Coagulation, bleeding and thrombosis (Part 2)

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Hemophilia treatment modalities

1. Supportive.
2. Factor replacement
3. Desmopressin (DDAVP)
4. Antifibrionlytic therapy

Factor replacement

Prophylaxis: primary, secondary , tertiary. For all severe pateints and moderate with frequent bleeding.

Bleed treatment.

Prior to procedures.

Dose

Prophylaxis: all severe patients and some moderate

FVIII: 25-40 IU/kg/dose 3x per week.

FIX: 50-100 IU/kg/dose 2x per week.

On demand: all mild and most moderate:

Bleed Location	Treatment	Comments
Intracranial	100% correction for at least 2 weeks	Continue treatment with prophylaxis dosing indefinitely
Retroperitoneal	80% correction for at least a few days	Follow up with short-term prophylaxis (weeks)
Muscle	40-60% correction	At least until can utilize muscle with no pain
Joint	40-60% correction	Generally 1-3 doses suffices
Mucosal	30-50% correction	Add antifibrinolytics
Subcutaneous hematomas	Observation is generally sufficient	Large hematomas in “bad” locations (buttocks) need factor
Surgery	100% correction pre-op	Maintain trough of 50% until risk for bleeding is over

Factor dosing

FVIII—1 IU/kg increases factor level by ~2%

FIX—1 IU/kg increases factor level by ~1% (plasma derived factor)

For recombinant FIX, 0.7% per IU/kg for patients <12 years and 0.8-0.9% for patients >12 years.

Desmopressin

Antifibrynolytics

Hematuria

FACTOR REPLACEMENT: CORRECT FACTOR LEVEL TO 80-100%

HYDRATION: 1.5-2X MAINTENANCE

ANTIFIBRINOLYTIC AGENTS ARE CONTRAINDICATED

Failure of Factor Replacement

Not enough dose.

Inhibitor.

Inhibitor

- Inhibitor: a neutralizing antibody, measured by Bethesda unit
- factor replacement becomes less effective or ineffective
- Bleeds are more difficult to treat
- Prophylaxis is not nearly as effective
- Inhibitor patients have worse morbidity

Risk factors for inhibitor development

- Disease severity
- Race
- Family history
- mutation

Management

Immune tolerance

Bypassing agents (FVIIa, APCC)

Low titer inhibitor (less than 5 BU) responds to higher prophylaxis dosing.

With high titers (more than 5 BU), stop prophylaxis.

von Willebrand disease

- Most common bleeding disorder
- Symptoms:

  Mostly mucocutaneous bleeding except type 3

  Type 3 have mucocutaneous bleeding and hemophilia-like bleeding
- Epistaxis, easy bruising, oral bleeding, post-surgical (oropharyngeal) bleeding
- Menorrhagia and post-partum bleeding in females of child-bearing age

von Willebrand factor

- vWF function:

  Platelet binding

  Carrier molecule for FVIII

- vWF is increased by physiologic stress, DDAVP, estrogen, pregnancy, and is an acute phase reactant

Types

A) Type 1(AD): Heterozygous defect, reduced production of normal vWF
B) Type 2A (AD): Multimerization defect, absent large/intermediate size multimers
C) Type 2B (AD): Gain of function mutation (too adherent to platelets so large multimers are attached to platelets and not circulating)
D) Type 2M (AD): Loss of function mutation (opposite of 2B), vWF doesn't bind well to platelets
E) Type 2N (AD): Loss of vWF binding function to FVIII
F) Type 3 (AR): Absence of vWF production

Lab testing

- PT is normal, PTT is only abnormal if FVIII is low.
- VWF antigen: doesn’t assess function
- Platelet aggregation based test assessing vWF platelet binding function
- Factor VIII activity (same assay as for hemophilia)
- vWF multimer analysis: Assesses molecular structure of vWF

VWF Levels: Influence of Blood Type

Blood Type	Lower VWF:Ag Limit
Type O	35.6 U/dL (mean 74.8 U/dL)
Type A	48.0 U/dL (mean 105.9 U/dL)
Type B	56.8 U/dL (mean 116.9 U/dL)
Type AB	63.8 U/dL (mean 123.3 U/dL)

Treatment

- Increase circulating vWF: Desmopressin (DDAVP), releases stored vWF from Weibel-Palade bodies in endothelium
- Replacement with plasma-derived vWF concentrate
- Hormonal therapy: Effective for menorrhagia management

