# Monitoring Intraoperative Hemostasis

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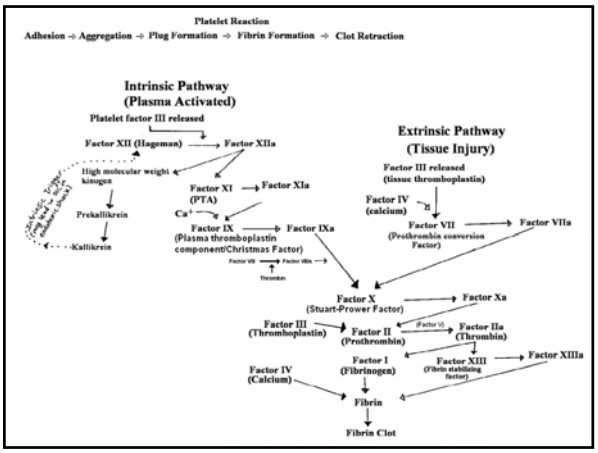
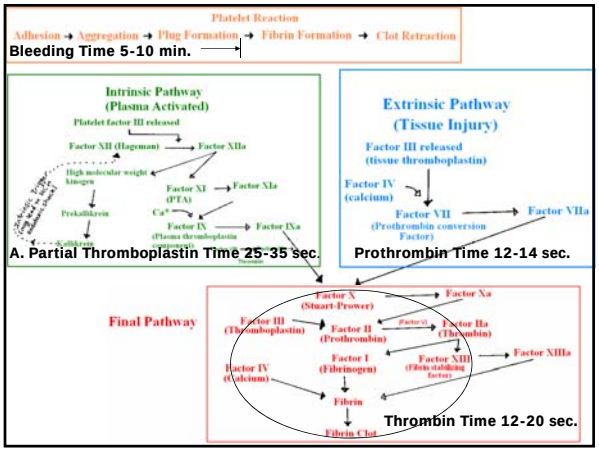


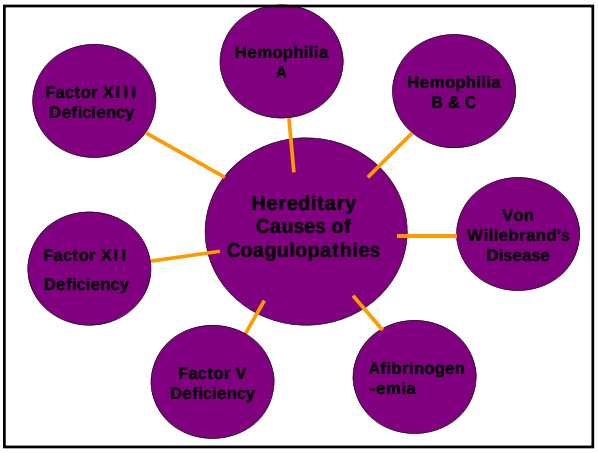




## Coagulation Factors

I. Fibrinogen Hypofibrinogenemia, leukemia, liver disease, DIC
II. Prothrombin Hypothrombinemia, liver disease, Vit K deficiency, ASA
III. Thromboplastin Thrombocytopenia
IV. Calcium Hypocalcemia, malabsorption, malnutrition, hyperphosphatemia, citrate
V. Proaccelerin Parahemophilia, liver disease
VI. -
VII. Proconvertin Hepatitis, liver cancer, vit K deficiency, antibiotics, anticoagulants
VIII. Antihemophilic Factor Hemophilia A, DIC, Myeloma, Lupus

## Coagulation Factors

IX. Plasma Thromboplastin Component (Christmas) Hemophilia B
X. Stuart-Prower Liver disease, vit. K deficiency, anticoagulants
XI. Plasma Thromboplastin Antecedent Hemophilia C, congenital heart disease, malabsorption of vit. K, liver disease
XII. Hageman Factor Liver disease
XIII. Fibrin Stabilizing Factor Agamaglobulinemia, myeloma, lead poisioning

