

# Recent advances in understanding the clinical relevance of antiplatelet alloantibodies

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## KEY WORDS

human platelet antigens, fetal and neonatal alloimmune thrombocytopenia, platelet transfusion refractoriness, posttransfusion purpura

## ABSTRACT

Alloimmunization to human platelet antigens (HPAs) may occur either during pregnancy, when a HPA-negative mother gives birth to a newborn who inherits HPAs from the father, or following blood transfusion or stem cell transplantation. Antiplatelet alloantibodies do not cause thrombocytopenia in a patient, but their detection must always be recorded in medical records because they may induce fetal and neonatal alloimmune thrombocytopenia in present and all subsequent pregnancies, platelet refractoriness, posttransfusion purpura, or prolonged thrombocytopenia with engraftment failure after stem cell transplantation. Passive transfer of platelet alloantibodies through transfused blood components may trigger thrombocytopenia and severe posttransfusion reactions in the recipient. In a Caucasian population, such clinical outcome of platelet alloimmunization is mostly due to anti-HPA-1a antibodies, less frequently to anti-HPA-5b, anti-HPA-1b, and others. Information on anti-HPA alloantibodies is crucial for the prevention and treatment of their consequences.

**Introduction** In this review, we discuss the current knowledge on alloimmunization with human platelet antigens (HPAs), including its pathophysiological mechanisms, clinical manifestations, and natural course, as well as diagnostic evaluation and treatment. We also describe the future directions to prevent their consequences. Alloimm  $\alpha$  unization by platelet antigens occurs mainly during or after pregnancy but also following blood transfusion and stem cell transplantation. It is a threat not only to pregnant women but also to recipients of transfused blood components and transplant stem cells, because it may induce platelet refractoriness, posttransfusion purpura (PTP), and prolonged thrombocytopenia with engraftment failure after stem cell transplantation. Passive transfer of platelet alloantibodies through transfused blood components may trigger thrombocytopenia and severe posttransfusion reactions in the recipient.

**Pathophysiology of alloimmunization by platelet antigens** HPAs are expressed on the platelet

membrane as polymorphic forms of glycoproteins. The single nucleotide polymorphisms in the encoding genes are responsible for the differences in the protein structure of antithetic antigens.<sup>1,2</sup> To date, 35 HPAs expressed on 6 different platelet glycoproteins (GPIIb, GPIIIa, GPIb $\alpha$ , GPIb $\beta$ , GPIa, and CD109) have been described (TABLE 1). Most HPAs are expressed on GPIIIa as part of the GPIIb/IIIa (integrin  $\alpha$ 2b $\beta$ 3) complex, which is the most important receptor of human platelets for fibrinogen, vitronectin, fibronectin, and von Willebrand factor. GPIIIa is also expressed on endothelial cells as part of  $\alpha$ V $\beta$ 3 integrin, which is the receptor for vitronectin and other proteins. HPAs can trigger alloantibody production following pregnancy or platelet transfusion. The most frequently detected alloantibodies in a Caucasian population are directed to HPA-1a antigen. The risk group for the development of these alloantibodies includes HPA-1a-negative individuals (2% of a Caucasian population).

Several authors described the mechanisms of alloantibody production.<sup>3,4</sup> Our review is focused

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**TABLE 1** Human platelet antigens<sup>1,2</sup>

Glycoprotein	Antigen	Gene (chromosome)	Nucleotide change	Mature protein	Allele frequencies in a Caucasian population
GPIIIa (integrin subunit $\beta$ 3 CD61)	1a/1b	<i>ITGB3</i> (chr. 17q21.32)	176T>C	L33P	0.85 / 0.15
	4a/4b		506G>A	R143Q	0.9995 / 0.0005
	6bw		1544G>A	R489Q	0.001
	7bw		1297C>G	P407A	0.0002
	8bw		1984C>T	R636C	0.0002
	10bw		263G>A	R62Q	0.0001
	11bw		1976G>A	R633H	0.0001
	14bw		1909–11delAAG	K611del	<0.0001
	16bw		497C>T	T140I	<0.0001
	17bw		622C>T	T195M	0.0001
	19bw		487A>C	K137Q	<0.0001
	21bw		1960G>A	E628K	0.0009
	23bw		1942C>T	R622W	<0.0001
	26bw		1818G>T	K580N	<0.0001
29bw	98C>T	T7M	<0.0001		
GPII $\alpha$ (CD42b)	2a/2b	<i>GP1BA</i> (chr.17p13.2)	482C>T	T145M	0.90/0.10
GPIIb (integrin subunit $\alpha$ 2b, CD41)	3a/3b	<i>ITGA2B</i> (chr.17q21.32)	2621T>G	I843S	0.6/0.4
	9bw		2602G>A	V837M	0.002
	20bw		1949C>T	T619M	0.0003
	22bw		584A>C	K164T	<0.0001
	24bw		1508G>A	S472N	<0.0001
	27bw		2614C>A	L841M	0.004
	28bw		2311G>T	V740L	<0.0001
GPIa (integrin subunit $\alpha$ 2, CD49b)	5a/5b	<i>ITGA2</i> (chr.5q11.2)	1600G>A	E505K	0.92/0.08
	13bw		2483C>T	T799M	<0.0001
	18bw		2235G>T	Q745H	<0.0001
	25bw		3347C>T	T1087M	<0.0001
GPIb $\beta$ (CD42c)	12bw	<i>GP1BB</i> (chr.22q11.21)	119G>A	G15E	<0.0001
CD109	15a/15b	<i>CD109</i> (chr.6q13)	2108C>A	S682Y	0.50/0.50

