Treatment of Inherited Platelet Disorders: Current Status and Future Options

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Abstract

Inherited platelet disorders (IPDs) comprise a heterogeneous group of entities that manifest with variable bleeding tendencies. For successful treatment, the underlying platelet disorder, bleeding severity and location, age, and sex must be considered in the broader clinical context. Previous information from the AWMF S2K guideline #086–004 (www.awmf.org) is evaluated for validity and supplemented by information of new available and future treatment options and clinical scenarios that need specific measures. Special attention is given to the treatment of menorrhagia and risk management during pregnancy in women with IPDs. Established treatment options of IPDs include local hemostatic treatment, tranexamic acid, desmopressin, platelet concentrates, and recombinant activated factor VII. Hematopoietic stem cell therapy is a curative approach for selected patients. We also provide an outlook on promising new therapies. These include autologous hematopoietic stem cell gene therapy, artificial platelets and nanoparticles, and various other procoagulant treatments that are currently tested in clinical trials in the context of hemophilia.

Keywords
► blood platelet disorder
► therapy
► inherited platelet disorder

Schröffelwörter
► Angeborene Thrombozytenerkrankung
► Therapie

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**Introduction**

Inherited platelet disorders (IPDs) comprise a heterogeneous group of more than 60 rare bleeding disorders with abnormal platelet function and/or low platelet count. The true prevalence is unknown, but estimation is at least 2.7 cases per 100,000.1,2

IPDs are characterized by highly variable clinical presentation and prognosis. Clinical complications range from almost negligible to life-threatening. Some manifest as isolated platelet disorders, while others are associated with a variety of other abnormalities (syndromic), and still others predispose to the development of hematological malignancy and bone marrow aplasia.3–5

IPDs may remain unnoticed for many years with up to 60% of cases with proven platelet defects that cannot be assigned to any pre-described IPD.6 Moreover, genotype–phenotype correlation of different types of mutations is mostly poorly defined.7

Typical clinical symptoms of IPDs are mucocutaneous bleeding including epistaxis, oral cavity bleeding, purpura, hematomas, and heavy menstrual bleeding (HMB). In case of trauma and surgical intervention, clinically relevant bleeding and blood loss may occur unexpected and independent of platelet count.1–4

Although many efforts have been made on diagnosing and characterizing IPDs and “new disorders” are identified on a regular and frequent basis, therapeutic options for the prevention and treatment of bleeding due to IPDs remain limited.

Since 2014, the THROMKIDplus working group of the “Gesellschaft für Thrombose- und Hämostaseoforschung e. V.” (GTH) aims to develop and distribute useful guidelines for the diagnosis as well as treatment of platelet disorders.8 This article updates previous information and presents current knowledge on treatment options, which are supplemented by clinical scenarios that need specific measures. For treatment details including dosing, readers are referred to the AWMF guideline on treatment of platelet disorders (AWMF S2K guideline #086–004; www.awmf.org).9

**Methods**

A literature search strategy was developed by consulting the PubMed platform of the National Center for Biotechnology Information (NCBI). The literature search included peer-reviewed articles, published in English and German language, updated from January 2018 to January 2023. We used the MeSH term “blood platelet disorders” and the search terms “tranexamic acid” or “platelet concentrate” or “rFVIIa” or “eptacog alfa” or “eptacog beta” or “desmopresin” or “splenectomy” or “fitusiran” or “conczumab” or “marstacimab” or “befovacimab” or “haematopoietic stem cell transplantation” or “gene therapy”. A total of 521 references were screened for their relevance and quality. Of these, 100 articles including review articles, guidelines, meta-analyses, and additional literature from the respective reference sections (Supplementary Fig. S1, available in the online version only). For the outlook section (future therapies), we also searched clinicaltrials.gov using the term “blood platelet disorder.” Additionally, results from personal communication within the THROMKIDplus working group during the pediatric GTH (pedGTH) meeting held in September 2022 in Igls (Austria) were included.

**Current Treatment Options**

**General Considerations**

Today any possible effort to achieve the classification of the underlying platelet defect, including molecular genetic testing, is imperative to guide clinical management. For adequate prevention and treatment of bleeding, a distinction between IPDs with mere platelet function defect and those with (additional) low platelet count is important (Table 1).