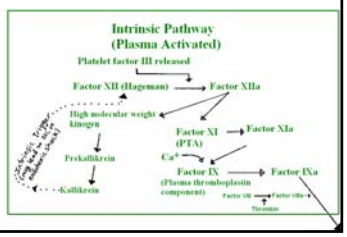


## Hemophilia A

- X-linked recessive
- 1 in 10,000 males
- Defective or deficient Factor VIII:C
- Have normal amount of vWF
- Screen via PTT
- Establish pre-op VIII >40% of normal, ideally 100%
  - Cryoprecipitate, factor VIII concentrate, or DDAVP

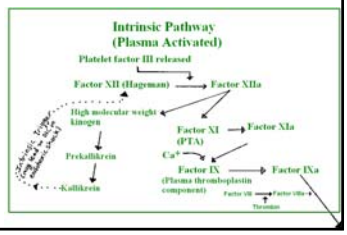
## Hemophilia B

- X-linked deficiency in factor IX
- Bleeding tendency, indistinguishable from Hemophilia A
- Treat with factor IX concentrate, to keep > 30% of normal
- PTT prolonged



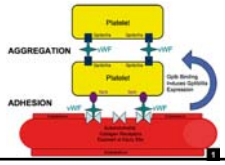

## Hemophilia C

- Recessive defect in gene for FXI
- Bleeding tendency, either sex, less prevalent intra-articular
- Bleeding after surgery or injury often first sign
- PTT prolonged;
- PT, TT normal
- Rx: FFP, FXI, rFVII




## Von Willebrand's Disease

- Autosomal dominant (both sexes)
- Deficient vWF, which adheres platelets to exposed endothelium
- Hx of bruising; esp. mucosal bleeding
- DDAVP, Factor VIII (that preserves vWF), or cryoprecipitate



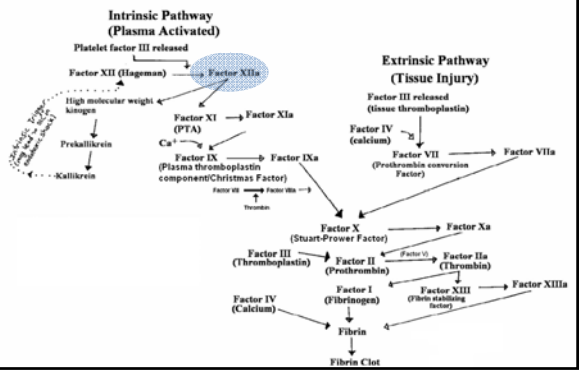

## Afibrinogenemia

- Congenital absence
- Umbilical cord bleeding 1st sign
- Bleeding time, PT, PTT, TT prolonged
- Treat with cryo to raise fibrinogen >50 mg/dl

## Factor V deficiency

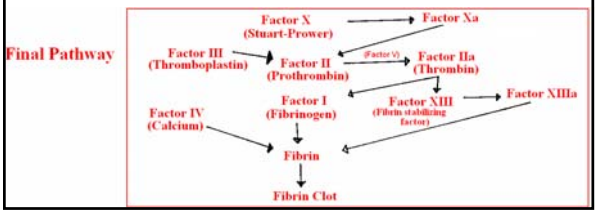
- Autosomal recessive
- Usually mucous membrane bleeding
- BT, PT, PTT prolonged
- Treat with FFP

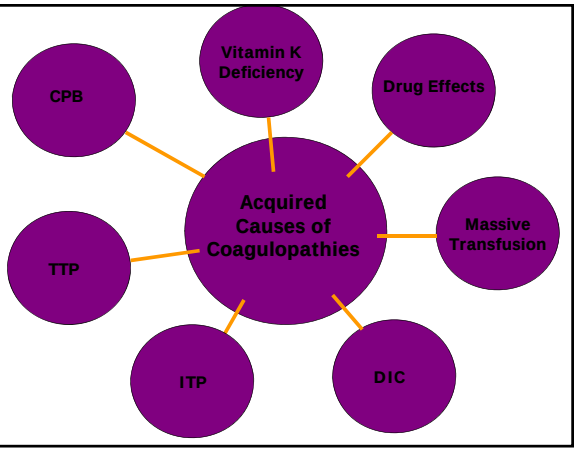
## Factor XII deficiency




## Factor XIII deficiency

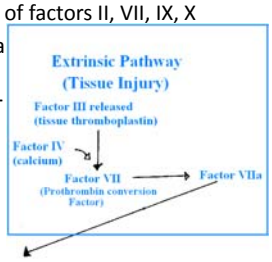
- Congenital inability to form insoluble fibrin
- CNS hemorrhage common
- Routine coag. tests will miss it
- Treat with FFP or cryo