  Estrogen increases vWF and FVIII

  Reduces blood flow to endometrium
- Topical therapy

  Antifibrinolytics for oral bleeding

  Topical thrombin for oral or nose bleeding

Factor	Bleeding pattern	Other features
Fibrinogen (I)	Post-trauma/surgery Soft tissue	Splenic rupture Pregnancy loss
Prothrombin (II)	Similar to hemophilia?	Extremely rare
Factor V	Similar to hemophilia?	Extremely rare
Factor VII	Similar to hemophilia (mild, moderate, severe based on levels)	Intracranial hemorrhage can occur
Factor X	Intracranial hemorrhage relatively (to other deficiencies) common	
Factor XI	Post-trauma/surgery Mucocutaneous	Common in Ashkenazi Jews Most patients don't bleed
Factor XIII	Umbilical stump bleeding Intracranial hemorrhage common	Highest (relative) prevalence of causing intracranial hemorrhage

Dysfibrinogenemia

- Rare inherited disorder due to a dysfunctional fibrinogen
- Can cause bleeding or thrombosis

  Thrombosis due to dysfibrinogens which resist fibrinolysis
- Lab findings: prolonged TT, abnormal ratio of fibrinogen antigen to fibrinogen function
- Treatment

  Bleeding: Replace with pd-fibrinogen concentrate or cryoprecipitate

  Thrombosis: Anticoagulation

Prolonged thrombin time

- Due to:

  Absent or very low fibrinogen

  Dysfibrinogenemia

  Heparin contamination
- Ensure that there is no heparin contamination
- Measure functional fibrinogen
- If normal, measure fibrinogen antigen and function together to assess for dysfibrinogens

Natural Anticoagulant proteins

Protein C, protein S, anti-thrombin

Reduced at birth

Interpret results in first year of in the context of age appropriate values.

Liver disease leads to deficiency and decreased clearance of activated factors increasing risk of coagulopathy and thrombosis.

Thrombophilia

- Predisposition to develop thrombi
- Examples of venous thrombotic events (VTE):

  Deep vein thrombosis (DVT),

  Pulmonary embolism (PE)

  Cerebral Sino venous thrombosis

  Renal vein thrombosis

  Portal vein thrombosis

  Mesenteric.
- Arterial events : arterial ischemic stroke and catheter-related events.

Causes

Inherited:

Antithrombin deficiency

Protein C deficiency

Protein S deficiency

Factor V Leiden mutation

Prothrombin G20210A mutation

Dysfibrinogenemia

Hyperhomocysteinemia

Elevated FVIII

Elevated lipoprotein A.

Acquired:
Antiphospholipid antibody syndrome (APS)
Anticardiolipin
Anti-β2 glycoprotein
Lupus anticoagulant
Some medical conditions such as malignancies, bed ridden state etc.

Antithrombin

Made in liver

Neutralizes thrombin (IIa), Xa, and IXa.

Reaches adult levels by 12 months of age.

Heparin potentiates its activity.

2 binding sites: Heparin binding site and a reactive center.

Deficiency can be congenital or acquired such as: DIC, sepsis, burns, trauma, liver disease, nephrotic syndrome or heparin

AT deficiency results in thrombotic events, mainly venous.

High rate of recurrence

Homozygous state results in fetal demise

Protein C

- Vitamin K dependent protein produced in the liver.
- Needs to be activated by thrombin/thrombomodulin complex.
- Deficiency is autosomal Dominant.
- Levels low in infancy and don’t normalize until adolescence.
- Acquired Causes of deficiency: Liver disease, DIC, sepsis, uremia.
- 70% spontaneous thrombosis risk, mainly venous
- High risk of recurrence.
- Purpura fulminans, ophthalmologic injury, renal injury, and neurologic complications in neonates.
- Requires anticoagulation for life.

Protein S

- Vitamin K dependent
- Produced in liver, endothelial cells, platelets and brain cells.
- Reaches adult levels by 12 months of age.
- A rare congenital deficiency.
- Acquired causes: estrogen, OCPs, Pregnancy, DIC, Liver disease, Acute thrombosis and Inflammatory states.
- Majority of cases are venous with high recurrence rates.

Factor V Leiden mutation

increases the risk for venous thrombosis.

It causes activated protein C resistance.