on the crucial steps or stages of this process relating to the production of alloantibodies directed to the antigens present on the blood cells.

The first step of initiation of alloantibody production is the “foreign” antigen presentation. Blood cell antigens on platelets as well as those on red blood cells (RBCs) are presented to the recipient or maternal CD4<sup>+</sup> T cells through T-cell receptors in the context of human leukocyte antigen (HLA) class II molecules present on antigen-presenting cells. As a result, the T cells become activated. Several costimulatory signals are involved: type 2 helper T cells, a subset of CD4<sup>+</sup> T-helper cells, secrete interleukin (IL)-4, IL-5, IL-6, and IL-10, which finally activates B cells and initiates the primary antibody response. Single B cells become memory cells and initiate secondary alloantibody response at subsequent exposure to HPA.

There are 2 ways in which the antigens are presented: by donor antigen-presenting cells (ie, monocytes, macrophages, dendritic cells, B cells in platelet concentrate [PC]), or by recipient antigen-presenting cells, after the transfused platelets are digested and recognized as foreign.<sup>4</sup> Both mechanisms are involved in alloimmunization related to the transfusion of nonleukoreduced

PCs. The second mechanism is involved in alloimmunization both from transfused leukoreduced platelets as well as during pregnancy. Additional mechanisms of antigen presentation, for example through exosomes from apoptotic allogeneic cells, have also been reported.<sup>4,5</sup>

The primary immune response occurs usually some days or weeks (2–4 weeks) after exposure. The persistence of alloantibodies in the patient’s blood varies. Usually the alloantibodies induced by pregnancy persist for decades or even a lifetime, whereas the levels of transfusion-induced alloantibodies more often decrease below the detection limit within 6 months.<sup>4,6</sup> However, even though they disappear shortly after the first exposure, the next contact with the antigen (at transfusion, transplantation, or pregnancy) results in a rapid production of alloantibodies since memory B cells need no costimulatory signals to become activated.

This review focuses on the significance of antiplatelet alloantibodies for an adult patient, especially in the context of transfusion or transplantation. We present the pathogenesis of the complications involved. It is worth noting, however, that primary alloimmunization occurs most

**TABLE 2** Clinical consequences of the presence of anti-HPA alloantibodies

	Alloantigens involved	Treatment/Prevention
Fetal and neonatal alloimmune thrombocytopenia	HPA-1a (75%–90%), HPA-5b (5%–15%), HPA-15a or -15b (2%–4%), HPA-3a or -3b (2%), HPA-5a (1%), others <0.1%	During pregnancy: intravenous immunoglobulin, steroids In the newborn: transfusion of HPA negative PCs from the mother or donor, intravenous immunoglobulin
Platelet transfusion refractoriness <sup>a</sup>	HPA-1b, -5b, -1a, -15a, -15b, -3a, -2b, -2a	Transfusion of HPA-compatible PCs, intravenous immunoglobulin, immunosuppressive treatment, massive prophylactic PCs, plasma exchange, transfusion of frozen autologous PCs
Posttransfusion purpura	HPA-1a (>90%), single cases HPA-3a, -5a, -2b, -5b, -15a	Transfusion of HPA-compatible blood components
Transplantation-mediated alloimmune thrombocytopenia	HPA-1a, HPA-5b	Transfusion of HPA-compatible PCs, plasma exchange before stem cell transplantation
Passive alloimmune thrombocytopenia	HPA-1a, HPA-5b	Individuals with anti-HPA alloantibodies should be deferred from regular blood donation; however, they can serve as donors of PCs for alloimmunized patients after removing of plasma with antibodies

**a** Involvement of anti-HLA, the main source of refractoriness and ABO antigen incompatibility, is not included.

Abbreviations: HPA, human platelet antigen; PC, platelet concentrate

often during pregnancy and anti-HPA alloantibodies are detected after delivery of a newborn with fetal and neonatal alloimmune thrombocytopenia (FNAIT) or during screening of pregnant women for risk of FNAIT. Such screening programs were performed in several countries, including Poland.<sup>7-12</sup> Information on the pathogenesis, clinical symptoms, and incidence rate of FNAIT is valuable not only for gynecologists but also for family doctors, specialists in internal medicine, and hematologists because the women usually turn to them for support once alloantibodies are detected. It happens that the diagnosis of FNAIT after delivery of a thrombocytopenic newborn is disregarded by gynecologists since from their point of view the information is relevant only for the next pregnancy.

