Platelet function disorders: A review

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Introduction

- Platelet function disorders (PFD): rare, bleeding severity varies, and clinicians are often unfamiliar with the appropriate evaluation and treatment.

- PFDs include heritable and acquired conditions.

- Some are associated with thrombocytopenia, and some have a normal platelet count.

Acquired causes of platelet dysfunction and thrombocytopenia

- Kidney or liver disease: Uremia or chronic liver disease (including due to chronic excess alcohol)
- Dysproteinemias :Abnormal paraproteins in multiple myeloma or Waldenstrom macroglobulinemia, Hyperviscosity
- Myeloproliferative neoplasms (MPNs): cause acquired von Willebrand syndrome.
- Drug-induced:

-*Aspirin: Irreversibly inhibits cyclooxygenase-1, causing aggregation abnormalities similar to inherited aspirin-like defects.*

-NSAIDs: reversibly inhibit cyclooxygenase-1 and cause abnormal platelet aggregation similar to aspirin

-P2Y12 inhibitors – Impair ADP aggregation responses

-BTK inhibitors – Inhibitors of Bruton tyrosine kinase (BTK), used for lymphoid malignancies, can increase bleeding risk due to platelet dysfunction.

-SSRIs – are not considered a major cause of platelet dysfunction, although some agents have been reported to interfere with certain aggregometry tests

-Agents that inhibit integrin alphaIIbbeta3 (previously called GPIIb/IIIa) can induce Glanzmann thrombasthenia-like abnormalities in platelet function

Epidemiology

- In the world:

-GT: The prevalence is approximately 1 in 1 million. Transmission is autosomal recessive

-BSS: The prevalence is approximately 1 in 1 million. Transmission is usually autosomal recessive, but autosomal dominant forms also exist.

- In Iran:

1398:

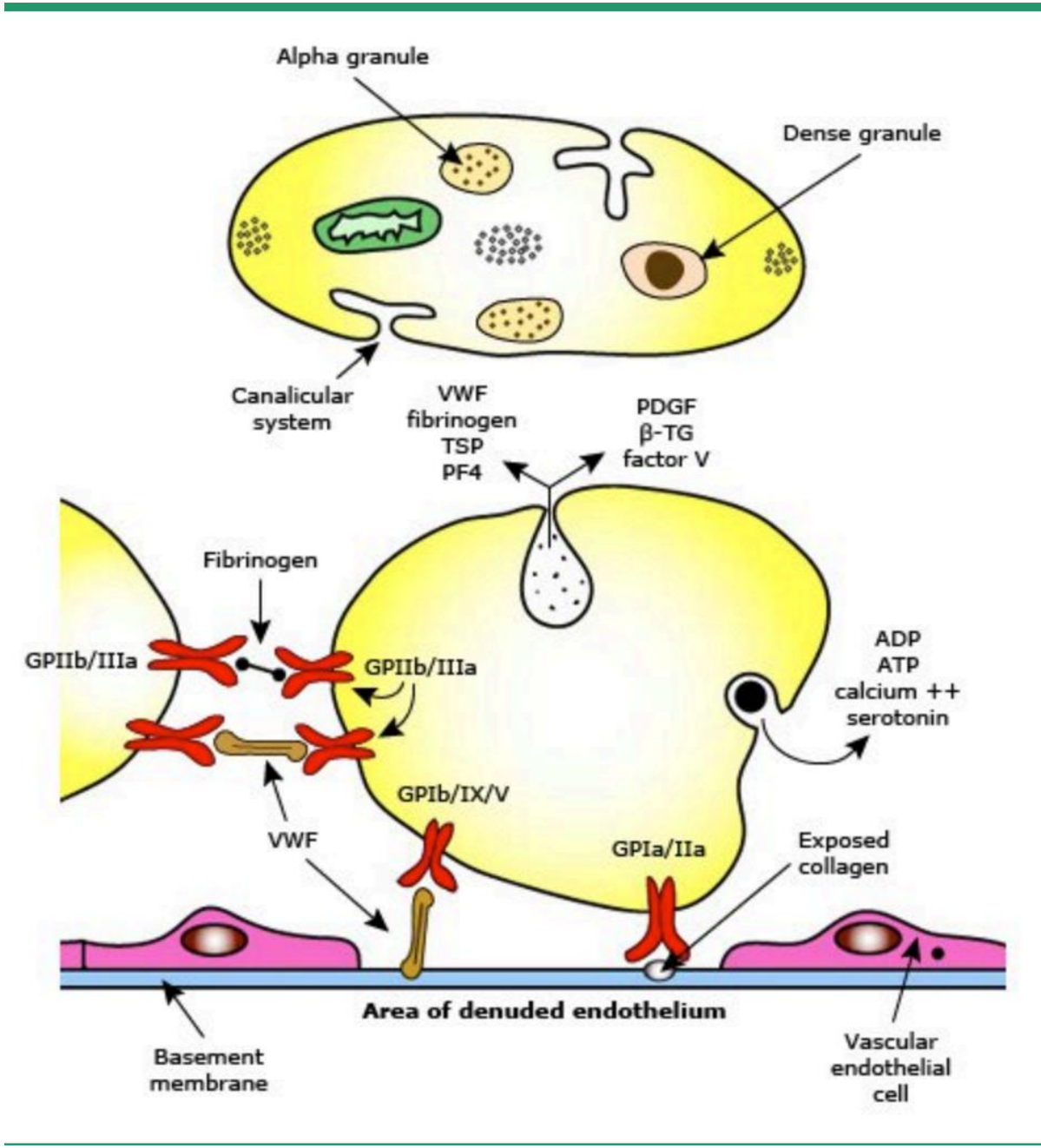
Disorders	Patients
Hemophilia	5948
VWD	1137
Plt.disorders	518 (GT=406/BSS=112)
Others	3175

Mechanism

- Platelet adhesion to the vascular subendothelium at the site of injury:

Disorders of platelet surface receptors include Glanzmann thrombasthenia and BSS

- Platelet activation and secretion of granule contents
- Aggregation of multiple platelets
- Platelet interactions with clotting factors



When to suspect?

- there is a bleeding phenotype despite normal screening tests of hemostasis
- bleeding disproportionate to the degree of thrombocytopenia
- thrombocytopenia unresponsive to immune thrombocytopenia (ITP) therapies
- multiple affected relatives
- syndromic features suggestive of a particular IPFD

Bleeding

- mucocutaneous bleeding and bruising, beginning soon after trauma, rather than joint and muscle bleeds or delayed soft tissue hematomas
- Quebec platelet disorder is an exception that causes delayed bleeding

- bleeding due to an IPFD is identified earlier and more frequently in females.
- Females with IPFD have higher bleeding scores than males and more skin bleeding and increased bleeding related to menses and childbirth.
- Males may only present after bleeding with hemostatic challenges.

