Bleeding Disorders Learning Points

1. *General Points:*

a. This section is concerned with non-thrombocytopenic causes of bleeding.
b. It also excludes non-hematological conditions that cause bleeding manifestations due to vasculitis (eg, Henoch-Schonlein Purpura).
c. The three commonest inherited causes of excessive and/or spontaneous bleeding are (in order of frequency) Von Willebrand's Disease (vWD, sometimes called Hemophilia C), Factor VIII Deficiency (Hemophilia A), and Factor IX Deficiency (Christmas Disease or Hemophilia B).
d. vWD is usually autosomally inherited; factor VIII and IX deficiencies have X-linked inheritance.
e. vWD usually presents with mucosal bleeding, particularly epistaxis, dental and post-surgical bleeding, and menorrhagia. Factor VIII and IX deficiencies present with hemarthroses and intramuscular bleeding, but may also be associated with internal bleeding (eg, subdural hematomas in the newborn). Clinical manifestations usually begin when the child starts to walk and fall frequently. Purpura and petechiae are not usually manifestations of these disorders.
f. Diagnosis depends on suspecting one of these conditions (not infrequently at birth or circumcision), taking a thorough history, particularly a family history, and performing the appropriate laboratory work-up.
g. Secondary causes of excessive bleeding not primarily or solely due to platelet deficiency or dysfunction include liver failure (due to non-synthesis mainly of factors II, VII, IX, and X, that are made in the liver), septic shock and DIC, excessive consumption of coagulation factors, particularly due to catastrophic blood loss, excessive tissue trauma and burns.

2. V*on Willebrand's Disease*

a. Von Willebrand's Disease is an autosomal dominant disorder, marked by platelet non-adhesion to damaged endothelium secondary to decreased vWD antigen, which (a) facilitates platelet adhesion and (b) is the carrier protein for Factor VIII (Factor VIII coagulant: VIII:C). Both the factor VIII antigen and coagulant are low in vWD, usually between 20% and 50%, while in classical hemophilia A only the coagulant is low usually less than 1% to 10%).
b. By history, these patients will often have a positive family history (on either parental line) of nose bleeds, excessive bleeding after surgery or menorhagia.
c. Primary laboratory screening assay includes a platelet function assay (PFA), which has replaced the now defunct bleeding time, and which reproduces the in vivo interaction between the vascular endolelium, platelet adhesion, and vWF interaction. If this value is normal most hematologists do not recommend further laboratory evaluation.
d. If the PFA is abnormal, definitive laboratory testing is performed. This should include a PTT (usually prolonged), factor VIII antigen and coagulant (activity), vWF multimers (normal in Type I vWD but abnormal in Type II and III vWD), and ristocetin cofactor (low in Type I and Type II, and undetectable in Type III).
e. Treatment for Type I vWD is usually with desmopressin or DDAVP, which causes increased release of endogenous Factor VIII from endothelial cells. It can be given IV or more often by nasal spray, in a dose of 1 150 mcg spray in 1 nostril

(under 50kg) or in both nostrils (over 50kg). This is given q12hrs for a maximum of 3 days (because of its antidiuretic effect). Aminocaproic acid (Amicar) is often used as supplementary therapy after dental or other surgery because of its antifibrinolytic property. The dose is 100mg/kg (max 30g/24 hrs) IV or oral (swish and spit after dental surgery), with a loading dose if possible beforehand, then every 4 hours for 5+ days. For more major bleeding, or for vWD Types II and III, semi-purified factor VIII concentrates must be used, that contain the entire factor VIII/vWF complex, must be used. The more recent genetically engineered facto VIII concentrates do not contain vWF.

3. *Hemophilia*

a. X-linked disorders marked by spontaneous bleeding usually muscle or joint bleeds.
b. Severe disease (less than 1% Factor VIII (Hemophilia A) or Factor IX (Hemophilia B) – is seen in the majority of patients.
c. Moderate disease indicates a factor level between 1% and 5%.
d. Mild disease indicates a factor level greater than 5%.
e. Although mildly and moderately affected patients rarely bleed spontaneously, all patients tend to bleed excessively after trauma.
f. Genetically engineered recombinant factor replacement is the treatment of choice. There is no proven advantage to one over another.
g. 1 unit/kg of factor VIII raises the plasma level by 2% for 12 hours (half life = 8-12 hrs); 50 units/kg raises the level to 100%. Continuing doses of 25 units/kg every 8-12 hours will usually maintain 100% factor levels.
h. Because of its longer half-life (16-24 hrs), 1 unit/kg of factor IX raises the plasma level by 1% for 24 hours or 100 units/kg will raise levels to 100%. Continuing doses of 50 units/kg every 12 hours will maintain 100% factor levels.
i. At age of 3-4, or earlier if there are frequent early bleeding episodes, patients start on prophylactic therapy. This consists of 50% replacement (25 units/kg Factor 8 or 50 units/kg Factor 9) 3 times per week. An infusaport is usually inserted in younger patients. Patients from about aged 10 can usually learn to give their own IV infusions.
j. Following muscle or joint bleeds, the factor level should be corrected to 50%, while for CNS bleeds, other internal or life-threatening bleeding, or major surgery, levels should be maintained at 100% for several days.
k. For elective surgery, standard orders are available, that usually include the use of a continuous infusion (CI) of factor, which is cost-effective in maintaining an adequate level with less overall factor replacement. This includes guidelines for laboratory monitoring of factor levels and sliding scales for extra bolus doses according to levels obtained.
l. Regular follow-up by a trained pediatric hematologist is essential. Patients should be screened for understanding of their condition, compliance with the prescribed regimen, recurrent joint bleeding (“target joints”), dental care, LFT’s and hepatitis if they have received non-recombinant factor, and factor VIII antibodies. Dose adjustments should be made to allow for growth. An orthopedic surgeon and dentist trained in hemophilia care should see all patients regularly.
m. The table lists the laboratory findings in these three and other rarer coagulation disorders.

Table: Laboratory Findings in Coagulation Disorders

Disorder	Platelet Fxn	PTT	PT	TT	Ancillary Tests
	Assay				
Hemophilia A	N	A	N	N	vWF normal or increased, Factor VIIIC usually under 5%
Hemophilia B	N	A	N	N	Factor IX usually under 5%.
von Willebrand's disease	A	A	N	N	vWF and F VIIIC usually 20%-50%, ristocetin-induced platelet aggregation and ristocetin cofactor activity usually low.
Afibrinogenemia	A	A	A	A	Fibrinogen low; platelet function may be abnormal
Dysfibrinogenemia	N	A	A	A	Reptilase time prolonged, FDP levels increased.
Hypoprothrombinemia	N	A	A	N	Two-stage assay abnormal.
Factor V deficiency	N	A	A	N	Factor V level low
Factor VII deficiency	N	N	A	N	Factor VII level low; Russell's viper venom time normal.
Factor X deficiency	N	A	A	N	Factor X level low; Russell's viper venom time abnormal.
Factor XI deficiency	N	A	N	N	Factor XI level low
Factor XII deficiency	N	A	N	N	Factor XII level low
Factor XIII deficiency	N	N	N	N	Clot solubility tests abnormal.

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