Platelet Defects: Glanzmann's Thrombasthenia & Bernard-Soulier Syndrome

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National Hemophilia Foundation

Hello!

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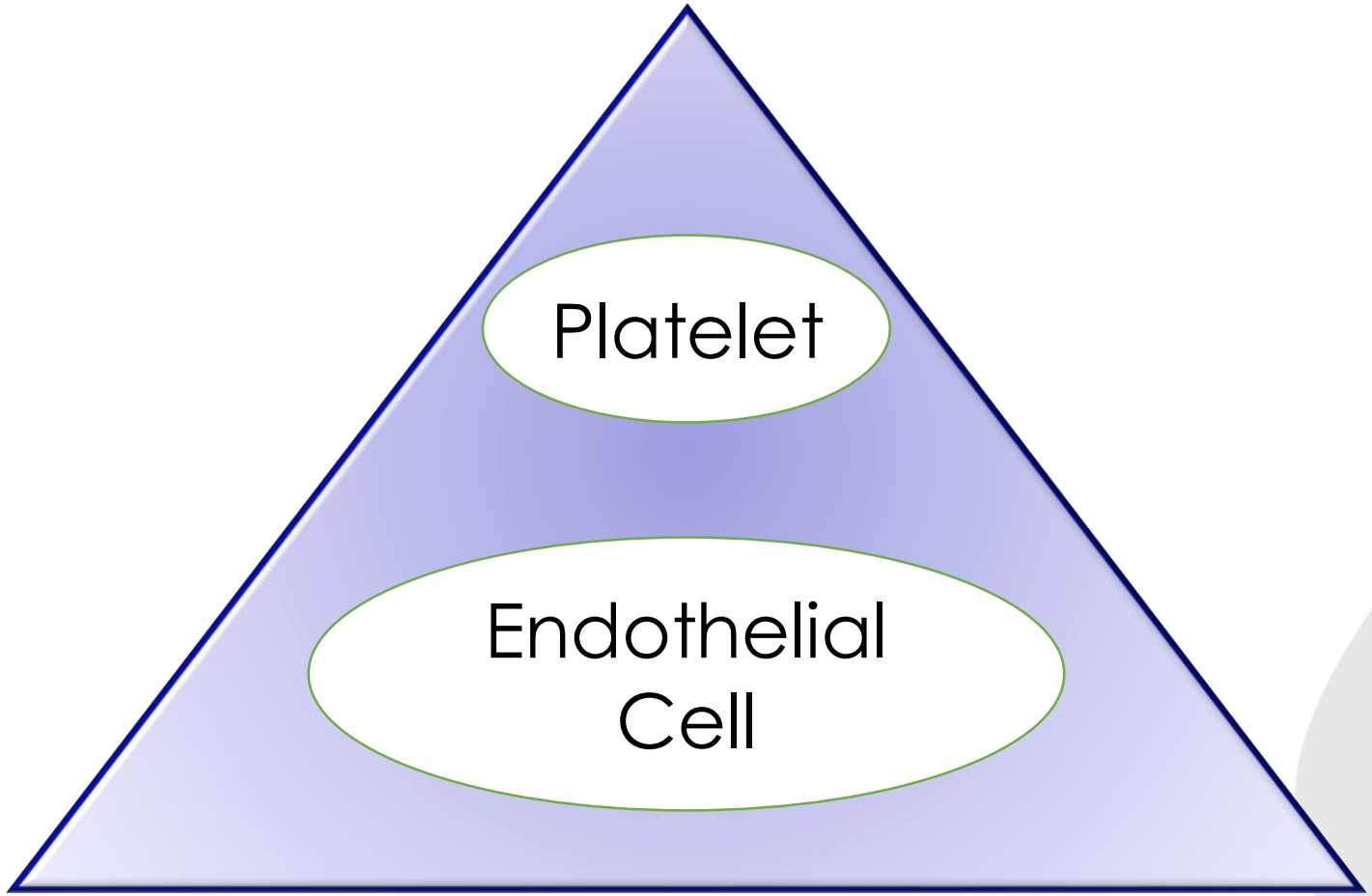
Consulting Fees (e.g. advisory boards): Bayer; Bioverativ; CSL Behring; Genentech; Novo Nordisk; Octapharma; Takeda

Procoagulants



Fibrinolysis

Inhibitors

Role of platelets in hemostasis

- Primary hemostatic plug
- Secretion of substances to promote
  - Platelet recruitment
  - Vessel contraction
  - Coagulation
- Provides optimal surface for coagulation to proceed
  - Phospholipid membrane
  - Optimizes formation of complexes