## Vitamin K Deficiency

- Necessary for production of factors II, VII, IX, X
- Due to malnutrition, mala
  obstructive jaundice
- Prolonged PT, normal PTT
- FFP if immediate need,
  or Phytonadione




## Vitamin K antagonist reversal

- Lypholyzed II, VII, IX, X + protein C & S
- Dose 25-50 units (based on Factor IX), depending on INR
- Should bring INR < 1.3 within 30 min
- Serious thromboembolic complications possible- indicated only for acute, emergent bleeding from vit K antagonists

## Vitamin K

## Drug effects

- Heparin- long PTT usually normal PT
- Coumadin- prevents carboxylation of vit K
  - PT prolonged (as in Vit. K deficiency)
- Aspirin- inhibits COX-1
  - Bleeding time prolonged within 3 hours
  - Platelets affected for life (10 days)
  - Reverse with platelet transfusion
  - Bleeding time < 10 min for surgery
  - ? Safety of spinal/epidural
- Herbs- Many prolong bleeding

## Low Molecular Weight Heparin

- Subcutaneous, peak in 3-5 hours, clearance independent of dose, requires 12 hours to subside
- Delay regional placement 12 (24) hours after last dose
- Delay start of therapy for 24 hours following bloody aspiration
- Remove catheter 2 hours prior to start of therapy
- Delay catheter removal for 12 hours after last dose
  - Thames, B.C., Allen, D. (2000) AANA Journal Course: Update for Nurse Anesthetists- Low Molecular weight heperin: Pharmacology and regional anesthetic implications. *AANA Journal* 64(4) 357-364.

## Follow ASRA Guidelines

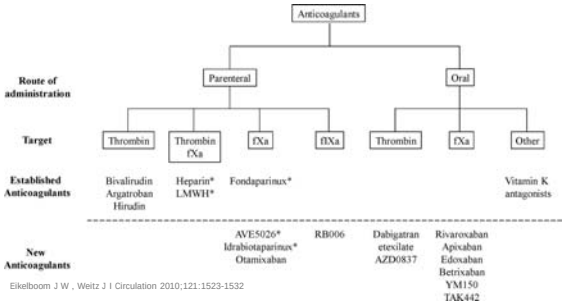
- Of incidences of epidural hematoma over past 40 years, almost all have corresponded with patients being on anticoagulant drugs.

## Epidural Hematoma

- Weakness
- The block that lasts too long
- Back pain with radicular component
- Sensory deficit

- Prompt recognition (MRI) and treatment are crucial

## Other new anticoagulants



Eikelboom J W , Weitz J I Circulation 2010;121:1523-1532

## Platelet Inhibitors

- Abciximab (Rheo-pro)
- Anagrelide (Agrylin)
- Cilostazol (Pletal)
- Clopidogral (Plavix)
- Ticlopidine (Ticlid)
- Eptifibatide (Integrilin)
- Ticagrelor (Brilinta)
- Tirofiban (Agrastat)

## Regional anesthesia and anticoagulants

**Regional anaesthesia in the patient receiving antithrombotic and antiplatelet therapy**

| Agent | Effect on coagulation variables | | Time to peak effect | Time to normal haemostasis after discontinuation |
|---|---|---|---|---|
| | PT | APTT | | |
| I.V. heparin | ↑ | ↑↑↑ | Minutes | 4–6 h |
| Subcutaneous heparin | – | ↑ | 40–50 min | 4–6 h |
| Low molecular weight heparin | – | – | 3–5 h | 12–24 h |
| Warfarin | ↑↑↑ | ↑ | 4–6 days (Less with loading dose) | 4–6 days |
| Dabigatran | ↑ | ↑↑ | 2 h | 4–7 days |
| Antiplatelet agents | | | | |
| Aspirin | – | – | Hours | 5–8 days |
| Other NSAIDs | | | Hours | 1–3 days |
| Ticlopidine, clopidogrel, prasugrel | | | Hours | 5–14 days |
| Platelet glycoprotein IIb/IIIa receptor inhibitors | | | Minutes | 8–48 h |
| Fibrinolytics | ↑ | ↑↑ | Minutes | 24–36 h |