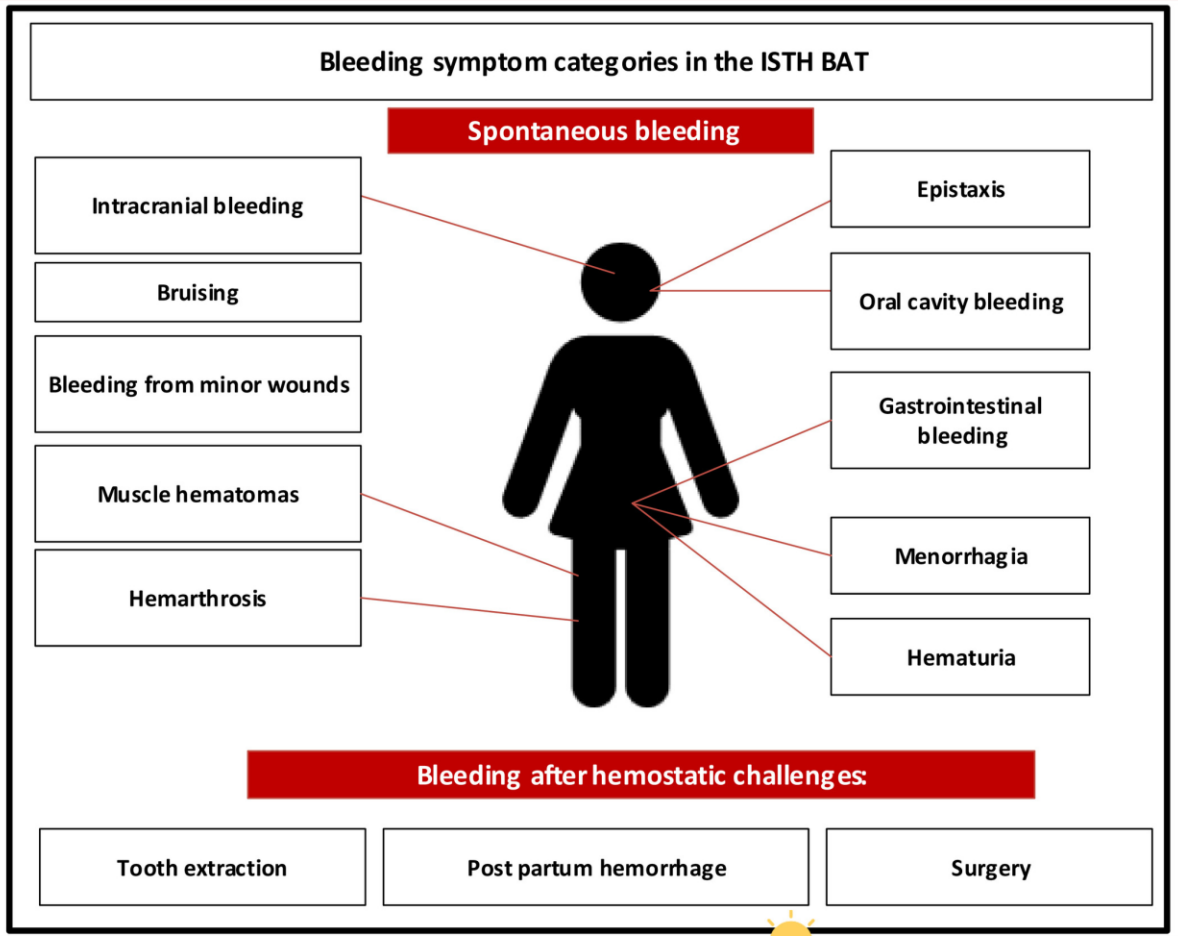
Bleeding assessment tool

ISTH Major Bleeding event	ISTH Clinically relevant non-Major bleeding events
• Fatal Bleeding • Bleeding event that decreases hemoglobin level by 2.0 g/dL or more. • Symptomatic bleeding in a critical area or organ: - Retroperitoneal - Intracranial - Intraocular - Intra-articular - Intraspinal - Pericardial - Intramuscular with compartment syndrome	• Requiring medical intervention by a healthcare professional • Leading to hospitalization or increased level of care • Prompting a face-to-face evaluation

How to use the BAT

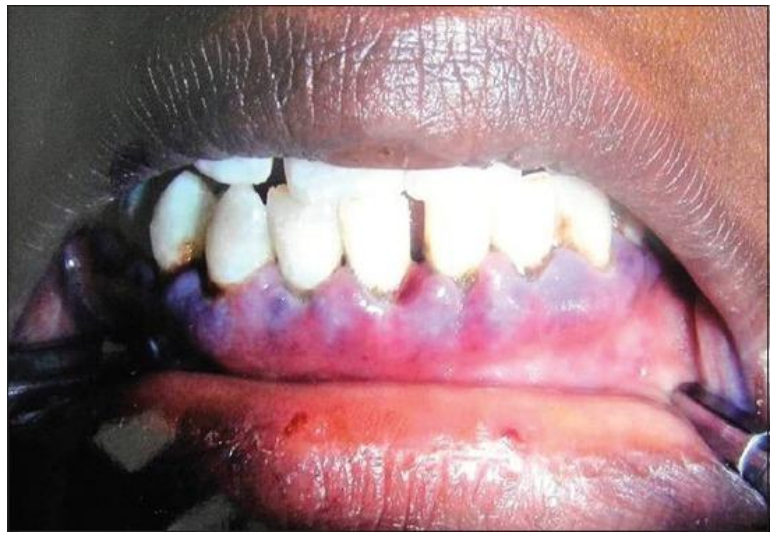
How BATs differ

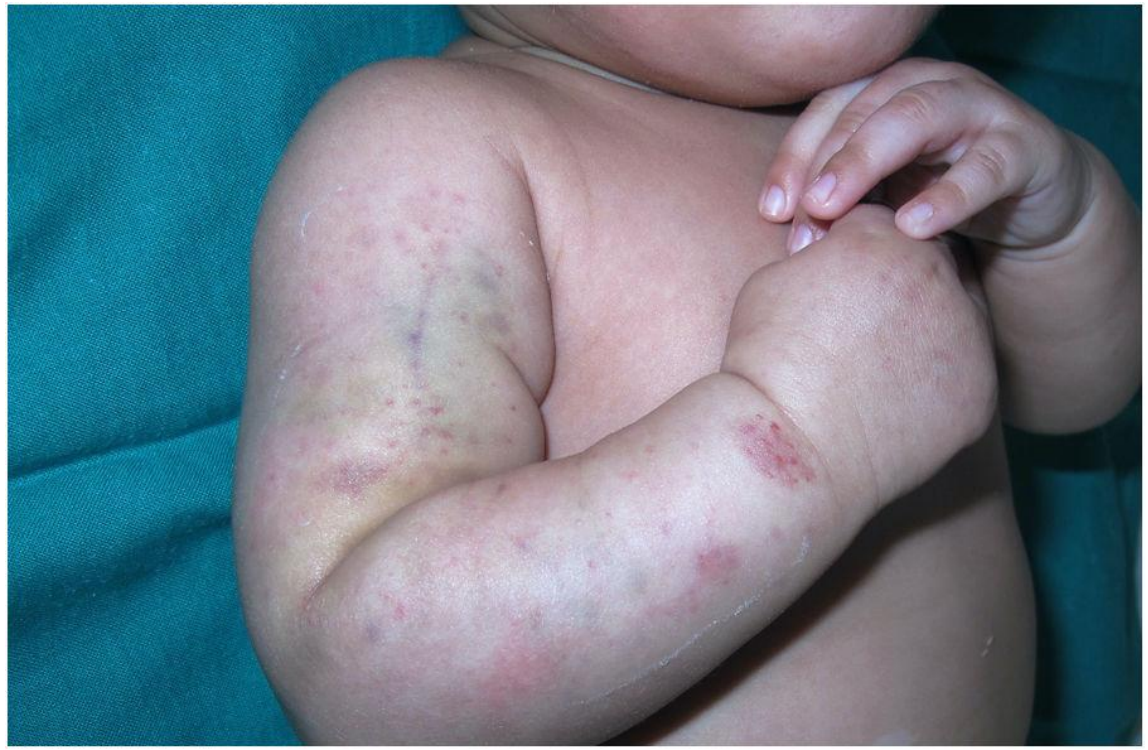
There are many validated BATs. The following are some key distinctive features:
- The MCMDM-1 VWD and PBQ assign negative points for hemostatic challenges without bleeding complications (i.e. surgeries, deliveries, dental extractions).
- The ISTH BAT and PBQ evaluate pediatric bleeding symptoms in the "other bleeding" category (i.e. cephalohematoma, umbilical stump bleeding, cheek hematoma and conjunctival hemorrhage)
- The ISTH BAT assesses menorrhagia more comprehensively and is the only BAT that evaluates hematuria.