FNAIT is usually recognized when the neonate presents minor (petechiae or purpura) or severe (intracranial hemorrhage) bleeding. The diagnosis may be incidental when the newborn presents thrombocytopenia from no other causes. FNAIT can also be detected prenatally if the fetus is diagnosed with intracranial hemorrhage or ventriculomegaly.<sup>13-18</sup> The diagnosis of FNAIT consists in detection of an anti-HPA alloantibody in maternal blood and identification of its specificity. The diagnosis is confirmed by HPA genotyping of the parents and the newborn.<sup>19-21</sup> Most often the diagnosis refers to HPA-1a-negative women, who produce alloantibodies to the fetal HPA-1a alloantigen inherited from the father. Anti-HPA-1a alloantibodies are also detected in screening programs for pregnant women which are performed with the aim of preventing this rare but severe disorder. Such programs involve HPA-1a antigen tests for pregnant women. All HPA-1a-negative (*HPA-1bb*) women (~2% of the population) are

at risk of anti-HPA-1a production. An “HPA antibody card” is issued for every HPA-1a-negative woman and for every pregnant woman affected by FNAIT. The card informs that the woman should be examined for anti-HPA alloantibodies during the next pregnancy or whenever she requires transfusion or transplantation. It should be stressed that alloantibodies do not cause thrombocytopenia in the mother and there is no need to monitor or check her platelet count. However, if a thrombocytopenic woman (eg, idiopathic thrombocytopenia) is HPA-1a negative, she is also at risk of developing alloantibodies with all the ensuing consequences.

Our recent study performed during the screening program “Prevention of fetal neonatal alloimmune thrombocytopenia in Polish newborns” (PREVNAIT) demonstrated that alloantibodies against HPA-1a antigen can be detected in about 1 in 500 pregnant women.<sup>12</sup> Schnaidt and Wernet<sup>6</sup> found that up to 4.2% of previously pregnant female blood donors had circulating anti-HPA alloantibodies (most often anti-HPA-5b, anti-HPA-1a, and anti-HPA-5a). All these women are at risk of posttransfusion and posttransplantation adverse reactions. Alloimmunization by platelet antigens should therefore be of interest not only to gynecologists and obstetricians but also to general practitioners, hematologists, and specialists in transfusion medicine.

**Pathogenesis of posttransfusion and posttransplantation reactions caused by anti-HPA** Anti-HPA-1a alloantibodies may be responsible for immunological platelet transfusion refractoriness and for rare but severe posttransfusion reactions, for example PTP.<sup>4,22-32</sup> They may also induce prolonged thrombocytopenia and stem cell engraftment failure.<sup>33-35</sup>

Immune platelet refractoriness is mostly observed in patients with anti-HLA class I antibodies.<sup>4,36</sup> However, in about 2% to 10% of refractory patients, anti-HPA alloantibodies which cause platelet destruction are detected. Anti-HPA alloantibodies are also present in around 15% to 20% of patients with anti-HLA class I antibodies. Most of them develop during pregnancy and some are produced following transfusions of nonleukoreduced blood components.

As described above, previously unsensitized patients develop primary immune response and produce antiplatelet alloantibodies approximately 3 to 4 weeks after transfusion, whereas patients who were previously immunized (as a result of transfusion, pregnancy, or organ transplant) develop antiplatelet alloantibodies as early as 4 days following the procedure. Platelet-specific alloantibodies responsible for refractoriness are usually directed to HPA-1b and HPA-5b antigens; other specificities (-1a, -15a, -15b, -3a, -2b, -2a) of anti-HPAs are detected occasionally<sup>4</sup> (TABLE 2).