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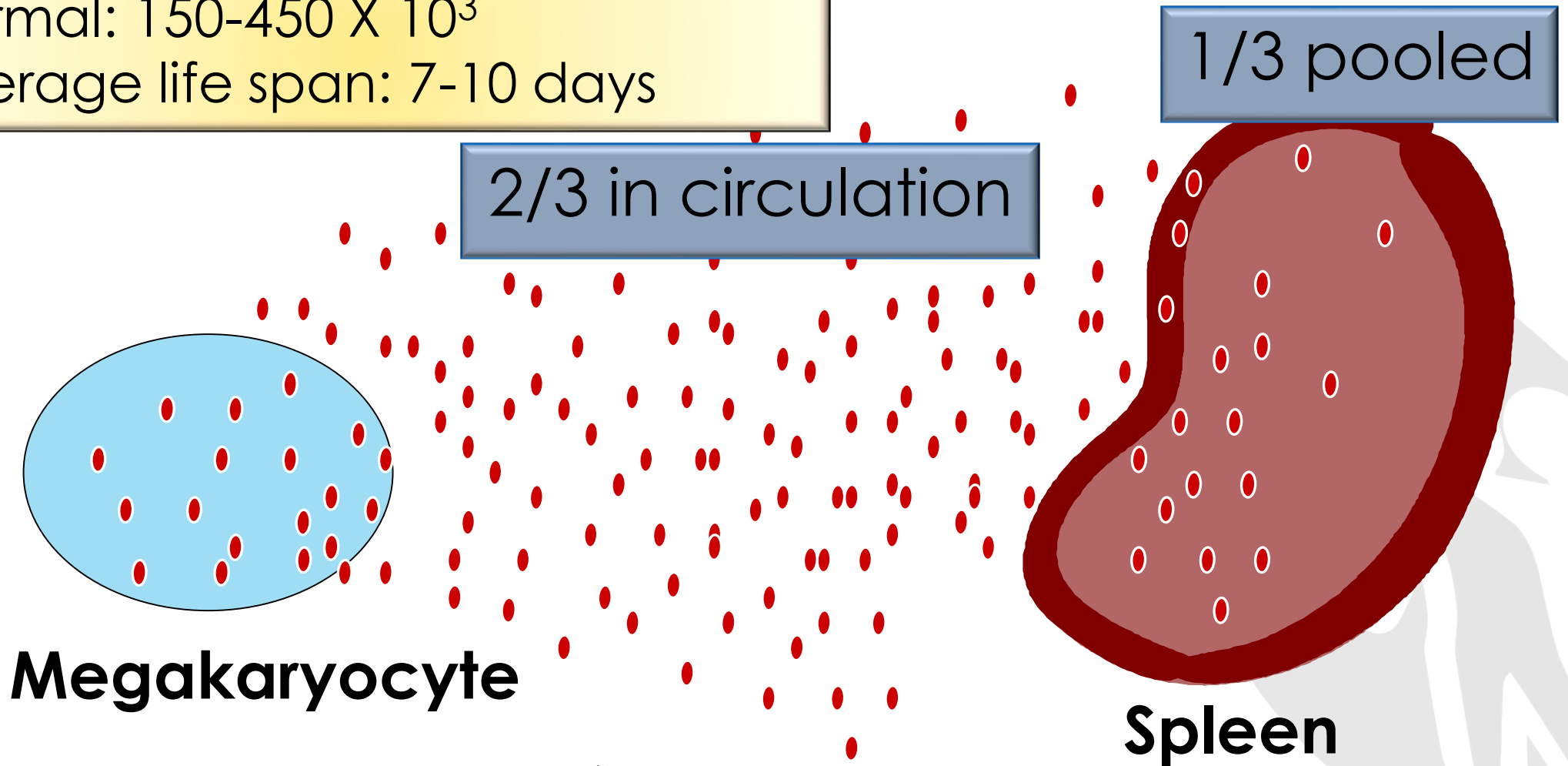
Brass LF, Diamond SL, Stalker TJ. Platelets and hemostasis: a new perspective on an old subject. Blood Adv 2016;1:5-9.

Ware J, Suva LJ. Platelets to hemostasis and beyond. Blood 2011;117:3703-4.

Platelet distribution

Normal: 150-450 X 10^3
Average life span: 7-10 days



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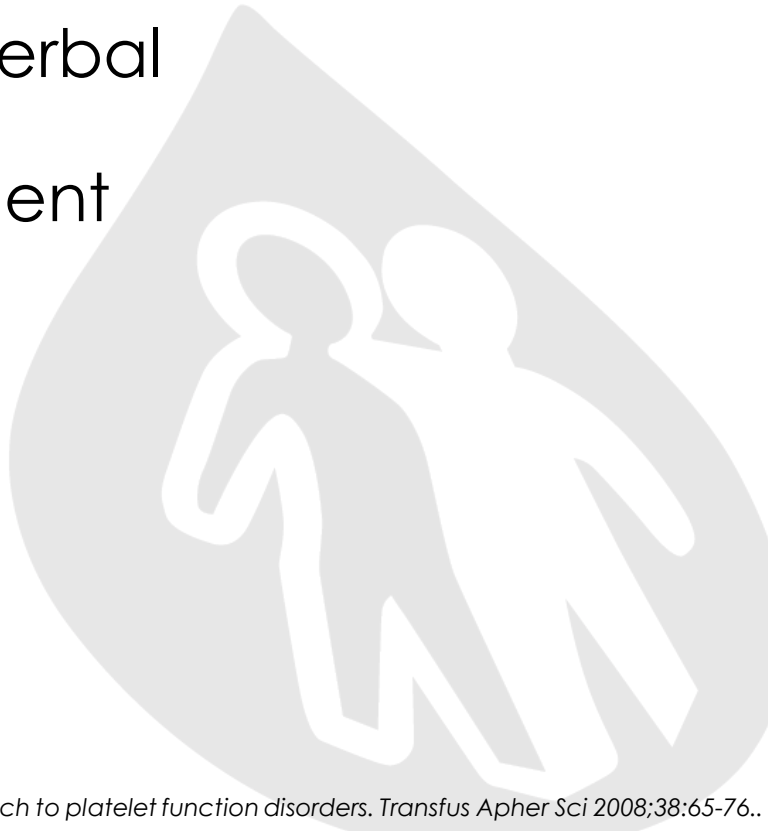
Daly ME. Determinants of platelet count in humans. Haematologica 2011;96:10-3.