Horlocker, T. **Regional anaesthesia in the patient receiving antithrombotic and antiplatelet therapy** *Br. J. Anaesth. (2011) 107 (suppl 1): i96-i106.*

## University of Washington guidelines

- http://depts.washington.edu/anticoag/home/sites/default/files/Neuraxial%20Guidelines.pdf
- http://depts.washington.edu/anticoag/home/

## Massive Transfusion


## Reversing dilutional coagulopathy

- Hetastarch impairs clotting at lower dilution (impairs platelets at 20% and factors at 40% dilution, where saline does so only at 80% and 60%)
  - DeLorenzo et al. Anesthesia & Analgesia April 2006 p. 1149

**WARNING: MORTALITY AND RENAL INJURY REQUIRING RENAL REPLACEMENT THERAPY**
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**-Mortality**
**-Renal injury requiring renal replacement therapy**
**in critically ill adult patients, including patients with sepsis and those admitted to the ICU**
**Do not use Voluven® in critically ill adult patients, including patients with sepsis and those admitted to the ICU**

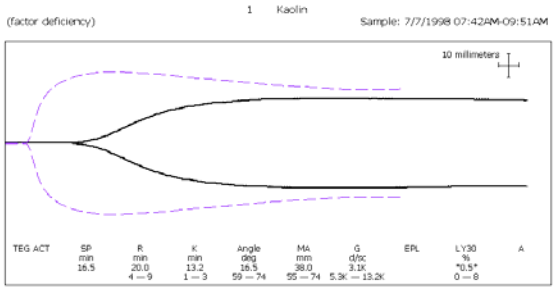
## Reversing dilutional coagulopathy

- TEG variables increased after 60% dilution.
- Fibrinogen administration improved clotting in all samples (crystalloid and colloid dilutions)
  - Fires, et. Al. Anesthesia & Analgesia Feb 2006 p. 347

## Disseminated Intravascular Coagulation

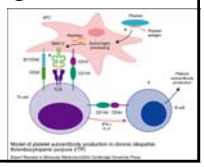
- Uncontrolled activation of the coagulation system, with consumption of platelets and procoagulants, leading to generalized bleeding.
- Excess thrombin is key culprit.
- Multiple causes, bacterial toxins, placental tissue, shock (acidosis), hemolysis, PE, ARDS,

## Laboratory tests in Disseminated Intravascular Coagulation



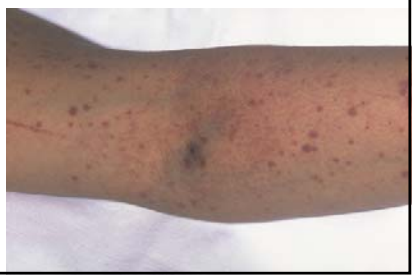

## Idiopathic Thrombocytopenic Purpura

- Autoimmune; antiplatelet immunoglobulin caused premature destruction of platelets
- Prolonged bleeding time; petechiae
- Rx with steroids until PLTC >50,000
- Beware of intracranial hemorrhage
- Compare to heparin-induced thrombocytopenia



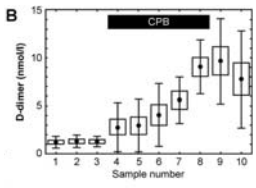
## Thrombotic Thrombocytopenic Purpura

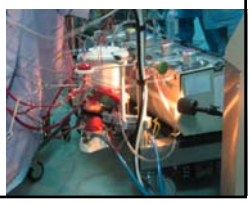
- Disseminated aggregation of platelets, diminishing the circulating number



## Cardiopulmonary Bypass

- Platelet dysfunction due to trauma from oxygenator
- Usually a transient effect
- Can treat with platelet infusion