Many commonly used drugs affect platelet function and should be avoided including frequently prescribed nonsteroidal anti-inflammatory drugs, particularly acetylsalicylic acid and selective serotonin reuptake inhibitors.1–3,10 Selective COX-2 inhibitors without effect on platelet function may be used for pain control, but are approved for use only from the age of 16 years.11

Testing for iron-deficiency anemia in patients with frequent bleedings should be performed on a regular basis.12 Adequate treatment is provided by oral and/or intravenous iron supplementation.12

A good dental hygiene is essential to prevent gum bleeding and tooth loss.2,13 Recommended vaccinations should not be withheld but administered preferentially subcutaneously whenever approved.14 As with other hemorrhagic disorders, children and families should be trained to avoid bleeding and carry an identification card with them bearing information about their medical condition.1,15

**Local Hemostatic Treatment**

Topical hemostatic measures are considered first-line treatment, irrespective of the underlying pathology. Mechanical hemostats include foams, sponges or gauze soaked with porcine gelatins, bovine collagen or oxidized regenerated cellulose, and polysaccharide spheres. Further biologically active hemostats with human, bovine, or recombinant thrombin are available. Fibrin sealants, tissue adhesives, and topical tranexamic acid (TXA) are successfully used in
Chitosan-covered gauze is an efficient local treatment option in postpartum hemorrhage and proved to support wound healing. Tranexamic Acid (TXA) inhibits activation from plasminogen to plasmin and thus inhibits fibrinolysis and supports clot formation. TXA administered parenterally, locally, or as mouth wash is generally recommended in IPDs. Combination with other hemostatic treatment options including recombinant activated factor VII (rFVIIa), and desmopressin (DDAVP), and long-term therapy is recommended and reasonable in selected cases. Occasionally, headache or gastrointestinal side effects such as nausea, vomiting, and diarrhea may occur. TXA is contraindicated in patients with a history of or in acute arterial or venous thrombosis, in severe renal failure.

### Table 1: Overview of IPDs mentioned in this article

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene</th>
<th>Underlying defect (size of thrombocytes: small [S], normal [N], large [L]), main features</th>
<th>Bleeding tendency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nonsynodmic IPDs with normal platelet count and abnormal platelet function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glanzmann thrombasthenia</td>
<td>ITGA2B, ITGB3</td>
<td>Platelet receptor defect (N), bleeding tendency</td>
<td>Variable, but likely severe</td>
</tr>
<tr>
<td><strong>Nonsynodmic IPDs with low platelet count</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bernard-Soulier syndrome</td>
<td>GP1BA, GP1BB, GP9</td>
<td>Platelet receptor defect (L), bleeding tendency</td>
<td>Variable, but likely severe</td>
</tr>
<tr>
<td>Platelet-type von Willebrand disease</td>
<td>GP1BA</td>
<td>Platelet receptor defect (L), platelet count may decrease under stress conditions</td>
<td>Absent to mild</td>
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<tr>
<td><strong>Syndromic IPDs with normal platelet count</strong></td>
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<td></td>
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<tr>
<td>Chediak-Higashi syndrome</td>
<td>LYST</td>
<td>8-Granule secretion defect (N), immunodeficiency with predisposition to recurrent infections, risk of accelerated phase of hemophagocytic lymphohistiocytosis, oculocutaneous albinism</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td><strong>Syndromic IPDs with low platelet count</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WAS</td>
<td>WAS, WIPF1</td>
<td>Cytoskeleton defect (S), immunodeficiency, eczema, lymphoproliferative and autoimmune disorders</td>
<td>Variable</td>
</tr>
<tr>
<td>X-linked thrombocytopenia</td>
<td>WAS</td>
<td>Cytoskeleton defect (S), mild form of WAS</td>
<td>Absent to moderate</td>
</tr>
<tr>
<td>CAMT</td>
<td>MPL</td>
<td>Defect of megakaryopoiesis (N), progression to aplastic anemia</td>
<td>Variable</td>
</tr>
<tr>
<td>MECOM-related thrombocytopenia</td>
<td>MECOM</td>
<td>Defect of megakaryopoiesis (N), radioulnar synostosis, potential renal or cardiac anomalies, risk of sensorineural hearing loss</td>
<td>Severe</td>
</tr>
<tr>
<td>Thrombocytopenia with absent radii</td>
<td>RBM8A</td>
<td>Defect of megakaryopoiesis (N), bilateral absence of radius w/o other skeletal abnormalities, potential kidney, cardiac or central nervous system anomalies</td>
<td>Severe</td>
</tr>
<tr>
<td>THPO-related thrombocytopenia</td>
<td>THPO</td>
<td>Defect of megakaryopoiesis (N), biallelic mutations resemble CAMT</td>
<td>Severe</td>
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<tr>
<td><strong>IPDs with low platelet count and predisposition to malignancy</strong></td>
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<tr>
<td>FPD with propensity to AML</td>
<td>RUNX1</td>
<td>Defect of megakaryopoiesis (N), high risk (ca. 40%) of developing acute myeloid leukemia or myelodysplastic syndrome</td>
<td>Absent to moderate</td>
</tr>
<tr>
<td>Thrombocytopenia type 2</td>
<td>ANKRD26</td>
<td>Defect of megakaryopoiesis (N), risk (ca. 10%) of developing myeloid neoplasms</td>
<td>Absent to mild</td>
</tr>
<tr>
<td>Thrombocytopenia type 5</td>
<td>ETV6</td>
<td>Defect of megakaryopoiesis (N), predisposition (ca. 30%) to acquired lymphoid, myeloid, and myeloproliferative syndromes</td>
<td>Absent to mild</td>
</tr>
</tbody>
</table>

