurrence of HLA class I antibodies in patients who in the past have been

transfused with random or non-leukocyte reduced platelet transfusions. Also, screen patients with platelet refractoriness that do not yet receive HLA-matched platelets or have a HLA-donor match based on test-results that do not fully match the own HLA-haplotype. Consider extra screening in pregnancies. It

is not clear from what age children will benefit from this surveillance;

- Perform HPA genotyping at diagnosis for at least HPA-1, and if possible also HPA-2, 3 and 5.
- Screen for the occurrence of iso-antibodies and HPA antibodies when HLA antibodies have been formed. Also, screen in case of platelet refractoriness despite HLA-matching. Consider this extended screening in pregnancy to assess peripartum and neonatal risk strategy;
- Screen neonates on the occurrence of postnatal low platelets when maternal iso-antibodies or HPA antibodies are present.

#### *Recommendations on treatment in GT and BSS-patients*

- Avoid platelet transfusions in GT-patients for example, by using recombinant FVII when possible;
- Give preventive transfusion of HLA-matched platelets in elective setting in GT and BSS-patients;
- Transfuse HLA-matched platelets when HLA antibodies have been formed unless medical care cannot be delayed while waiting for matched platelets in an acute medical setting;
- Transfuse HPA-matched platelets when HPA antibodies have been formed or platelet refractoriness remains under HLA-matched platelets;
- Consider additionally HPA-matching of platelets in patients with a HPA profile predisposing to the formation of clinical relevant HPA antibodies such as anti-HPA-1a; Discuss the need for preventive matching in a team with expertise on HPA-immunogenicity
- Perinatal management should be applied to all pregnant women in a medical center with expertise in bleeding disorders and FNAIT. A postnatal transfusion strategy for the neonate should be made in advance when HPA antibodies are detected during pregnancy.

### 4.3 | Limitations and future perspectives

Our study has several limitations. It does not yield the possibility to deduct incidence numbers for antibody formation in the Dutch GT and BSS-patients. Overlap of reported patients remains possible because responding physicians may have been involved in treatment of the same patients in different institutes. Therefore we do not give an incidence number in this article.

Although we have based our recommendations on the current body of evidence, trial results from literature remain meager and this topic will need more research. With the absence of thorough incidence numbers of HLA

and HPA alloimmunization as well as iso-antibody formation at one side and the lack of identification for risk factors such as age of the patient, HPA genotype profile, non-platelet expression of HPA and the underlying molecular GT and BSS-genotypes, it remains impossible to detect the patients that will benefit the most from preventive matching. Obtaining more detailed information on this patient characteristics and disease characteristics in relation to platelet refractoriness and FNAIT should be the main targets of future research to define the risk groups that will benefit the most from preventive matching programs. In line with this, high-quality trials providing data on preventive matching should follow. The lack of these data makes a meta-analysis impossible to implement. While awaiting these research results, we have chosen a conservative strategy in order to prevent as much alloimmunization against HLA and HPA as possible, for the possibility to match on HLA and if necessary also for HPA-antigens is available in The Netherlands. The recommendations are based on the current Dutch blood bank facilities and may not be implementable in other settings.

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EH developed the survey, conducted the literature search, and wrote the article. MS and JJZ revised the survey. EH and NH analyzed the survey. EH NH LP and JJZ developed the recommendations and the flowchart. NH, MS, MH, MC, LP and JJZ revised the article.

#### CONFLICT OF INTEREST STATEMENT

Jaap-Jan Zwaginga is occasionally professionally employed by Sanquin for educational purposes.

#### ORCID

Elise J. Huisman  <https://orcid.org/0000-0002-0700-2194>

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