Diagnosing platelet disorders

- History
- Physical Examination
- Laboratory Evaluation

Historical assessment of platelet function

- Age of onset of symptoms
  - Young age - inherited
  - Older age - acquired
- Medications
  - Including prescribed, over the counter, and herbal remedies
  - Timing of medications in relation to development of symptoms
- Assess bleeding history of other family members
  - Parent with symptoms (dominant disorders)
  - Parent without symptoms (recessive, X-linked disorders)



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Hayward CP. Diagnostic approach to platelet function disorders. Transfus Apher Sci 2008;38:65-76..

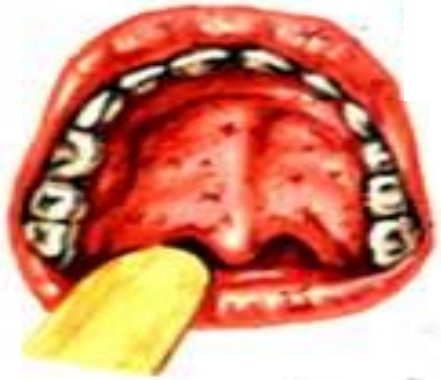
Genetic risk

- Severe congenital platelet dysfunction is rare
  - More common
    - Consanguinity
    - Small geographically isolated communities
- Common secretory deficits
  - Heterozygous mutations are more frequent

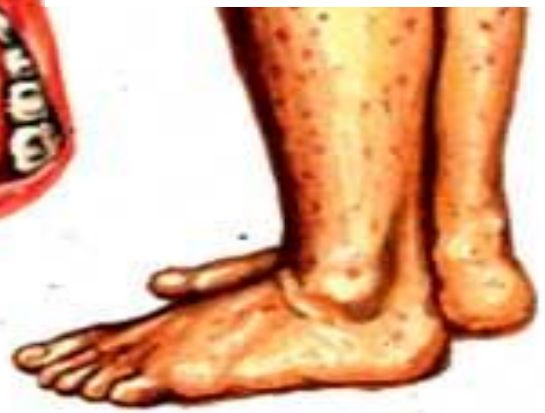
Hinckley J, Di Paola J. Genetic basis of congenital platelet disorders. Hematology Am Soc Hematol Educ Program 2014;2014:337-42.

Physical examination

Cutaneous ecchymoses and hematomas

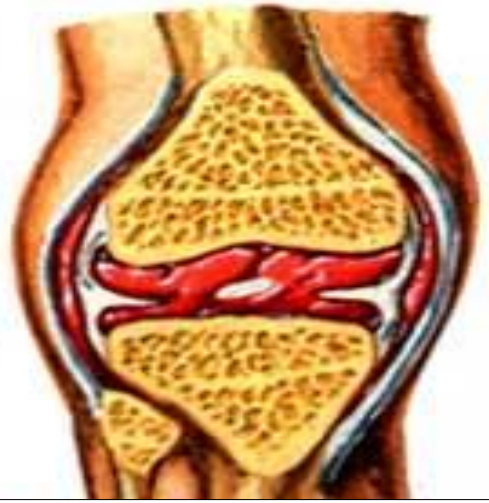


Mucosal or cutaneous petechiae



Jaundice or enlarged liver or spleen

Bleeding into muscles or joints



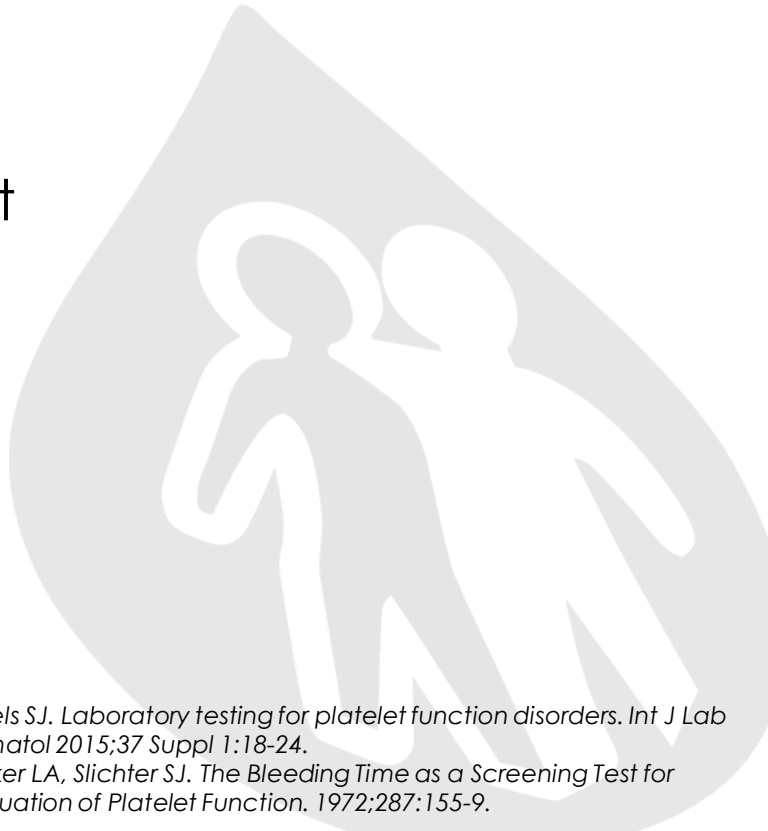
Muscle atrophy and limited range of joint motion