Score	[Max Score 56 points]

Interpretation:	
Normal Range: Adult Males	0-3 A score ≥4 is considered 'abnormal'
Normal Range: Adult Females	0-5 A score ≥6 is considered 'abnormal'
Normal Range: Child [Age <18 years]	0-2 A score of ≥3 is considered 'abnormal' A Bleeding Score <2 makes a Bleeding Disorder unlikely





American Journal of Hematology 77:198–199 (2004)

Presentation and Pattern of Symptoms in 382 Patients With Glanzmann Thrombasthenia in Iran

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Glanzmann thrombasthenia (GT) is a rare autosomal recessive disease characterized by prolonged bleeding time with normal platelet count and morphology. It is caused by the quantitative or qualitative deficiency of the platelet glycoprotein IIb–IIIa. In 382 Iranian patients with GT diagnosed at a single center during the period 1969–2001, consanguinity between parents was 86.6%, in accord with the high frequency of intrafamilial marriages in Iran. Almost all patients had had abnormal mucocutaneous bleeding (epistaxis and gum bleeding); at follow-up, 4/5 of the patients had been transfused at least once to control hemorrhagic episodes. As expected, almost all the patients had a normal platelet count while the leukocyte count was increased in 19.3%. Among women, an unexpected low rate of pregnancies was observed. Am. J. Hematol. 77:198–199, 2004.

Key words: Glanzmann thrombasthenia; consanguineous marriage; genetic consultation

TABLE I. Number and percentage of Iranian Patients With Glanzmann Thromboasthenia Who had a Given Clinical Manifestation at Least Once

Clinical manifestation	Number (percentage)*
Epistaxis	190 (49.7)
Gingival bleeding	87 (22.8)
Ecchymosis	54 (14.1)
Gastrointestinal bleeding	18 (4.7)
Hematoma	18 (4.7)
Menorrhagia	17 (12.9)
Excessive bleeding at circumcision	14 (3.6)
Excessive bleeding at surgery	11 (2.8)
Bleeding at injection sites	8 (2.0)
Petechia and purpura	4 (1.0)
Umbilical cord bleeding	1 (0.3)
Excessive bleeding at delivery	2 (0.5)
Central nervous system bleeding	1 (0.3)
Hemarthrosis	1 (0.3)

*The total number is greater than 382 because several patients had more than one bleeding symptom.

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ISLH

Glanzmann thrombasthenia and Bernard–Soulier syndrome in south Iran

Correction(s) for this article ›

A. AFRABIASI, A. ARTONI, M. KARIMI, F. PEYVANDI, E. ASHOURI, P. M. MANNUCCI

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Laboratory testing

- CBC:

Plt count: *with or without thrombocytopenia*

- PBS:

-Plt size: *small /giant*

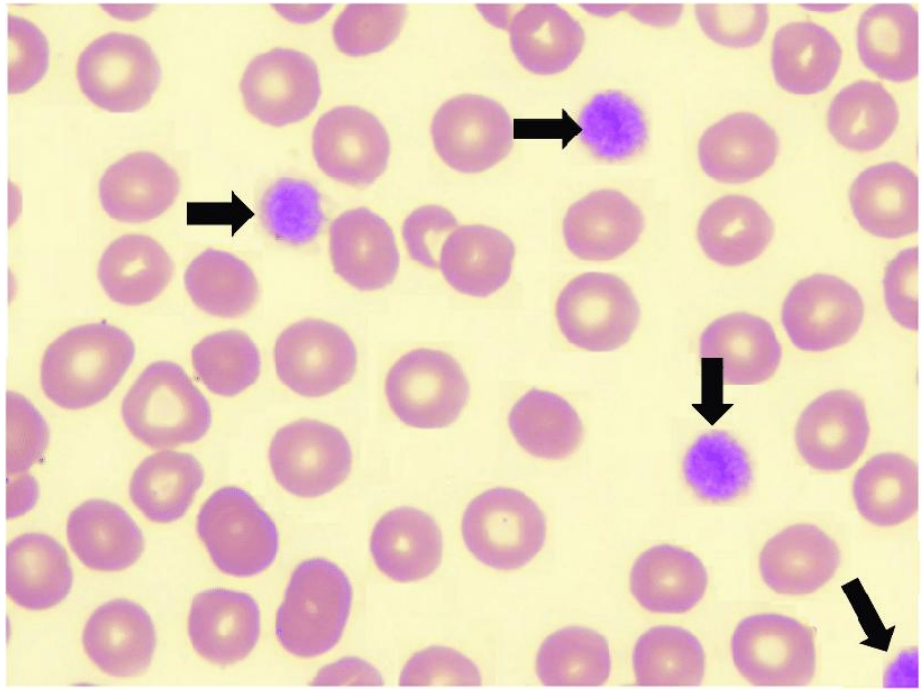
-Plt granules: *hypo/ giant plt granules*

Giant granules in neutrophils

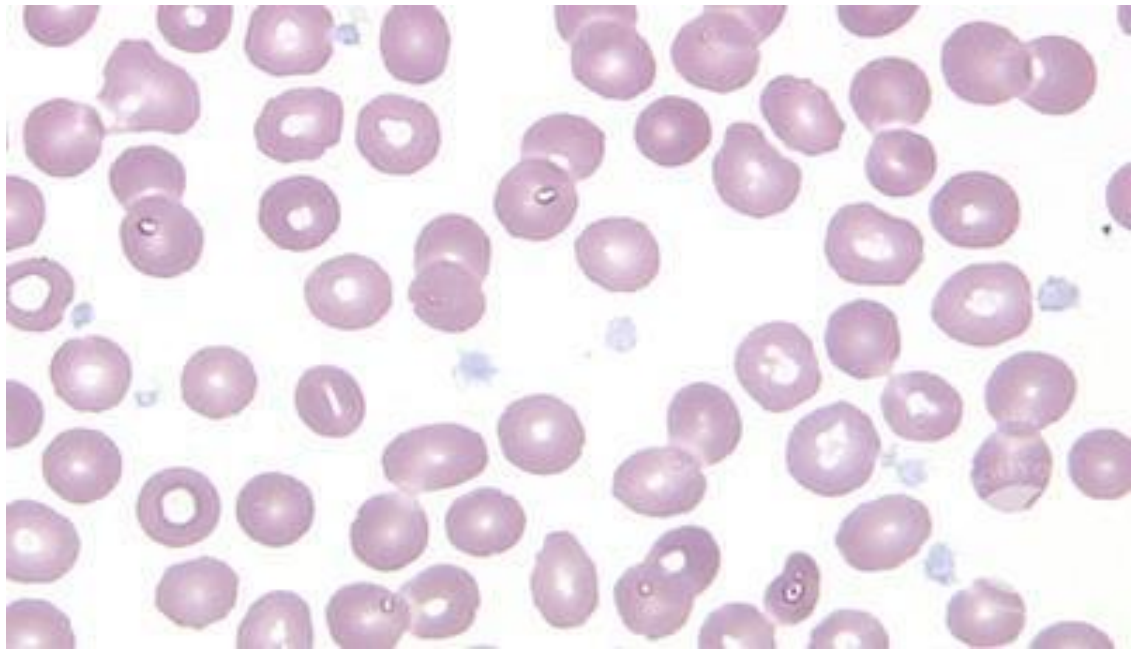
- Coagulation testing: PT/PTT/VWF
- Basic metabolic panel, liver function tests, iron studies