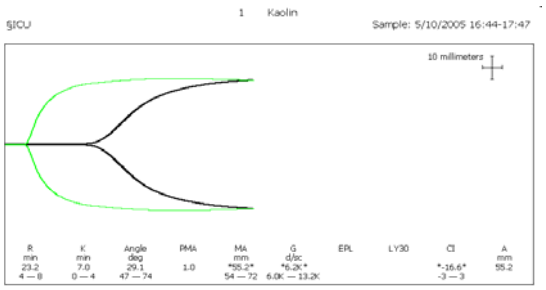


## Cardiopulmonary Bypass

- Lab tests can be misleading: aPTT adds more confusion than useful info.
- There is no correlation between elevated PTT often seen post-CPB and residual heparin effect.
- **PTT elevation does not predict bleeding post-CPB**

Elevated activated partial thromboplastin time does not correlate with heparin rebound following surgery" Teneja et al *Can J Anesth* 2009;56:7




## Preop Lab Assessment

"Screening coagulation tests…are only infrequently abnormal in the absence of a history indicating coagulation dysfunction."

"The presence of an unexpected abnormality…does not appear to contribute to the care of the patient."

(Longenecker, D., Tinker, J., & Morgan, G. (1998) *Principles and Practice of Anesthsiology*. Chicago: Mosby p. 928)

"No information is gained from either an abnormal or a normal result on clotting studies in low-risk patients".

(Miller, R. (Ed.), Anesthesia (5th ed) Philadelphia: Chruchill Livingston)

- Patient history. Most important test.
  - Lab tests without indication yield false positives
  - Isolated abnormality without symptoms, or supporting history difficult to interpret

## Preop Lab Assessment

- When are preoperative tests useful?
  - History suggestive of coagulation disorder
  - Anticoagulant/antiplatelet
  - Co-existing disease
  - Anticipated surgical alterati
    - CPB
    - Liver Transplant

## Preop Lab Assessment

- What tests to order?
  - If routine screening is indicated,
    - PT
    - PTT
    - Bleeding Time
    - Fibrinogen
    - Platelet Count
  - These will assess all phases of the cascade

## Laboratory Assessment

| | Normal Value | Measures |
|---|---|---|
| Prothrombin Time | 12-14 sec. | I, II, V, VII, X |
| APTT | 25-35 sec. | I, II, V, VIII, IX, X, XI, XII |
| Platelet Count | 150- 400K/mm$^3$ | |
| Bleeding Time | 5-10 min. | Platelet count and function |
| Fibrinogen | 200-400 mg/dl | I |
| Thrombin Time | 12-20 sec. | I, II |
| TEG | | Procoagulants, platelets |

## Intraoperative Laboratory Assessment- Activated Clotting Time

- Fresh whole blood added to tube containing negatively-charged particles: diatomaceous earth (celite), kaolin, or glass
- Formation of a clot displaces a mechanical device and is noted as the clotting time
- Results influenced by:
  - Heparin effect, Hypothermia, Platelet dysfunction Haemodilution, Cardioplegic solutions, Hypofibrinogenaemia, Factor deficiencies
- Normal 100-170. Need 300-480 sec. for CPB

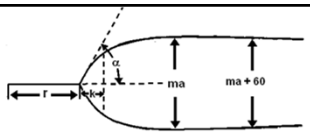
## Intraoperative Laboratory Assessment- Thromboelastogram

- Celite-activated whole blood (0.4ml) is placed into a pre warmed cuvette.
- A pin suspended from a torsion wire is then lowered into the cuvette, which is rotated backward and forwards.
- As fibrin strands and platelets interact with the pin, the rotational movement of the cuvette is transmitted to the pin.
- The stronger the clot the more the pin moves, and the coagulation profile is then displayed on the screen as aThromboelastograph.