Abbreviations: AML, acute myeloid leukemia; CAMT, congenital amegakaryocytic thrombocytopenia; FPD, familial platelet disorder; IPDs, inherited platelet disorders; WAS, Wiskott-Aldrich syndrome.
insufficiency, and should not be given to patients with bleeding in the urogenital region or the pleural space, because of increased risk of insoluble hematomas.22 TXA can cause postoperative seizures, especially in cardiac surgery patients, and is therefore contraindicated in patients with a history of seizures.23

**Desmopressin**

DDAVP is a synthetic analog of the antidiuretic hormone L-arginine vasopressin, and has an antidiuretic but not a vasoconstrictive effect. DDAVP develops its hemostatic effect by increasing levels of von Willebrand factor (VWF), Factor VIII, and platelet adhesiveness, although its exact mechanisms remain unknown.3,15,24–26 In patients with IPDs, DDAVP induces the formation of procoagulant platelets.27 Repeated administration leads to prompt decrease in response of the hemostatic effect (tachyphylaxis).3,15,24–26

Since the 1980s, DDAVP has been successfully used for the treatment of mild to moderate hemophilia A and von Willebrand disease type 1. Subsequently, the spectrum of clinical applications has been expanded to platelet disorders, especially storage pool diseases, where efficacy was demonstrated in some, but not all, cases.3 DDAVP is usually considered ineffective in patients with Glanzmann thrombasthenia (GT) and Bernard-Soulier syndrome (BSS).28,29 There is only poor evidence to support testing DDAVP responsiveness in patients with IPDs.16,29

Due to its effect on fluid retention and consecutive hyponatremic seizures, monitoring of vital functions and sodium plasma levels is indicated and fluid intake should be restricted. According to the AWMF guidelines on the treatment of IPDs (AWMF S2K guideline #086–004; www.awmf.org), DDAVP is not recommended in children younger than 3 years or in children with seizures in their history. The same applies for pregnant women and many other patients with cardiac and vascular conditions.3,15,16,25,29

**Transfusion of Platelet Concentrates**

Platelet concentrates (PCs) are commonly administered to prevent and treat bleeding in IPDs with severe bleeding phenotype. At least in acquired thrombocytopenia, recent data have highlighted uncertainties in the risk–benefit ratio (►Fig. 1).30 In neonates, it has been shown that liberal transfusion of PCs increases the risk of hemorrhage and mortality.31,32 Using PCs bears an inherent risk of alloimmunization, transfusion-transmitted infections, and allergic reactions.1,3,15,16,25,33 PCs can be obtained either from apheresis (single donor) or from pools of buffy-coats (four to six donors).33 In IPDs, PCs from a single-donor, leukocyte depleted, and, if available, human leukocyte antigen (HLA)-matched are preferred due to a lower risk of immunization.1,3 After administration of PCs, the platelet count should always be reevaluated.