Peripheral Blood Smear

BSS

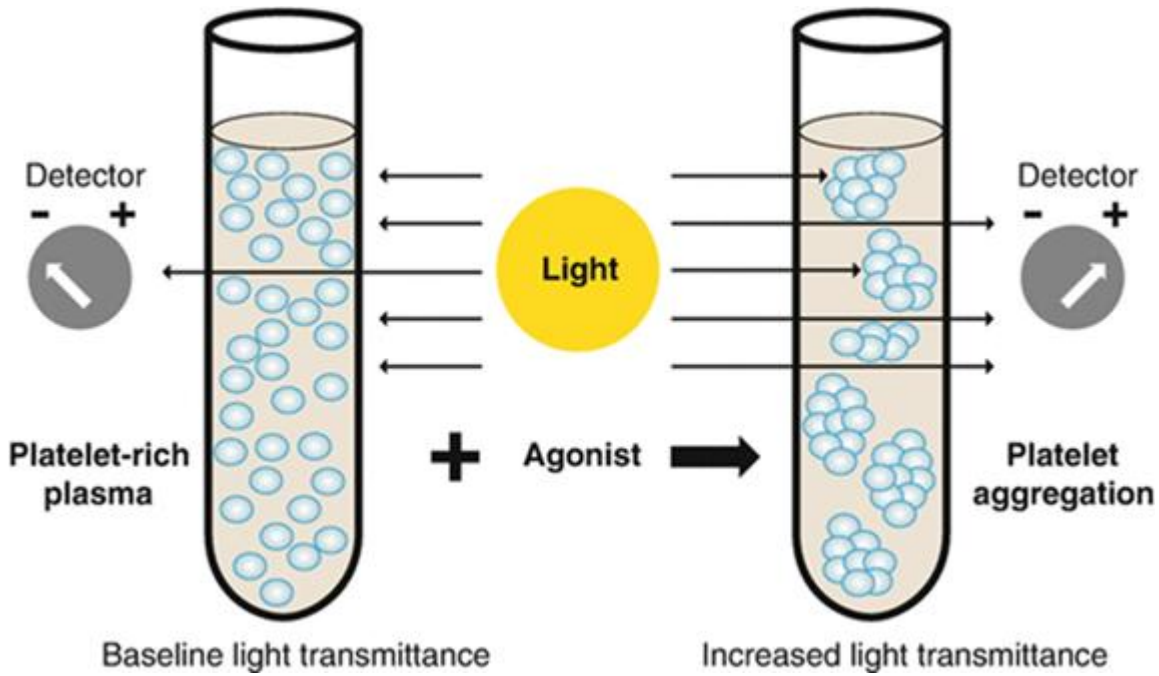


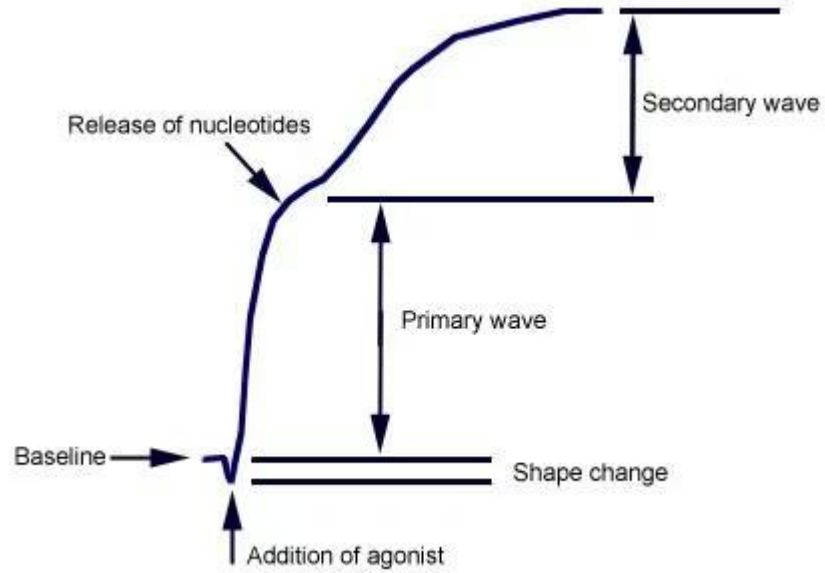
Gray PLT syndrome



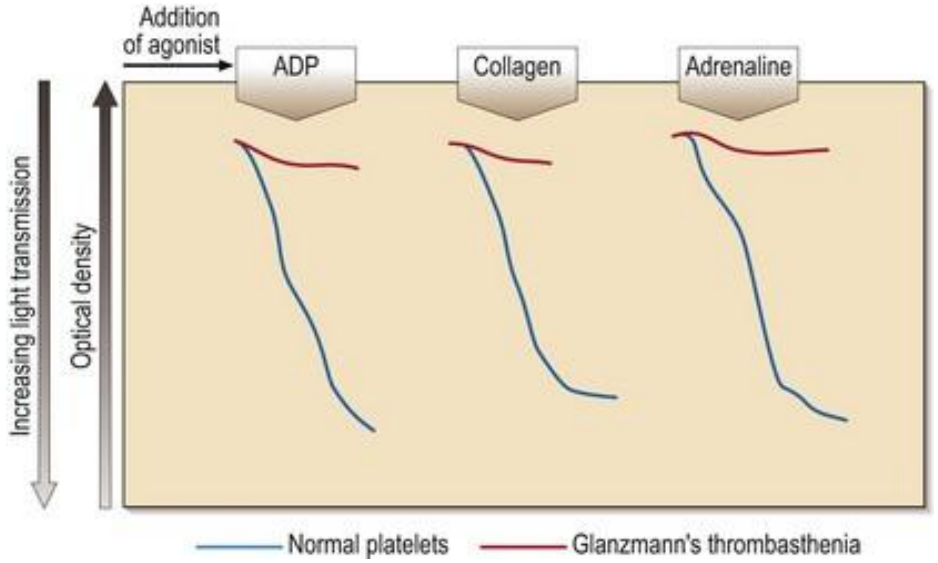
Platelet function testing

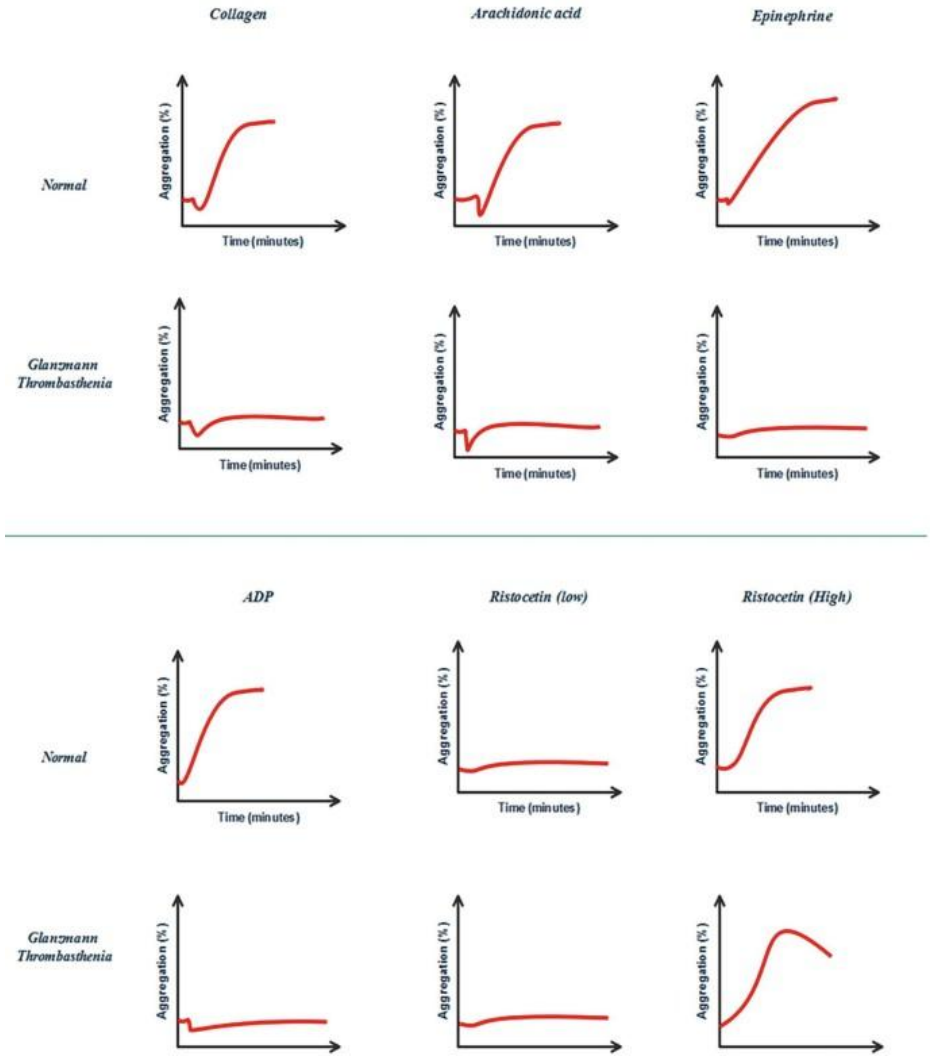
- Platelet aggregometry is the gold standard test for diagnosing platelet function disorders.
- Traditional aggregation assays use a panel of platelet agonists to evaluate platelet activation and aggregation in vitro.