## Intraoperative Laboratory Assessment- Thromboelastogram

1. **R value = Time to the initial fibrin formation and pin movement**
2. **k value = Time from the beginning of clot formation until the amplitude of the TEG reaches 20mm.**
3. **alpha angle = This is the angle between the line in the middle of the TEG tracing and the line tangential to the developing "body" of the TEG**
4. **Maximal Amplitude**
5. **Amplitude at 60 minutes = Amplitude 60 minutes after the Maximal Amplitude is recorded.**
6. **Clot Lysis Index = The amplitude at 60 minutes expressed as a percentage of the maximal amplitude.**

TEG Example




Normal Values
r = 7.5 - 15 min.
k = 3-6 min.
α = 45-50°
ma = 50-60 mm.
ma + 60 = ma - 5mm

| Variable | Measures | Abnormality | Example |
|---|---|---|---|
| | | | Normal |
| r reaction time | thromboplastin generation via intrinsic pathway | ↑r Factor deficiency Heparin ↓fibrinogen | Factor deficiency |
| α & k angle of divergence | rate of clot formation | ↓α ↓platelet function ↓fibrinogen ↑k ↓platelets | ↓fibrinogen |
| | | ↑α ↓k hypercoagulability | hypercoaulability |
| ma maximum amplitude | maximum clot strength/elasticity | ↓ma ↓Factor XIII ↓platelet function ↓fibrinogen ↓platelets | ↓platelets |
| ma + 60 | clot retraction after 60 minutes | ↓ ma + 60 Fibrinolysis | Fibrinolysis |

## Assessing Abnormal Coagulation

| Result | Cause | Treatment |
|---|---|---|
| Decreased Platelet Count | Inadequate production | Platelets |
| | ITP | Steroids |
| | DIC (with ⇓fibrinogen, ⇑FDP) | Rx DIC, Platelets |
| Increased Bleeding Time | Low Platelets | Platelets |
| | Von Willebrand's Disease | Cryoprecipitate |
| | Uremia | Dialysis, Cryo, RBC's |
| | IV Nitroglycerine | None if PLTC normal |

| Result | Cause | Treatment |
|---|---|---|
| PT elevated | Factor 7 deficiency | FFP |
| PTT elevated Patient bleeding | Factor 8 def. (Hemo A) | Factor 8 concentrate |
| | Von Willebrand's Dis. (⇑ bleeding time, nl PLTC) | Cryoprecipitate, DDAVP |
| | Factor 9 deficiency | Factor 9 concentrate |
| | Factor 11 deficiency | FFP |
| | Heparin (if not corrected in mixing study and ⇑ TT ) | Protamine |
| PTT elevated Without bleeding | Factor 12 deficiency Deficient prekallikrein Deficient HMW kininogen | None needed |
| PT and PTT elevated | Liver disease | FFP, Vit K? |
| | Factor 1 def. ( ⇑TT, BT, Fib) | FFP or Cryoprecipitate |
| | Factor 2, 5, 10, deficiency | FFP |
| | Vitamin K deficiency | Vitamin K or FFP |
| | DIC | Rx DIC, FFP, Pltc, Cryo |
| | Heparin/coumadin (high dose) | Protamine, FFP |

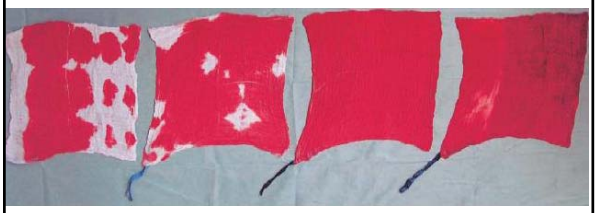
## Managing Hemostasis Intraop.

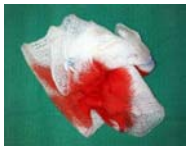
- Multiple potential causes- liver dis., DIC, hypotension, transfusion, hypothermia…
- Assess:
  - persistent oozing from raw surfaces
  - Oozing from IV sites
  - Nasal bleeding from NGT
  - Blood in urine or ETT
  - Sweat on the surgeon's brow

## Managing Hemostasis Intraop.

- Estimate Blood Loss
  - Historically, anesthetists overestimate diluted blood and underestimate blood on sponges
  - 4X4 = **10 ml**
  - Ray-tech = **10-20 ml**
  - Lap sponge = **100 ml**