In GT and BSS patients, platelets are deficient in specific glycoproteins (GPs), so patients are at risk to develop antibodies against GPs (in GT: anti-GP Ib/IIa, in BSS: anti-GP1b/IX) and become refractory to PCs.3,34 In GT patients, a past history of immunization, GT type 1, and female sex might increase the risk of immunization against GP Ib/IIa and favor therapy with rFVIIa over PCs.35 In the presence of platelet antibodies, an increased dose of PCs in combination with rFVIIa or VWF may control bleeding.25 In case of high

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**Fig. 1** Benefits and risks of platelet transfusions depending on platelet product and recipient. BSS, Bernard-Soulier syndrome; GT, Glanzmann thrombasthenia; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation; NAIT, neonatal alloimmune thrombocytopenia.
urgency, immunoabsorption is another method to reduce antiplatelet antibodies. Flow cytometric analysis of GPIIb (IIb integrin)/GPIIIa (CD41/CD61) and GPIbα (CD42b), respectively, is recommended for monitoring the presence of transfused platelets. Three months after receiving a PC, testing for platelet-specific antibodies is highly recommended.

### Recombinant Activated FVII (Eptacog Alfa and Eptacog Beta)

Eptacog alfa develops its procoagulant activity through a tissue factor dependent and independent thrombin burst. It is approved for GT with or without antibodies to GP IIb/IIIa (integrin) and with past or present refractoriness to platelet transfusions. In 2018, the European Medicines Agency (EMA) extended the approval for those patients when platelets are not readily available. Its off-label use has shown benefits in patients with BSS and storage pool diseases, platelet type von Willebrand disease, and thrombocytopenia with absent radii (TAR) syndrome.

Eptacog beta has been approved for the treatment of hemophilia A and B with inhibitors in July 2022 in Europe. So far, no reports on its use in IPDs have been published.

In case of acute bleeding in patients with IPDs, of the aforementioned treatment options, local measures and TXA are the first choice. If bleeding cannot be adequately controlled, PCs and rFVIIa are options for further therapy escalation. PCs should be administered restrictively in patients with GT and BSS due to the risk of platelet antibody formation. DDAVP should not be administered in case of severe bleeding and should be administered only after a trial.

### Thrombopoietin Receptor Agonists

The two thrombopoietin receptor agonists, eltrombopag and romiplostim, are currently approved for immune thrombocytopenia (ITP), thrombocytopenia in adult patients with hepatitis C infection, and severe aplastic anemia in adults. Both drugs have shown effects in IPDs. For further details, readers are referred to the article Thrombopoietin receptor agonists for treatment of thrombocytopenias in pediatrics in the next issue of the journal.

### Splenectomy

Splenectomy is generally not recommended. In Wiskott-Aldrich syndrome (WAS) and X-linked thrombocytopenia, microplatelets and thrombocytopenia are caused by sequestration in the spleen. After splenectomy, platelet size and count normalize, leading to a significant reduction of bleeding episodes. Also in WAS, splenectomy should be performed very cautiously to avoid aggravation of infectious risk and impaired recovery following allogeneic hematopoietic stem cell transplantation (HSCT).

### Allogeneic Hematopoietic Stem Cell Transplantation

HSCT is a curative treatment option for some IPDs but due to associated risks, including development of graft-versus-host disease (GvHD), graft rejection, infections, and toxicities, it is reserved for selected patients.

HSCT should be considered in the presence of severe bleeding tendency, as in GT and BSS, with refractoriness to platelet transfusion. Furthermore, HSCT should be considered in syndromic IPDs, in which bleeding tendency is mild to moderate and other symptoms predominate.

In WAS, immunodeficiency and often severe symptoms of autoimmune response call for early HSCT. In fact, HSCT should already be considered at the time of diagnosis, as it should ideally be performed in children younger than 2 years, before disease progresses.

Patients with Chediak-Higashi syndrome, particularly those with lacking cytotoxic T-lymphocyte function, are at risk of developing hemophagocytic lymphohistiocytosis. In such cases, early HSCT should be considered.