Laboratory evaluation

- Initially bleeding time was used to assess platelet function
  - Challenges
    - Technically difficult
    - Problems with reproducibility
    - May not be good correlate of clinical bleeding

- Majority of platelet function defects have normal platelet count & morphology

- Platelet aggregation studies



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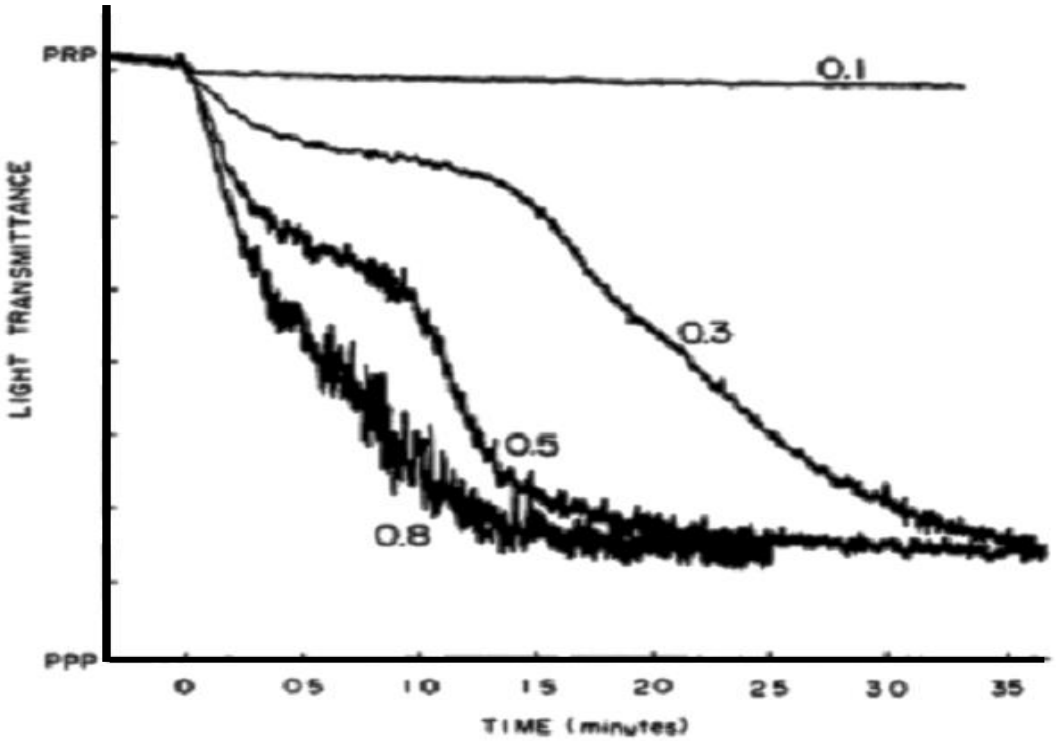
Israels SJ. Laboratory testing for platelet function disorders. Int J Lab Hematol 2015;37 Suppl 1:18-24.
Harker LA, Slichter SJ. The Bleeding Time as a Screening Test for Evaluation of Platelet Function. 1972;287:155-9.

Common agonists used in platelet aggregation studies

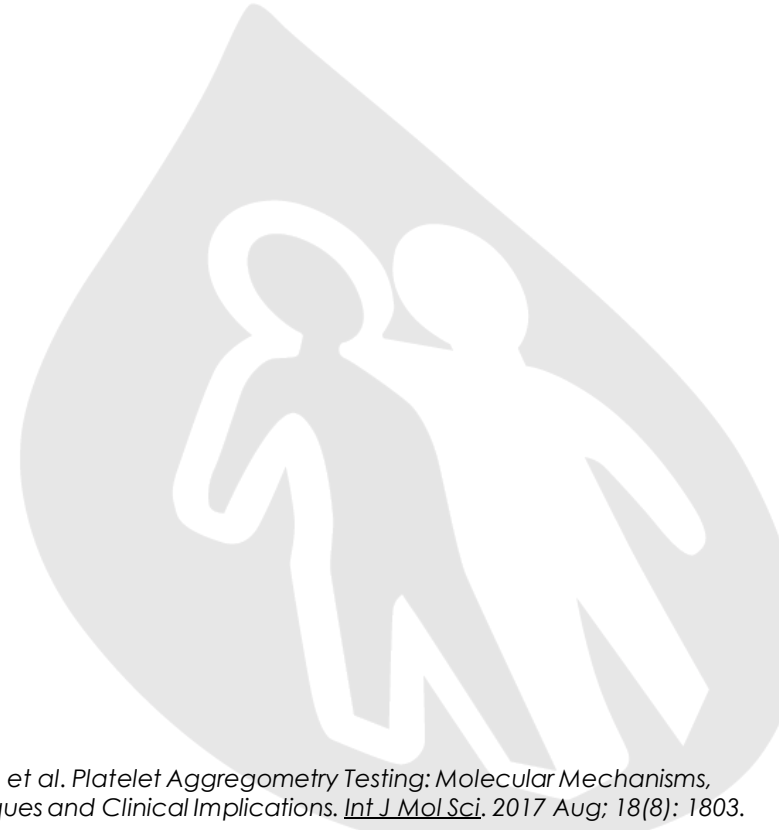


Ristocetin-induced platelet agglutination. Ristocetin at final concentrations indicated (mg/ml) was added to platelet-rich plasma (PRP) in a Payton aggregometer. Normal PRP under similar conditions shows little or no agglutination until ristocetin concentrations exceed 0.5 mg/ml. PPP, platelet-poor plasma