## Estimating Blood Loss





## Who does well with estimation?


| Role in OR | EBL (mL) Mean | EBL (mL) Range |
|---|---|---|
| Surgeon | 101 | 20-250 |
| MD Anesthesia | 132.5 | 75-200 |
| CRNA/ SRNA | 139.5 | 50-250 |
| OR RN/ Scrub Tech | 108 | 50-200 |

Correct Answer: 150mL

Overall percent error estimation = -20%

## Managing Hemostasis Intraop.

- Calculate allowable blood loss

1. Determine blood volume
   - Preemie 95 ml/kg
   - Neonate 85 ml/kg
   - Infant 80 ml/kg
   - Child 75 ml/kg
   - Adult Male 75 ml/kg
   - Adult Female 65 ml/kg
   - Obese- divide by 1.3

## Managing Hemostasis Intraop.

2. Calculate by proportion

$$ABL = EBV \times \frac{Hgb_{pt} - Hgb_{LA}}{Hgb_{pt}}$$

ABL = Allowable blood loss

EBV = Estimated blood volume (from prev step)

$Hgb_{pt}$ = Patient's present Hemoglobin

$Hgb_{LA}$ = Lowest allowable Hemoglobin

## Managing Hemostasis Intraop.

- Calculate allowable blood loss

80 kg Male (EBV = 80 X 75 = 6000ml.)

Hgb = 15. Lowest allowable Hgb = 10.

$$ABL = 6000 \text{ (EBV)} \times \frac{15 - 10}{15}$$

ABL = 6000 X 5/15

ABL = 6000 X .3

ABL = 2000 ml

## Transfusion Guidelines

- Hgb ≤7 g/dl in an asymptomatic patient.
- Hgb ≤8 g/dl in asymptomatic patient with cardiovascular disease
- Hgb ≤10 g/dl in a normovolemic patient with symptoms of anemia, in a patient with significant cardiovascular or respiratory disease or in a patient with a bone marrow disorder.
- Acute blood loss exceeding 15% of total blood volume.
- Chronic Transfusion Regimen
- Exchange Transfusion.
- Neonate with acute blood loss exceeding 10% of total blood volume.
- Neonate with Hgb ≤10 g/dl and cardiorespiratory disease
- Surgery: anticipated hypovolemia and decreased O2 carrying capacity.

## Blood Component Therapy

Platelets- for documented thrombocytopenia only. One unit raises PLTC by 5,000

Plasma- for documented procoagulant def., INR > 1.5 with bleeding or surgery, reversal of coumadin, or heparin resistance

- All procoagulants are present
- Each unit raises factor levels by 2-3%

Cryoprecipitate

- High concentration of Factor VIII and Fibrinogen, vWF and XIII

## Blood Component Therapy

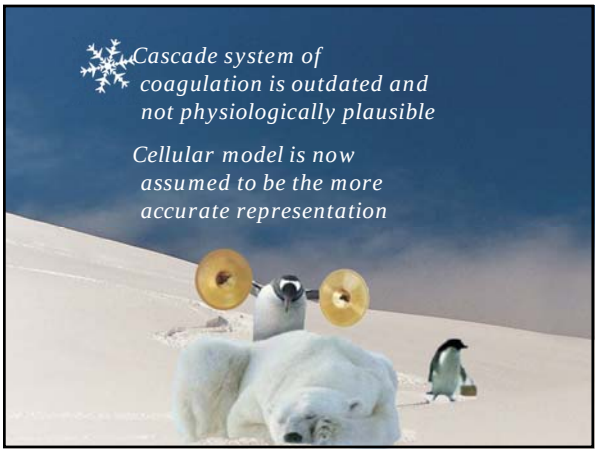
| | FFP | Cryoprecipitate |
|---|---|---|
| Volume | 250 mL | 20 mL |
| Factor 1 | 500 mg | 200 mg |
| Factor 2 | 225 U | |
| Factor 5 | 225 U | |
| Factor 7 | 225 U | |
| Factor 8-AHF | 225 U | 90 U |
| Factor 8-VWF | 225 U | 90 U |
| Factor 9 | 225 U | |
| Factor 10 | 225 U | |
| Factor 11 | 225 U | |
| Factor 12 | 225 U | |
| Factor 13 | 225 U | 90 U |