- Either whole blood or platelet-rich plasma is tested depending on the technique.
- Common agonists used include ADP, arachidonic acid, collagen, epinephrine, a thromboxane A2 mimetic, and ristocetin.


Detector
Light
Detector
Platelet-rich plasma
Agonist
Platelet aggregation
Baseline light transmittance
Increased light transmittance

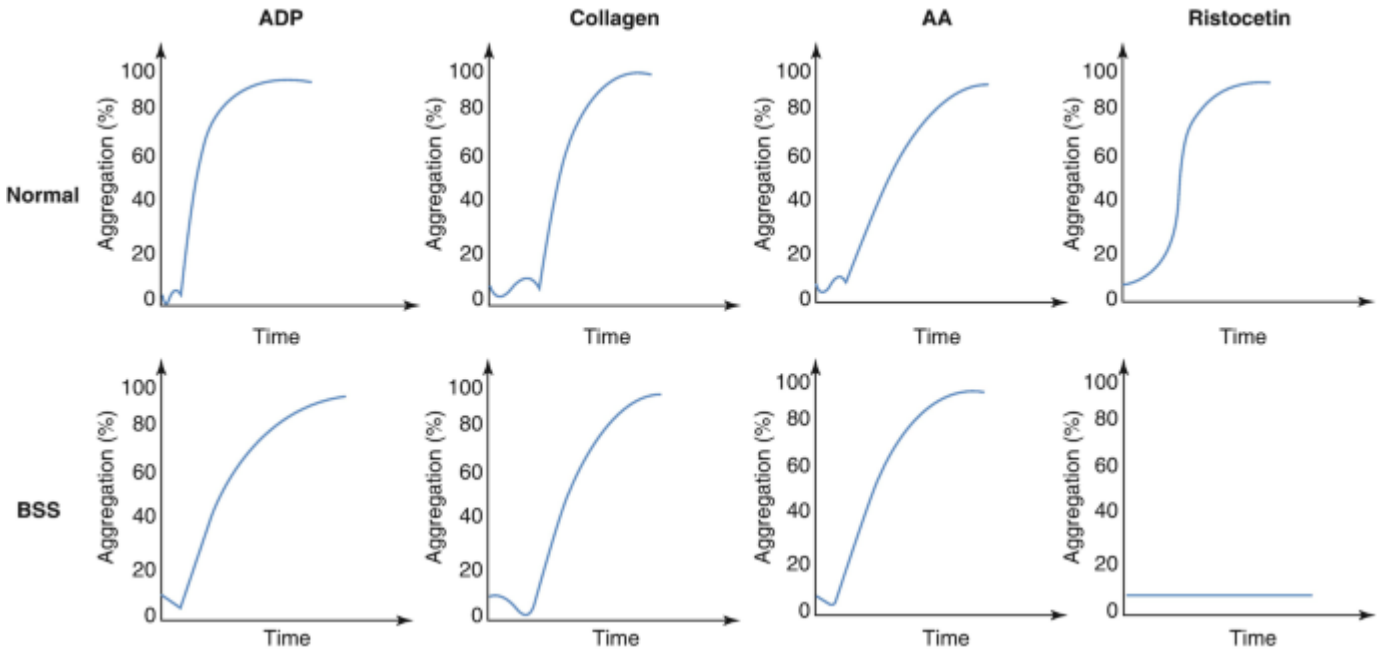

Release of nucleotides
Secondary wave
Primary wave
Baseline
Shape change
Addition of agonist