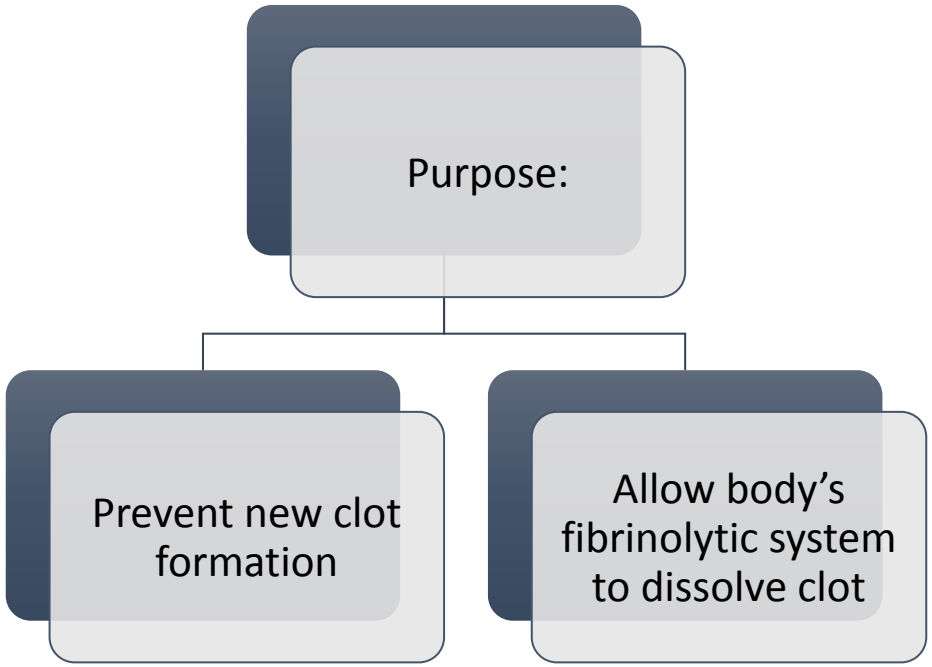
If the mutation is heterozygous the risk of recurrence is low..

Antiphospholipid syndrome

Ppresence of antiphospholipid antibodies or lupus anticoagulant for ≥ 12 weeks in context with an acute thrombotic event .

Venous or arterial thrombosis can occur, recurrent pregnancy loss < 10 week gestation and premature delivery or fetal demise >10 week gestation

Anticoagulation



Heparin

- Binds to antithrombin (cofactor) increasing antithrombin's inhibition of thrombin (factor IIa) and factors IXa, Xa, XIa, XIIa, and kallikrein.
- Binds non-specifically to plasma proteins / platelet derived proteins.
- Short half-life
- Can be reversed with protamine sulfate and is excreted by kidney.
- Risk of HIT.
- aPTT is very sensitive to heparin contamination.
- Monitoring is commonly done by PTT (Target range 65-80 seconds or 1.5-2.5X baseline). Measure every 4 hours and once therapeutic, daily.

HIT, score 6-8= more than 80% probability

	2	1	0
Thrombocytopenia	> 50% platelet count fall to nadir ≥ 20	30-50% platelet count fall to nadir 10-19	<30% platelet count fall to nadir ≤ 10
Timing of fall in platelet count or other sequelae	Onset d 5-10 or < 1 d (if heparin exposure within 30 d)	> d 10, or timing unclear, or < d 1 with recent heparin 31-100 d	Platelet count fall < d 4 (without recent heparin exposure)
Thrombosis or other sequelae	New thrombosis; skin necrosis; post-heparin bolus acute systemic reaction	Progressive or recurrent thrombosis; erythematous skin lesions; suspected thrombosis – not confirmed	None
OTher cause for thrombocytopenia	No other cause for platelet count fall is evident	Possible other cause is evident	Definite other cause is present

Direct thrombin inhibitors

Not commonly used in pediatric patients

Unless in cases like heparin induced thrombocytopenia where alternatives to both unfractionated and low molecular weight heparin need to be used.

Most of them have a very short half- life (around 1 hour or less) and most don’t have antidotes.

Direct Thrombin Inhibitors

	Argatroban	Lepirudin	Bivalirudin
	Synthetic L-arginine derivative	**Recombinant hirudin**	**Semi-synthetic hirulog**
Half-life in healthy subjects	39-51 min	1.3 hours	25 minutes
Elimination	Hepatic	Renal	80% Enzymatic 20% Renal
Monitoring needed	aPTT, ACT	aPTT	aPTT, ACT
Thrombin binding	Reversible	Irreversible	Partially reversible
Antidote	None	None	None

Low molecular weight heparin

- AT mediated, Xa and partial IIa inhibition.
- <50% the molecular weight unfractionated heparin, reducing anti-IIa activity due to its small MW.
- It carries Less risk of HIT
- Partially reversible with protamine sulfate.
- Renally cleared
- Levels 4-6 hours after dosing, goal 0.5 to 1.0 U/ml for treatment.

Fondaparinux

Works by AT mediated selected inhibition of Xa, is renally and is not reversible.