- ADP
- Epinephrine
- Collagen
- Arachidonic acid
- Ristocetin
- Thrombin

Variables impacting platelet aggregation

- Sample collection
- PRP preparation
  - Platelet count in PRP
- Temperature
- Lipemia
- Interval from venipuncture
- Size of cuvette
- Rate of stirring
  - 100 to 1200 rpm
  - Size and shape of stir bar
- Drugs/smoking



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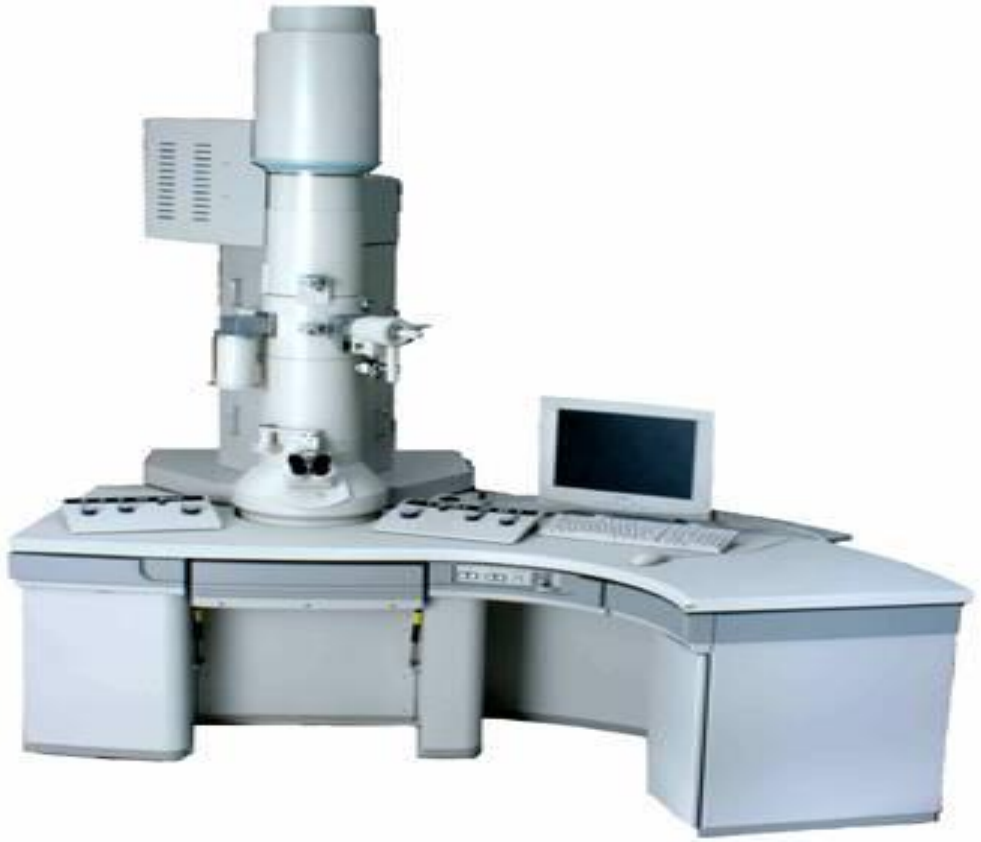
Koltai K, et al. Platelet Aggregometry Testing: Molecular Mechanisms, Techniques and Clinical Implications. Int J Mol Sci. 2017 Aug; 18(8): 1803.

Electron microscopy

- Helps classify some disorders
- Useful tool to differentiate defects of:
  - Cytoskeleton
  - Platelet organelles
  - Membrane defects