Glanzmann thromboasthenia





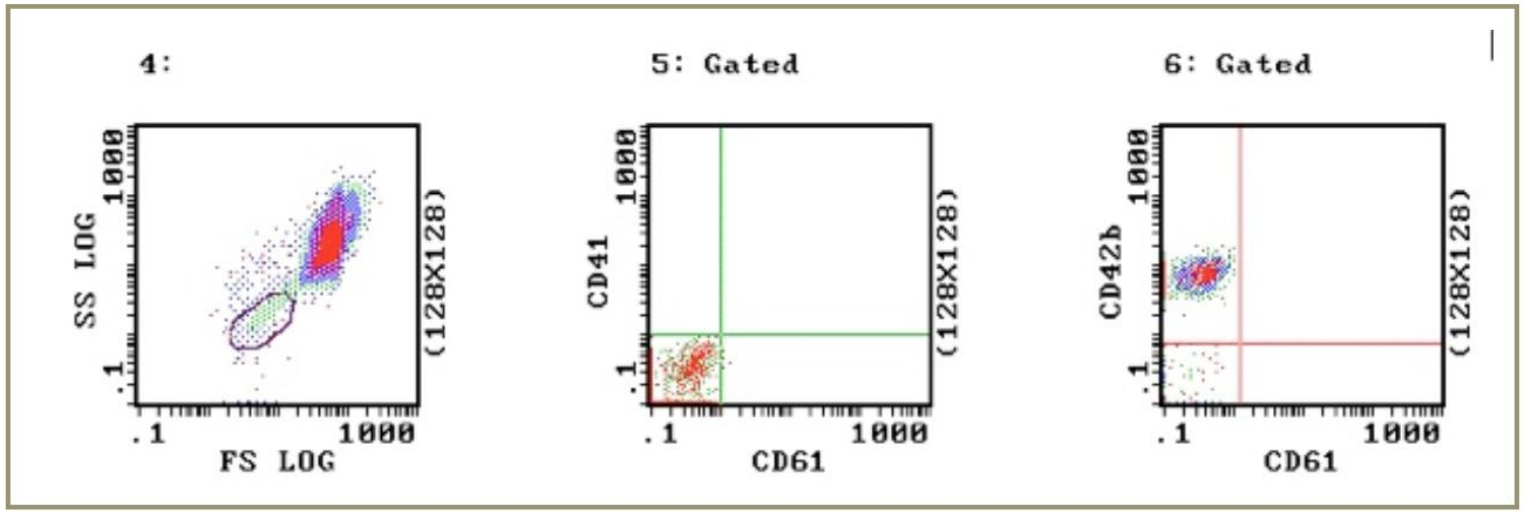
Bernard Soulier syndrome

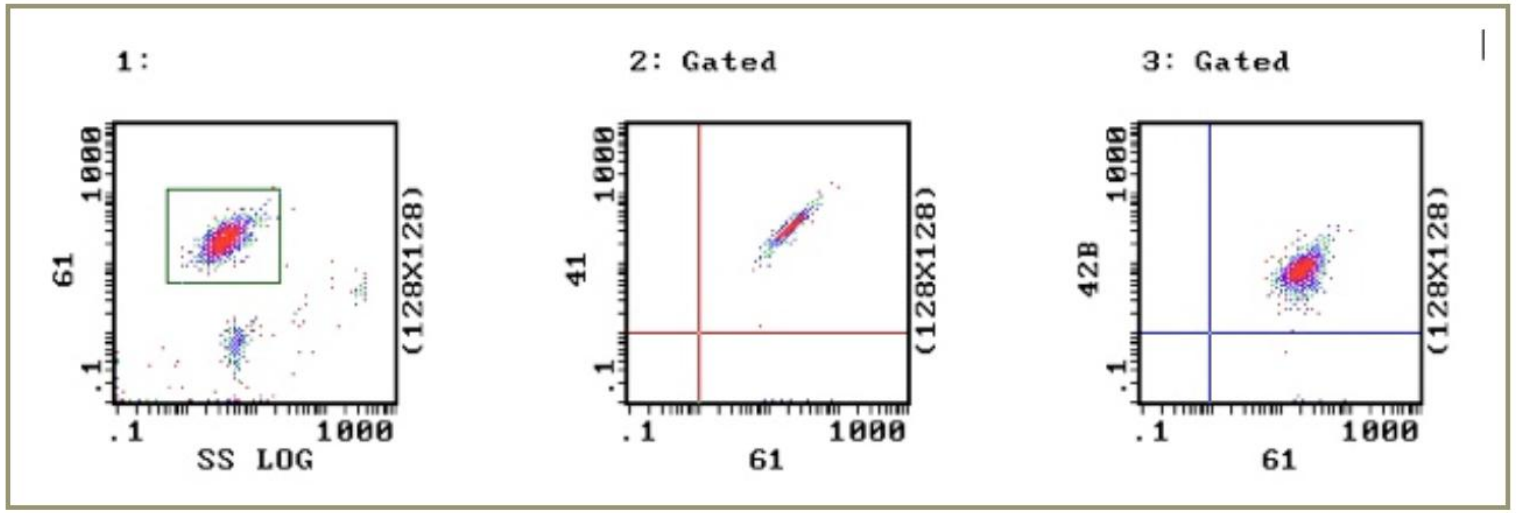


Patterns of platelet aggregation in selected disorders of platelet function and VWD

Disorder	Aggregation response				Other features
	Primary ADP	Secondary ADP	Collagen	Ristocetin	
VWD	+ + + +	+ + + +	+ + + +	Highly variable	Platelet morphology normal; VWD panel is usually abnormal
Bernard-Soulier syndrome	+ + + +	+ + + +	+ + + +	0	Giant platelets, thrombocytopenia; VWD panel is normal
Glanzmann thrombasthenia	0	0	0	+ + +	Normal platelet morphology
Storage pool disease	+ + + +	0 to + +	+ +	+ +	Platelet morphology normal (except in gray platelet subgroup); electron microscopy is abnormal
Secretion defect	+ + + +	0 to + +	+ +	+ +	Normal morphology by light and electron microscopy

Flow cytometry





- GT
- BSS

Treatment

- Counseling and communication
- Major bleeding or major surgery
- Minor bleeding or minor procedures
- Other treatments
- Obstetric considerations
- Implications for first degree relative

Counseling

- Drugs and medications to avoid, such as anti-platelet drugs, unless there is an important indication.
- Planning is needed to treat and prevent bleeding from hemostatic challenges.
- For some IPFDs with significant bleeding, avoidance of contact sports may be appropriate.
- Good dental hygiene is important to limit the need for future dental procedures.
- Routine cancer screening should be done.
- Related health issues requiring consideration include iron deficiency.

Platelet transfusion

- Platelet transfusions should be considered for serious bleeding and major surgery in patients with more severe IPFD

- Unique to GT is the risk of developing alloantibodies to integrin alphaIIbbeta3 and/or HLA antigens, resulting in refractoriness to platelet transfusions, This leads to the risk that a more serious bleeding event in the future could not be effectively treated with platelet transfusions.

- Dosing:

-Dosing Typically, one apheresis unit or six units of whole blood derived platelets are transfused, with clinical assessment.

-For IPFDs that impair aggregation or activation but not initial platelet adhesion (eg, Glanzmann thrombasthenia), animal models suggest there is in vivo competition between transfused platelets and the patient's dysfunctional platelets; dosing needs for those disorders may be fourfold greater.

Recombinant factor VIIa

- a "bypassing therapy" originally developed for hemophilia that can promote clotting by activating a later step in the coagulation cascade.
- It is thought to promote thrombin generation at sites of vascular damage in patients with IPFDs.
- Dosing: 90 mcg/kg
- most individuals would need from one to three doses per admission.
- risk of thrombosis and the cost.


AryoSeven™
4.8 mg
Eptacog alfa (activated)
Eptacog alfa (activated) recombinant coagulation Factor VIIa 4.8 mg
Powder and solvent for solution for injection.
Intravenous use, for single dose administration
AryoSeven™
۴/۸ میلی‌گرم
پودر لیوفیلیزه برای تهیه‌ی
محتویات ویال در ۸/۵ میلی لیتر
جهت تزریق وریدی
در دمای ۲ تا ۸ درجه سانتی
قبل از مصرف، بروشور
آب
سازمان غذا و دارو
IFDA
http://irc.fda.gov.ir/nfi

Minor bleeding or minor procedures

- Local therapies
- Desmopressin
- Antifibrinolytic agents:

-Tranexamic acid, 25 mg/kg per dose orally every six to eight hours or 10 mg/kg intravenously three times per day.

- Hormonal contraceptives

Desmopressin

- Dosing:

-IV/SC= 0.3 mcg/kg once daily for 3-5 days

-dilute in 50cc NS and infused over 30 min

Information Journal Paper

Title

EFFICACY AND SAFETY OF DESMOPRESSIN (DDA VP) AS A HAEMOSTATIC AGENT IN MILD HEMOPHILIA AND TYPE I, IIA

Author(s) LAK M. | MANAGHCHI M.R. | TOUGHEH GH.R. | SAFAEE S.R. | SHASHANI T. |

Keywords DESMOPRESSIN (DDA VP) Q4
ANTIDIURETIC HORMONE Q3
VON WILLEBRAND DISEASE Q4

Abstract Desmopressin is a synthetic analog of antiduretic hormone used for control and treatment of noctomal enurisis in patients with diabetes insipitus. Since 1977, desmopressin was shown to useful in prevention and treatment of bleedings in patients with mild hemophilia and vWD. This non transfusional haemostatic agent when infused interavenously, is expected to increase transiently F VIIIc and vWF, 3-5 times above the basal, levels, within 30-60 min and thereby corrects both aPTT and BT defects. The mode of action is only partially understood. With the aim to survey DDA VP haemostatic effect and to avoid the use of blood products to control or to prevent of bleeding episodes we used desmopressin in 30 Iranian patients with mild hemophilia and vWD (type 1, 2A)Desmopressin (Emosint-Kedrion-Italy) was administered intravenously, in a dose of 0.3 µg/kg body weight, diluted in 50 ml normal saline and infused over 30 min. From all patients, 5-7 ml blood sample was taken before and 30-60 min after DDA VP infusion. For evaluation of coagulation, F VIIIc was measured by a onestage clotting time method, vWF: Ag by Elisa and vWF activity by vWF R. CoF activity, and BT by IVY method. The results showed that clotting assays in 20 patients with mild hemophilia A (F VIII, 5-30%) 30-60 min after DDA VP infusion showed increasing of F VIIIc median 3.7 times above the basal level and aPTT corrected median 13 s, without any important side effects. This treatment in 10 patients with vWD (type 1, 2A) increased F VIIIc median 3.7 and vWF, 3 times above the basal levels, leading to shorting of aPTT 12.9 sand BT, 3.4 min in compare to pre treatment levels. Our results showed that desmopressin in mild hemophilia and vWD (type 1 & 2A) is effective and safe, because it provide a form of autologous replacement therapy and usually permits the avoidance of using clotting factor and with potential of decreasing in the cost of treatment.

- TPO-RAs – A thrombopoietin receptor agonist:

-TPO-RA : expected to raise the platelet count, not to correct the underlying platelet dysfunction.

used in several thrombocytopenic IPFDs including MYH9-related disease, Wiskott-Aldrich syndrome/X-linked thrombocytopenia, Bernard-Soulier syndrome, and ANKRD26-related thrombocytopenia

- Hematopoietic stem cell transplant and gene therapy:

some severe forms of IPFDs who have frequent major bleeding episodes may be treated with more aggressive (and potentially curative) therapy

Glanzmann thrombasthenia, congenital amegakaryocytic thrombocytopenia (CAMT), Chediak-Higashi syndrome and Wiskott-Aldrich syndrome

GT and pregnancy

Table 1. Investigations required for the initial characterization and evaluation of women with GT

Diagnostic parameters	Role
GT characterization	
Light transmission aggregometry	To confirm GT
Quantitative $\alpha_{IIb}\beta_3$ evaluation by flow cytometry and/or western blot	To classify GT subtype and evaluate the risk of anti-$\alpha_{IIb}\beta_3$ immunization
Genetic studies (*ITGA2B/ITGB3*)	To confirm GT, enable genetic counseling and prenatal diagnosis, and evaluate the risk of anti-$\alpha_{IIb}\beta_3$ immunization
Evaluation prior to pregnancy	
CBC (PLT, Hb, MCV), ferritinemia	To screen for anemia and iron deficiency
Previous history of PPH or other adverse pregnancy outcomes	To assess maternal and fetal/neonatal related risks
Recent platelets or RBC transfusion (<3-6 mo)	To assess the risk of recurrence or development of antiplatelet antibodies
Anti-HLA antibodies screening	To select treatment strategies, ensure efficacy, and anticipate tolerance of platelet concentrates administration
Anti-$\alpha_{IIb}\beta_3$ antibodies screening (MAIPA)	To select treatment strategies, ensure efficacy, and anticipate tolerance of platelet concentrates administration To evaluate the risk of fetal/neonatal thrombocytopenia
Oral and nasal clinical status	To assess needs and anticipate potential treatment needed to prevent further increase in gum- and nose-bleeding episodes during pregnancy
Fertility of couple	To evaluate the chances of obtaining pregnancy and avoid unnecessary exposure to heavy menstrual bleeding in case of infertility

CBC, complete blood count; Hb, hemoglobin; MCV, mean corpuscular volume; PLT, platelet count; RBC, red blood cell.

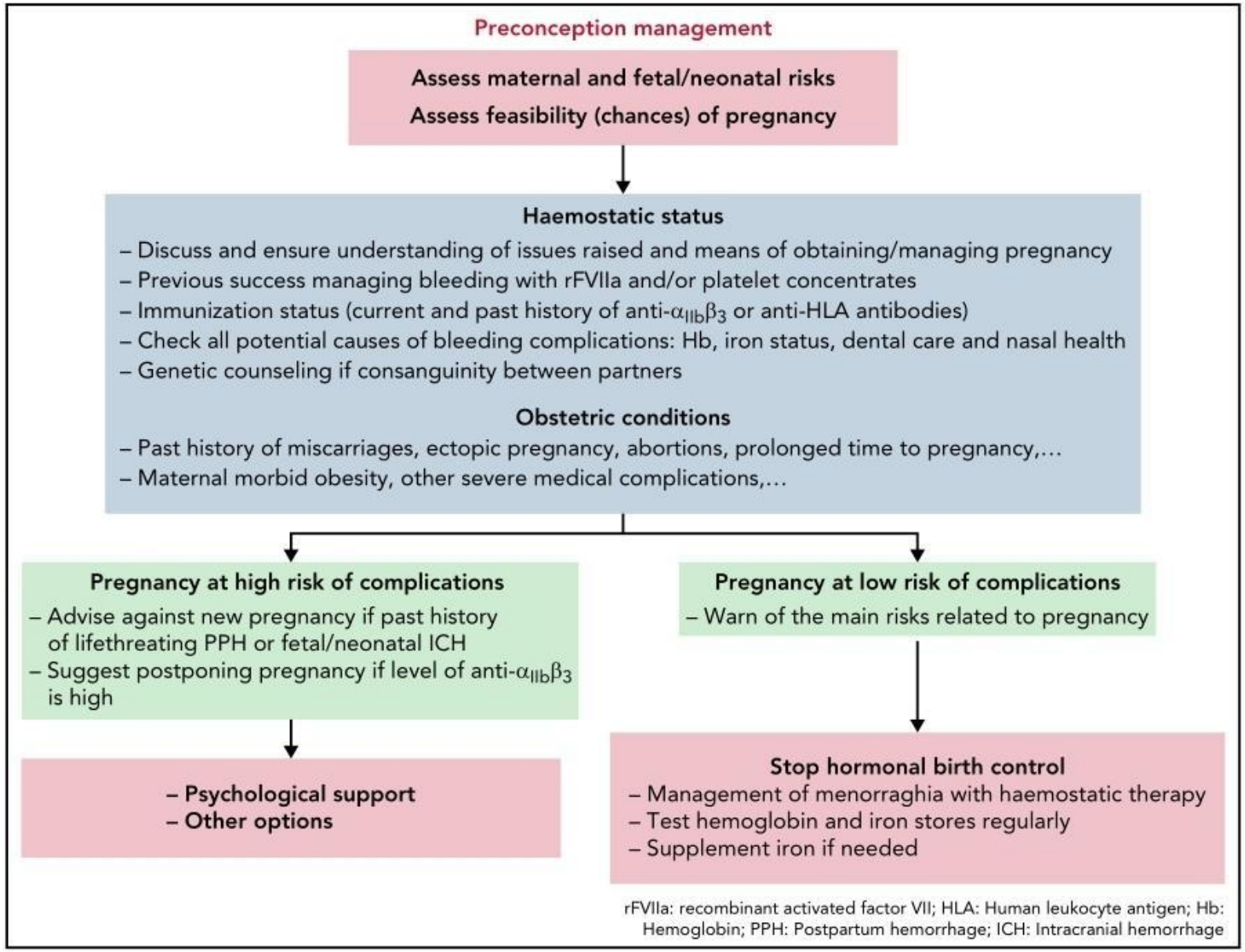


Figure 1. Proposals for preconception management in women with GT.