## Managing Hemostasis

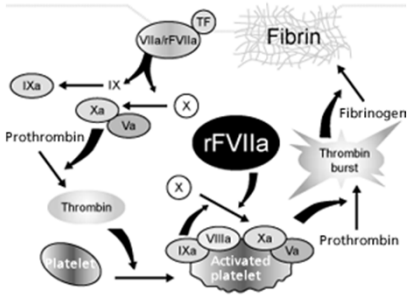
- Controlled hypotension
- Epidural Anesthesia
- Normovolemic Hemodilution
- Drugs- tranexamic acid/aminocaproic acid, DDAVP

## Managing Hemostasis

- Prostaglandins: Carboprost tromethamine (prostaglandin $F_2\alpha$: "Hemabate")
- Topical thrombin
- Gelfoam
- Avitene Flour
- Ultrafoam collagen sponge



## Recombinant VIIa

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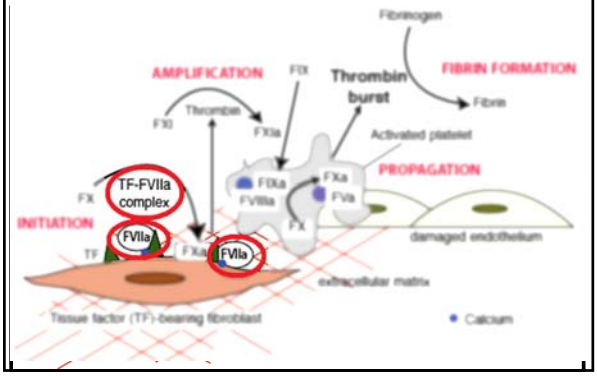


## Managing Hemostasis

- Recombinant Factor VIIa
  - spontaneous and surgical bleeding in congenital hemophilia A and B in patients with inhibitors to FVIII and FIX worldwide,
  - acquired hemophilia, congenital FVII deficiency and Glanzmann's thrombasthenia in Europe.

## Recombinant FVIIa

- 15 trauma or surgical patients with massive transfusion. Mean base deficit = 6
- 1-2 doses of RFVIIa
- 12 moribund patients survived 48 hours, 7 to discharge

Benharash, P. Bongard, F. Putnam, B. *The American Surgeon.* Sept 2005 71(9): 776-80.


## Recombinant FVIIa

- 2 pediatric neurosurgical cases with microvascular bleeding refractory to conventional therapy.
- RFVIIa restored normal hemostasis in both
  - Hatmann et. Al. *Journal of Neurosurgery* Jan 2006. P. 55.

NovoSeven® Recombinant Factor VIIa

## Factor VII Case Example

- A 38-yr-old**.** Excessive blood loss after hysterectomy. Pre-op: aPTT 23.4 sec, platelet count 267K
- Tranexamic Acid (2 x 500 mg), 10 units platelets, 31 units FFP, 31 units PRBC.
- Blood loss- 15,000 ml
- Developed v-fib. CPR including 7 mg epi.

## Factor VII Case Example

- Core temperature 31.9 degrees C.
- After successful resuscitation, bleeding started again with a blood loss of 2000 ml requiring 3 units of FFP and 3 PRBC.
- Received recombinant activated Factor VII 6 mg (300 KiU) Within 10 minutes the bleeding stopped. More transfusions were not necessary. The patient left the intensive care unit 8 days after the operation without neurological deficit.

## The downside of rFVIIa

- Thrombosis
- Expense
  - Amicar $4
  - Tranexamic acid $29
  - DDAVP $91
  - Aprotinin $1000
  - rFVIIa $3,000


## When it seems all hope is lost…

- 44-yr-old Jehovah's Witness who refused blood transfusion for ovarian CA surgery
- Hgb 2.5 post-op to (immeasurable) for 10 hours. Hgb *rose* to 1.5 by next day.
- high-dose iv erythropoietin therapy (600 IU/kg + Fe, folic acid and vitamins for 2 weeks
- hemoglobin 6.5 g/dl on day 24. She made a full recovery and is still free of cancer in remission.