Patients with congenital amegakaryocytic thrombocytopenia usually develop bone marrow failure within the first decade of life. They can be cured by HSCT. In contrast, a subgroup of patients with mutations in the gene encoding thrombopoietin does not benefit from HSCT.

### Table 2: Future directions of management of inherited platelet disorders

<table>
<thead>
<tr>
<th>What we have to do in the future</th>
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<tbody>
<tr>
<td>Decrease the rate of unidentified but suspected platelet defects</td>
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<tr>
<td>• 60% of suspected cases remain poorly described/classified</td>
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<tr>
<td>Introduce general use of bleeding scores to assess individual bleeding tendency</td>
</tr>
<tr>
<td>Develop escalating treatment strategies for prevention and treatment of bleeding episodes</td>
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<tr>
<td>Include patients with IPDs and bleeding in clinical trial programs</td>
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<tr>
<td>Establish registries to elucidate the clinical course of IPDs</td>
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<tr>
<td>Develop and adapt laboratory tests to monitor treatment success beyond clinical assessment</td>
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<tr>
<td>Identify and publish centers with expertise in advanced platelet diagnostics and IPD genetic testing</td>
</tr>
<tr>
<td>Ameliorate training of pediatric hematology/oncology treatment centers to increase awareness of IPDs versus other entities, especially those with low platelet count including chronic ITP</td>
</tr>
</tbody>
</table>

Abbreviations: IPDs, inherited platelet disorders; ITP, immune thrombocytopenia.
MDS1 and EVI1 complex locus–associated syndrome manifests as congenital radioulnar synostosis and amegakaryocytic thrombocytopenia progressing to pancytopenia and can be cured by HSCT.\textsuperscript{65,66}

HSCT should also be considered for IPDs with a known risk for development of malignancy. Among those are germline autosomal dominant mutations in RUNX1 (familial platelet disorder with propensity to acute myeloid leukemia), ANKRD26 (thrombocytopenia type 2), and ETV6 (thrombocytopenia type 5).\textsuperscript{67} As bleeding tendency is mild, and platelet number is only slightly reduced, these entities may be overlooked or even misdiagnosed as ITP. Once malignancy develops, HSCT may become necessary.\textsuperscript{1,68–71}

\textbf{Gene Therapy}

Gene therapy is based on transfer of genetic material into the cells of patients, and various types of gene therapy have led to therapeutic breakthroughs in different diseases.\textsuperscript{72} It is a potential alternative to HSCT for patients with WAS lacking a suitable donor. Furthermore, gene therapy requires a less toxic conditioning scheme and the risk of GvHD, and rejection is reduced.

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In a phase I/II pilot trial in 10 patients with WAS, a gamma-retroviral vector was used.\textsuperscript{73} Results showed a good response in terms of reduction of infections and of clinical signs of autoimmunity (autoimmune cytopenia, colitis, eczema), and elevation of platelet count in nine out of ten patients. However, vector-mediated insertional mutagenesis led to the development of acute leukemia in seven out of ten patients.\textsuperscript{73} As a consequence, subsequent trials used a self-inactivating lentiviral vector. A long-term follow-up over 4 to 9 (median: 7.6) years after gene therapy within an open-label, phase I/II clinical trial found resolution of severe infections and eczema, improvement of autoimmune disorders, and bleeding frequency.\textsuperscript{75} Notably, there was no occurrence of malignancy. Even though platelet number was under normal threshold levels and platelet size was still smaller and showed decreased α-granule density in six out of nine patients after gene therapy, none of the patients needed PCs. Despite incomplete correction of the platelet compartment, no spontaneous bleeding occurred.\textsuperscript{74–77}

Up to now, only one patient has undergone successful gene therapy in an adult age, for whom no donor for HSCT could be found.\textsuperscript{78}

There are promising preclinical studies and animal models for gene therapy in GT. Fang et al showed in a murine and a canine model that infusion of ex vivo lentiviral transduced hematopoietic stem cells resulted in circulating platelets with approximately 10% of normal integrin (αIIbβ3) levels, which was enough for the improvement of hemostasis.\textsuperscript{75,79,80}