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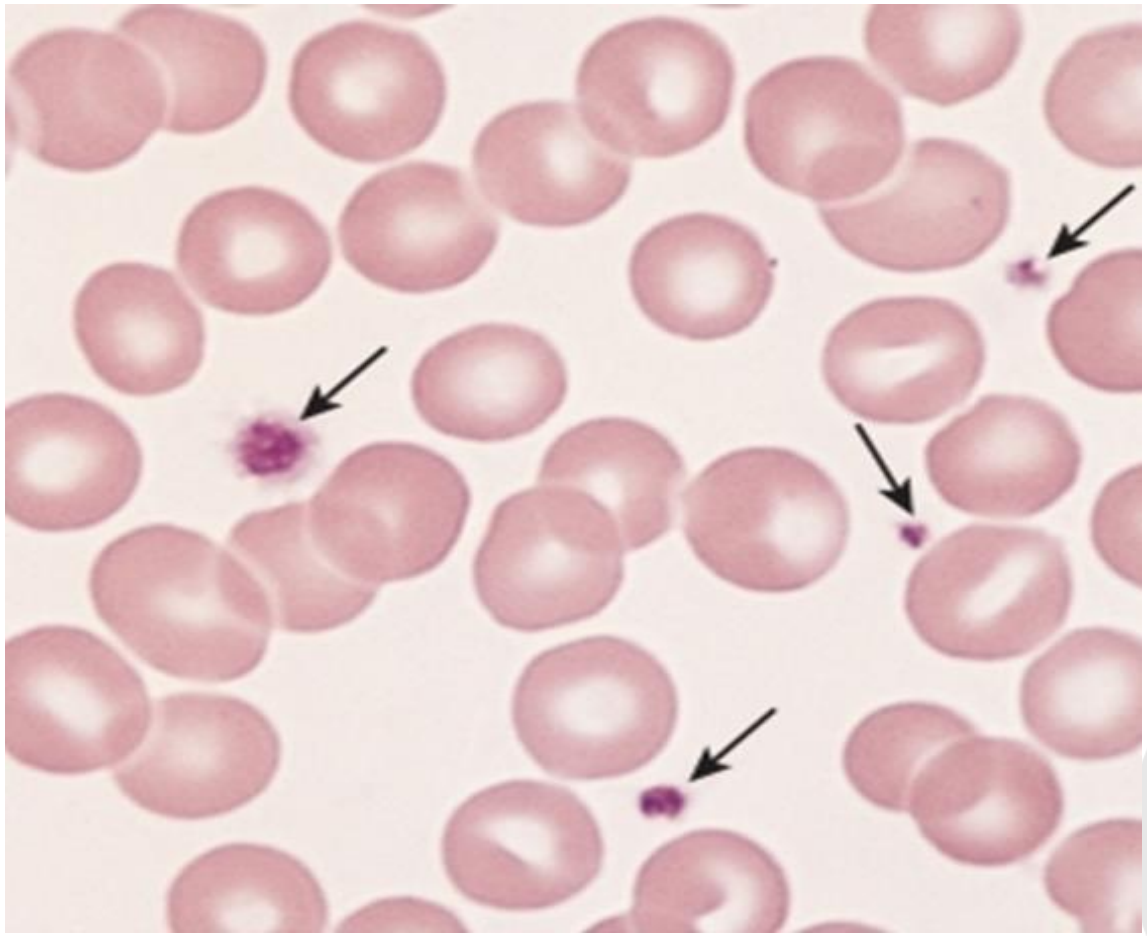
Clauser S, Cramer-Borde E. Role of platelet electron microscopy in the diagnosis of platelet disorders. Semin Thromb Hemost 2009;35:213-23.

Platelet Function



Normal peripheral blood smear showing red blood cells, with arrows designating platelets

Platelet function

- Transformation of inactivated platelets into well formed plug

- Three steps
  - Initiation
  - Extension
  - Cohesion

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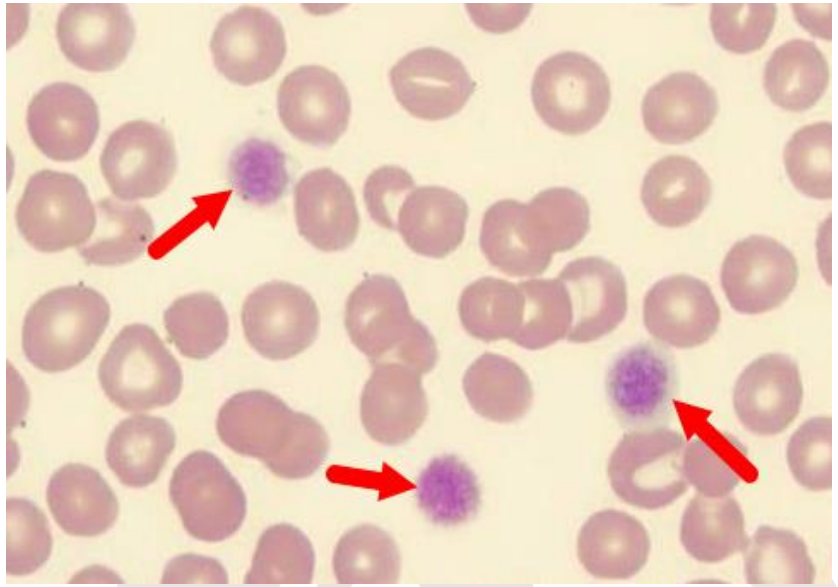
Holinstat M. Normal platelet function. Cancer Metastasis Rev 2017;36:195-8.