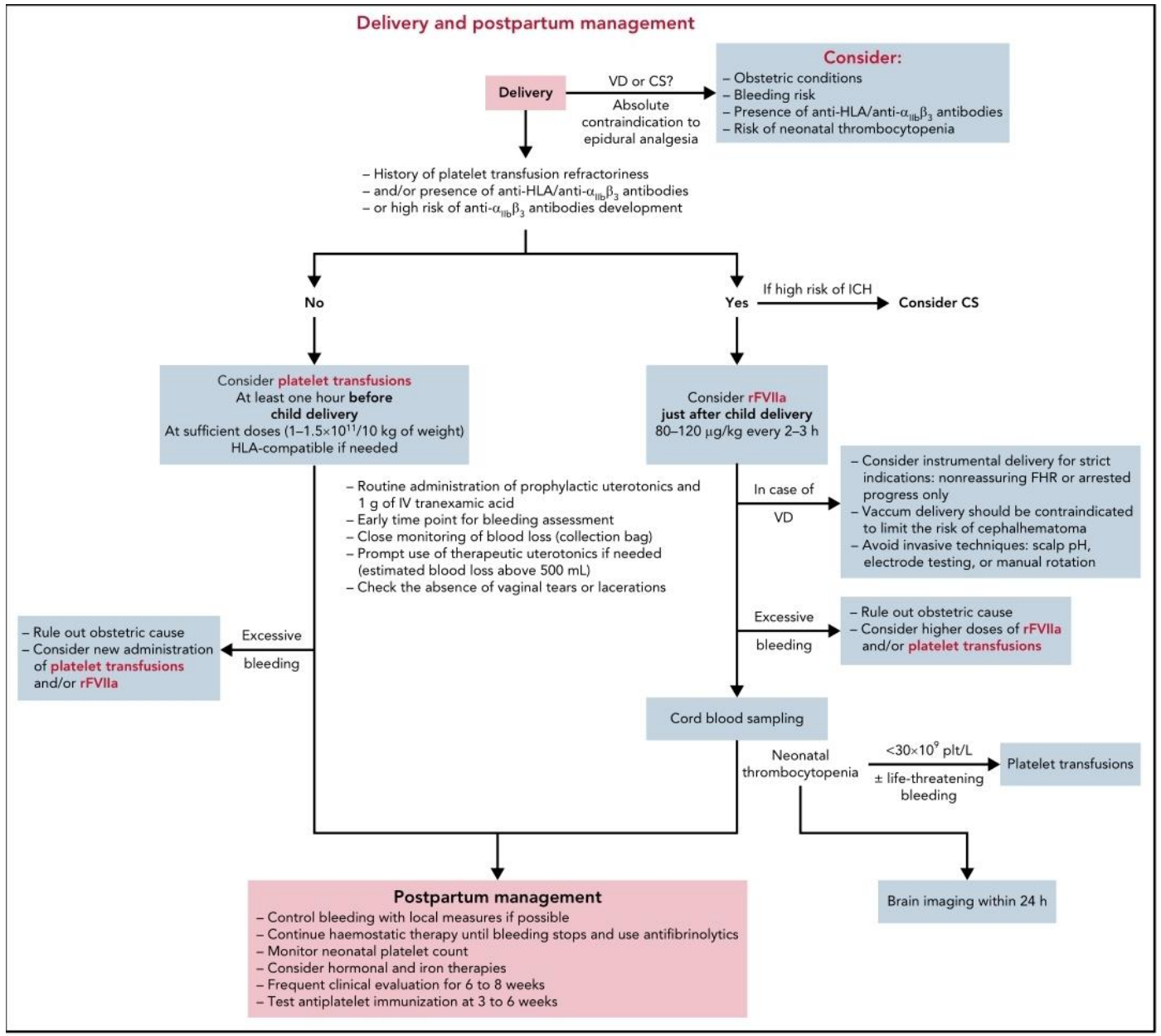

Delivery and postpartum management
Delivery
VD or CS?
Absolute contraindication to epidural analgesia
Consider:
– Obstetric conditions
– Bleeding risk
– Presence of anti-HLA/anti-$\alpha_{IIb}\beta_3$ antibodies
– Risk of neonatal thrombocytopenia
– History of platelet transfusion refractoriness
– and/or presence of anti-HLA/anti-$\alpha_{IIb}\beta_3$ antibodies
– or high risk of anti-$\alpha_{IIb}\beta_3$ antibodies development
No
Yes
If high risk of ICH
Consider CS
Consider platelet transfusions
At least one hour before child delivery
At sufficient doses (1–1.5×10^11/10 kg of weight)
HLA-compatible if needed
Consider rFVIIa
just after child delivery
80–120 µg/kg every 2–3 h
– Routine administration of prophylactic uterotonics and 1 g of IV tranexamic acid
– Early time point for bleeding assessment
– Close monitoring of blood loss (collection bag)
– Prompt use of therapeutic uterotonics if needed (estimated blood loss above 500 mL)
– Check the absence of vaginal tears or lacerations
In case of VD
– Consider instrumental delivery for strict indications: nonreassuring FHR or arrested progress only
– Vaccum delivery should be contraindicated to limit the risk of cephalhematoma
– Avoid invasive techniques: scalp pH, electrode testing, or manual rotation
Excessive bleeding
– Rule out obstetric cause
– Consider higher doses of rFVIIa and/or platelet transfusions
Excessive bleeding
– Rule out obstetric cause
– Consider new administration of platelet transfusions and/or rFVIIa
Cord blood sampling
Neonatal thrombocytopenia
<30×10^9 plt/L
± life-threatening bleeding
Platelet transfusions
Brain imaging within 24 h
Postpartum management
– Control bleeding with local measures if possible
– Continue haemostatic therapy until bleeding stops and use antifibrinolytics
– Monitor neonatal platelet count
– Consider hormonal and iron therapies
– Frequent clinical evaluation for 6 to 8 weeks
– Test antiplatelet immunization at 3 to 6 weeks

Table 3 Recommended therapies in different and specific clinical situations

Specific emergency situations	Recommendations
Skin injury	• Prolonged compression of the skin lesion (at least 10 min) using compresses eventually soaked with tranexamic acid • Antiseptic solutions, excluding alcool products • Eventually use a hemostatic and compressive bandage
Epistaxis	• Reassure the patient • Place the patient in a semi seated position with the head bent forward • Ensure of the absence of posterior bleeding by examination of the throat, especially in children • Be aware of the possibility of blood ingestion or inhalation mimicking gastrointestinal bleeding or hemoptysis with respiratory distress • Blow the nose to evacuate blood clots and limit local fibrinolysis • Nasal compression maintained at least 10 min using both fingers • Apply cold (ice pack) if necessary • Give oral tranexamic acid during 7 to 10 days to avoid recurrence of bleeding *In case of failure:* • Bilateral packing anterior to the septum using hemostatic and absorbable compresses eventually soaked with tranexamic acid • Antibiotherapy is required during all the period of packing • Patient monitoring should be planned with an ENT specialist • If bleeding persists, the use of a balloon or a packing posterior to the septum will be discussed
Loss of temporary teeth or gum bleeding	• Prolonged compression of the gum and application of a hemostatic tissue sealant if necessary • Use oral antifibrinolytics during 10 days • Mandatory monitoring to adapt the treatment in case of failure • If bleeding persists, patient should see a dentist
Heavy menstrual bleedings	• Evaluate the severity of bleeding (drop of hemoglobin level) • Give oral tranexamic acid • The use of NSAIDs should be avoided • Consider the possible need for hospitalization in case of major bleeding that could require blood transfusions • Gynecological assessement is required: discuss the use of hormonal therapy with a monophasic pill containing at least 30 µg of ethinylestradiol • Treatment of iron deficiency


Thanks for attention
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