\textbf{Special Recommendations for Women with IPDs}

\textbf{Heavy Menstrual Bleeding}

HMB is a common complaint in female adolescents. In 10 to 62%, there exists an underlying bleeding disorder, in up to 44% of IPD.\textsuperscript{81,82} TXA is considered the first choice of treatment in women with HMB, in the case of acute intervention, as well as long-term treatment in women who seek to conceive.\textsuperscript{1,11,83} If TXA alone is insufficient, a combination with DDAVP may be considered, but it is not recommended in the case of major blood loss.\textsuperscript{11} In patients who do not want to conceive, menorrhagia should be controlled by hormones. Among all options, a levonorgestrel-releasing intrauterine device (LNG-IUD) is the most effective therapy.\textsuperscript{11,84} If LNG-IUD is contraindicated or objected by the patient, combined oral contraceptives (COC) are suggested. If hormonal treatment fails or is insufficient, combination with TXA is recommended and is particularly effective in patients with GT and BSS.\textsuperscript{11,83}

Surgical options like endometrial ablation or hysterectomy should be considered only if the earlier-mentioned medical therapies fail and there is no desire to conceive in the future (see Fig. 2).\textsuperscript{11,83}

\textbf{Risk Management in Pregnancy}

Women with IPDs with previous menorrhagia, who stop taking COC to conceive, are at high risk of developing HMB in the prepregnancy period.\textsuperscript{85} Treatment options include TXA and rFVIIa.\textsuperscript{85} Particularly in women with GT, but also with BSS, PCs should be avoided in order not to increase the risk of platelet antibody formation.\textsuperscript{85,86} Platelet antibodies can cross the placenta, causing fetal or neonatal harm.\textsuperscript{85–87} Neonatal alloimmune thrombocytopenia may occur in up to 30% of newborns of mothers with GT.\textsuperscript{88} Thus, before and during pregnancy, antibodies should be monitored. In case of high levels, intravenous immunglobulins and/or corticosteroids should be considered during pregnancy.\textsuperscript{85,86}

\textbf{Potential Future Treatments of IPDs}

\textbf{Artificial Platelets}

In a first-in-human trial, pluripotent stem cells were generated from a patient’s peripheral blood and differentiated into immortalized megakaryocyte progenitor cell lines. A clone of those was then induced to produce pluripotent stem cell-derived platelets (iPSC-PLTs), which were successfully transfused for treating severe aplastic anemia in a 55-year-old woman without complications when followed up for 1 year.\textsuperscript{89} This trial of iPSC-PLTs administration not only showed promising results but raised expectations to generate HLA-class-I-depleted platelets or gene-corrected platelets as well.\textsuperscript{89–91}

\textbf{Platelet-Inspired Nanoparticles}

The surfaces of nanoparticles and microparticles (liposomes, latex beads, and albumin-based microparticles) are modified with platelet surface–relevant ligands and GPs to support various platelet mechanisms. For example, micro- or nanoparticles are coated with fibrinogen, GPIbα and recombinant GPⅠaⅡa, collagen-binding peptide, and von Willebrand binding peptide. Results from in vitro and animal models are encouraging.\textsuperscript{19,92–95}
HMB-001
HMB-001 is a bispecific antibody that binds endogenous FVIIa and platelet triggering receptor expressed on myeloid cells (TREM)-like transcript-1 receptor, which is present on the surface of activated platelets. Thereby HMB-001 promotes local FX activation and thrombin generation and thus restores clot formation in patients with GT and BSS.

Various Other Therapies to Achieve Hemostatic Correction
Tissue factor pathway inhibitors (TFPIs) influence the early stages of blood coagulation. Anti-TFPIs include concizumab, marstacimab, and befovacimab and have been evaluated for use in patients with hemophilia. Fitusiran is a small interfering RNA therapy that reduces antithrombin production, resulting in less bleeding episodes in hemophiliacs. In contrast to activated factor VII, which leads to an instant thrombin burst, all these new drugs develop their effect on coagulation continuously. Severe bleeding in IPDs occurs frequently in women taking hormones. All of these may increase the risk of thromboembolic events during long-term prophylaxis. So far, TFPIs and fitusiran are still in clinical development stages and there are no reports on their use in IPDs.

Conflict of Interest
The authors declare that they have no conflict of interest.

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