Platelet initiation disorders

- Bernard-Soulier Syndrome[1]
  - First described 1948
  - Autosomal recessive
  - Absence of GP-Ib/IX/V receptor
  - Macrothrombocytopenia
  - Loss of function
- Platelet-type VWD (pseudo-VWD or PLT-VWD)[2,3]
  - First described 1982
  - Autosomal dominant
  - Defect of GP-Iba receptor→spontaneous binding of VWF
  - Normal size or macrothrombocytopenia
  - Gain of function

Bernard-Soulier Syndrome, with arrows designating enlarged platelets



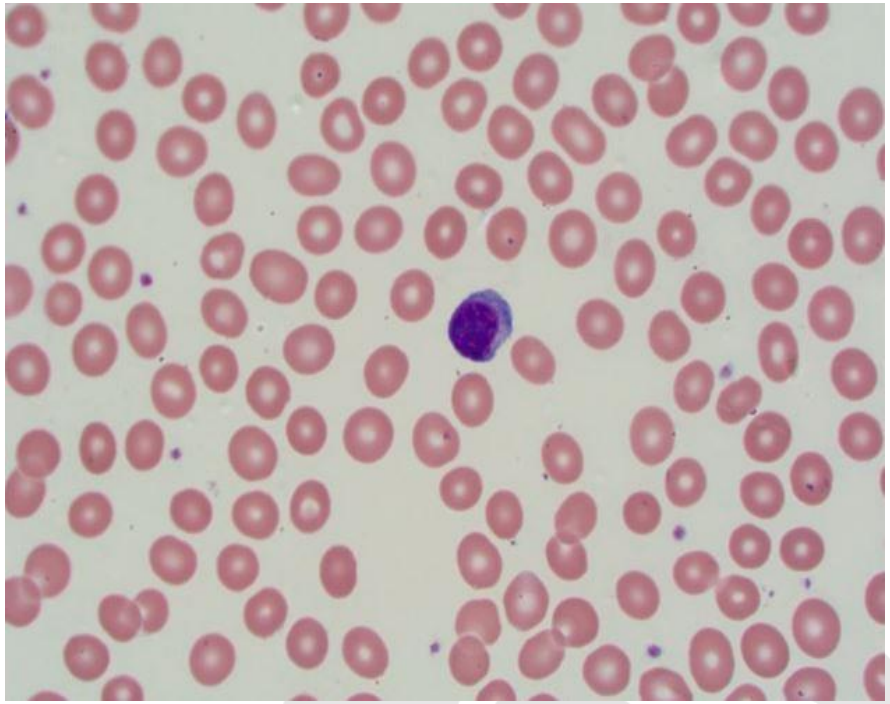
[1]*Bernard-soulier syndrome. Genetics Home Reference, 2016. (Accessed August 10, 2020, at https://ghr.nlm.nih.gov/condition/bernard-soulier-syndrome#sourcesforpage.)*

[2]*Othman M. Platelet-type von Willebrand disease: a rare, often misdiagnosed and underdiagnosed bleeding disorder. Semin Thromb Hemost 2011;37:464-9.*

[3]*Franchini M, Montagnana M, Lippi G. Clinical, laboratory and therapeutic aspects of platelet-type von Willebrand disease. Int J Lab Hematol 2008;30:91-4.*