Alloantibodies coat the transfused platelets, which are then phagocytized by macrophages in the recipient's liver, spleen, and other tissues. Refractoriness is mostly observed in female patients (approximately 75% of cases) and in recipients of multiple transfusions (>20).<sup>37</sup>

The desired platelet increment in patients with anti-HPA alloantibodies is achieved by administration of PCs without the platelet antigen that caused alloimmunization of that particular patient. In most cases, it means that the patient requires PCs from HPA-1b, -5b, -1a, or another antigen-negative donors, and such components are available in most blood transfusion centers in developed countries.<sup>4,28</sup>

Other approaches—though not fully successful—are directed towards blocking platelet destruction by intravenous immunoglobulin infusions, which results in immunosuppression (reduction of alloantibody production), absorption of alloantibodies by massive prophylactic PCs, or their dilution or removal by plasma exchange.<sup>38,39</sup> Transfusion of autologous cryopreserved platelets is still another option for alloimmunized refractory patients, if HLA and HPA compatible donors are unavailable.<sup>40-43</sup>

PTP is a rare reaction or complication characterized by acute thrombocytopenia in a previously unthrombocytopenic patient with the 10% to 20% risk of mortality.<sup>22-26,30</sup> It presents within 1 week after transfusion and most often after transfusion of RBC concentrates contaminated by platelets. In 90% of cases, PTP is caused by anti-HPA-1a and it concerns women.<sup>32</sup> The patient's alloantibodies bind to the “foreign” antigen on transfused platelets and destroy them. The detrimental effect of alloantibodies against foreign antigen expands and involves destruction or loss of the patient's antigen-negative platelets. Several explanations have been suggested. Roubinian and Leavitt<sup>23</sup> summarized them as follows: 1) immune complexes involving the alloantibody and

the foreign antigen bind platelets via the platelet Fc receptor and induce their clearance; 2) soluble platelet antigens from the transfused component stick to the patient's platelets rendering them susceptible to immune-mediated destruction once the alloantibody binds to the passively adhered antigen; and 3) autoreactivity of the alloantibody presents when the patient is reexposed to the foreign platelet-specific antigen.

PTP is diagnosed by identifying an anti-HPA alloantibody (anti-HPA-1a alloantibody is the most common) in the plasma of the patient who has no corresponding antigen. It is important to perform the differential diagnosis between PTP and heparin-induced thrombocytopenia (HIT) since they have some clinical similarities. In PTP, platelet count falls usually below  $15 \times 10^9/l$  approximately 7 days after transfusion, whereas in HIT platelet count is no lower than  $20 \times 10^9/l$  and observed from 5 to 10 days after surgery. The final diagnosis of PTP is based on the identification of anti-HPA alloantibodies, and HIT is confirmed by a heparin or platelet factor 4 enzyme-linked immunosorbent assay and serotonin-release assay. The treatment of HIT is to prevent thrombotic complications by thrombin inhibition. This, however, can induce severe hemorrhage in a patient with PTP. Therefore, misdiagnosis of this syndrome might lead to wrong treatment and a fatal outcome.<sup>31,32</sup> Since PTP is mainly observed in women immunized during pregnancy, the information about FNAIT symptoms in their newborns might be useful.

The treatment of choice for PTP is intravenous immunoglobulin at a dose of 0.5 to 1 g/kg administered for 2 days.<sup>24</sup> For PTP risk to be avoided, patients with antiplatelet alloantibodies should be transfused with HPA compatible RBCs and platelets. In emergency, when HPA antigen-negative RBC concentrates are unavailable, standard leukodepleted ABO- and RhD-compatible RBC concentrates (Kell negative) should be provided. The risk of PTP is then reduced as residual platelets and leukocytes are effectively removed by leukodepletion. It is recommended, however, to transfuse washed RBC concentrates, since HPA-1a antigens may also appear in plasma.

According to the literature, prolonged thrombocytopenia and failure of stem cell engraftment may occur in patients with anti-HPA alloantibodies.<sup>33-36,44</sup> Lucas et al<sup>35</sup> observed that anti-HPA-1a alloantibodies persist for as long as 10 months after bone marrow transplant and are responsible for prolonged thrombocytopenia and platelet refractoriness. For satisfactory platelet increment, patients had to be transfused with HPA-1a negative PCs.<sup>35</sup>

**An individual positive for anti-HPA alloantibodies as a blood donor** Although rarely, passive transfer of platelet alloantibodies through transfused blood components may cause thrombocytopenia,<sup>45,46</sup> which needs to be differentiated from other causes such as PTP-, heparin-, or drug-induced thrombocytopenia.<sup>32</sup>

In general, HPA-1a-negative women with anti-HPA-1a alloantibodies should be deferred from blood donation but they can serve as donors of platelets for immunized patients, including a newborn with FNAIT, provided the plasma with antibodies is removed. Such needs often occur if HPA-1a-negative donors of PCs are not available. In the future, women with anti-HPA-1a antibodies may become donors of plasma dedicated for preparation of vaccines against FNAIT.<sup>47</sup>

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