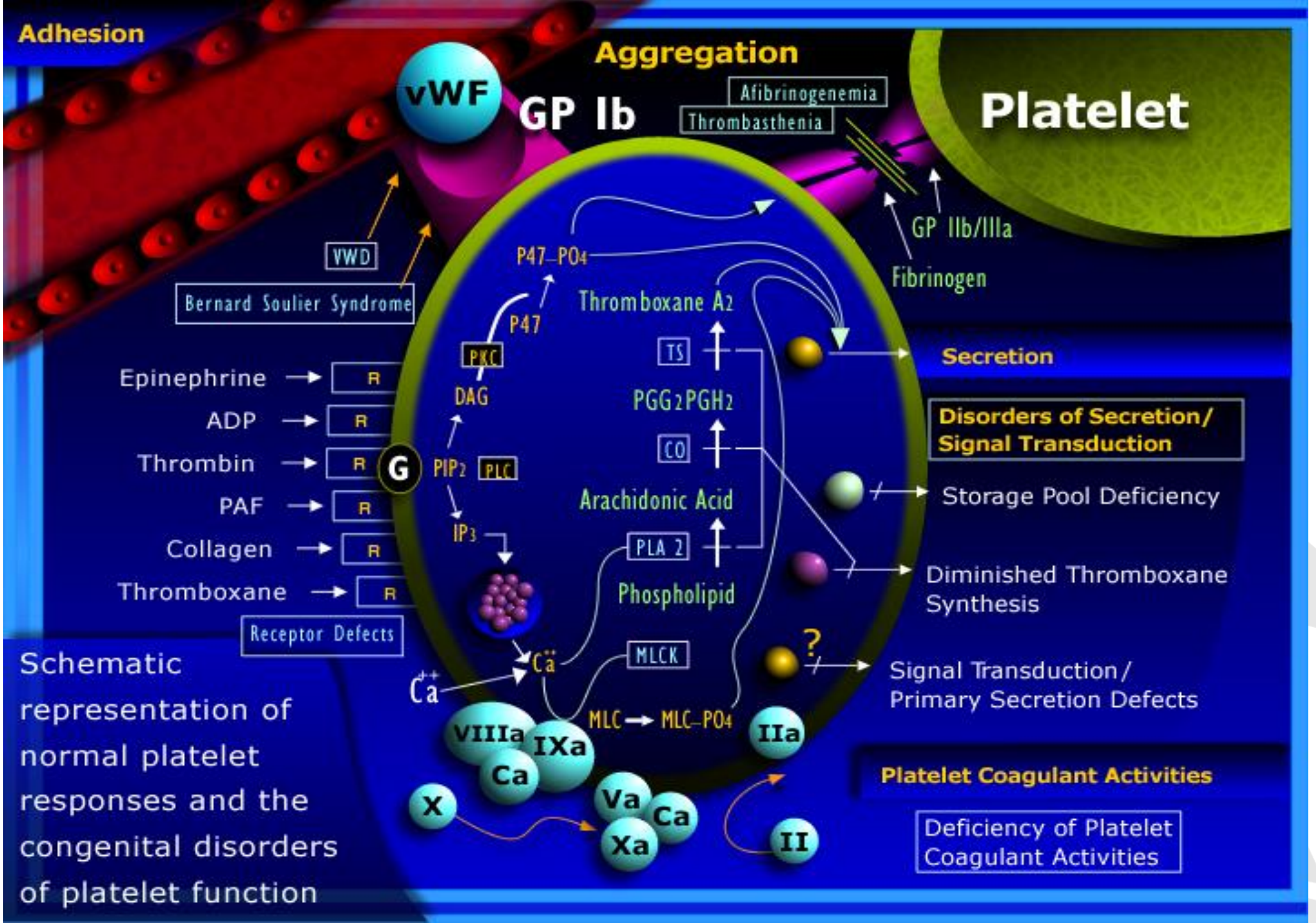
Cohesion defect

- Glanzmann Thrombasthenia
  - First described 1918, Eduard Glanzmann, Swiss pediatrician
  - "Weak" platelets
  - Defect of integrin αIIbβ3, formerly - GP IIb/IIIa receptor
    - Type I (complete absence)
    - Type II (10-20% antigen expression)
    - Type III (normal antigen; abnormal function)
  - Autosomal recessive (chromosome 17)
  - Aggregations show no response to all agonists except ristocetin



Peripheral blood smear showing normal platelet count and morphology seen in Glanzmann thrombasthenia

Solh T, Botsford A, Solh M. Glanzmann's thrombasthenia: pathogenesis, diagnosis, and current and emerging treatment options. J Blood Med 2015;6:219-27. https://www.sciencedirect.com/topics/medicine-and-dentistry/glanzmanns-thrombasthenia; accessed 8-10-20.



Schematic representation of normal platelet responses and the congenital disorders of platelet function

Treatment

- Patient and family education
  - Mucocutaneous bleeding is common
  - Severe hemorrhage
    - Trauma
    - Surgery
    - Gastrointestinal tract
    - Menses
    - Post partum period
  - Medications to avoid
  - Medic Alert
  - Hepatitis A & B immunizations
  - Contact of HTC

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Seligsohn U. Treatment of inherited platelet disorders. Haemophilia 2012;18 Suppl 4:161-5.
Neunert C. Acquired platelet disorders: diagnosis and management. In: Abutalib SA, Connors JM, Ragni MV, eds. Nonmalignant Hematology. Cham, Switzerland: Springer International Publishing; 2016:199-207.

Treatment

- Antifibrinolytic agents
- Desmopressin acetate (DDAVP®, Stimate®)
  - Storage pool disorders usually (but not always) respond
  - Increase in the levels of circulating VWF
  - Effects on platelet function remain undefined
- RBC transfusion if patient anemic
- Iron replacement for iron deficiency
- Recombinant factor VIIa
- Platelet transfusion
- Gene therapy

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Neunert C. Acquired platelet disorders: diagnosis and management. In: Abutalib SA, Connors JM, Ragni MV, eds. Nonmalignant Hematology. Cham, Switzerland: Springer International Publishing; 2016:199-207.
Wilcox D. Blood 2016 Mar 10; 127(10): 1260–1268.

Platelet transfusion

- Used for life threatening bleeding
  - Apheresis unit recommended (~5-6 pooled blood bank units)
    - Minimize multiple donor exposure
      - Can cause sensitization
      - Refractory state
  - Leuko-poor or leuko-depleted
    - Minimize long-term sensitization to HLA class 1 proteins expressed on platelets
- Avoid exposure in disorders with absence of membrane GP
  - GT and BSS
    - Isoantibody or alloantibody can develop
    - Refractory to future transfusions

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Neunert C. Acquired platelet disorders: diagnosis and management. In: Abutalib SA, Connors JM, Ragni MV, eds. Nonmalignant Hematology. Cham, Switzerland: Springer International Publishing; 2016:199-207.

Treatment by disease type

- GT, BSS
  - Major surgery
    - rVIIa
    - HLA platelets (if risk of bleeding with rVIIa)
    - Antifibrinolytic therapy
  - Minor surgery
    - rVIIa-90 mcg/kg immediately prior, every 2 for 12 hours, increasing intervals
      - Higher initial dose for children
      - HLA platelets, antifibrinolytics
      - Dental-rVIIa, antifibrinolytics 5-7 days, topical hemostatic agents

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Poon MC, Di Minno G, d'Oiron R, Zotz R. New Insights Into the Treatment of Glanzmann Thrombasthenia. Transfus Med Rev 2016;30:92-9.
Solh T et al. J BLOOD MED 2015; 6: 219-227. Solh T, Botsford A, Solh M. Glanzmann's thrombasthenia: pathogenesis, diagnosis, and current and emerging treatment options. J Blood Med 2015;6:219-27.
Diz-Kucukkaya R. Inherited platelet disorders including Glanzmann thrombasthenia and Bernard-Soulier syndrome. Hematology Am Soc Hematol Educ Program 2013;2013:268-75.

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- Will implement new ideas/skills?

How could this session be improved?

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