Vesalius SCALpel™ : Coagulation

Coagulation

injury attracts platelets
- chemoattractants: platelet derived growth factor (PDGF), transforming growth factor beta (TGF beta)
- platelets release ADP causing additional platelet aggregation, unstable white clot
- platelets release calcium and phospholipids which facilitate intrinsic pathway

extrinsic pathway facilitated by tissue thromboplastin
final common pathway factor Xa converts prothrombin to thrombin
thrombin converts fibrinogen (I) to (weak) fibrin
fibrin stabilizing factor (XIII) creates tight fibrin which stabilizes white clot

Clotting tests

PT: extrinsic pathway, II, V, VII, X, fibrinogen
- acted on by warfarin
- abnormalities: Vit K deficiency, liver disease, malabsorption (fat)

PTT: intrinsic pathway, everything else but VII and XIII
- acted on by heparin
- abnormalities: VIII deficiency (hemophilia A), IX (hemophilia B), XII

bleeding time:
- measures pl plug formation
- nl 8-9m = pl > 50k
- low VonWillibrand factor increases bleeding time

the most effective tool to detect coagulation abnormality is history

Bleeding disorders

Hemophilia A: VIII deficiency, sex-linked
- spontaneous bleeding: intraarticular, intramuscular, intracranial, GU
- PT normal, PTT may be elevated, factor VIII assay definitive Dx
- Rx: factor VIII concentrate; use cryo (80u of VIII/unit) if VIII not available; 1/2 life 8-12h, 50% level controls spontaneous bleed
  - Rx for bleeding: 30% factor VIII level, minor bleeding, 50% joint, muscle, 100% for severe
  - need 80-100% level pre-op; 40-50u/kg; maintain 30% post op

Hemophilia B: rarer, pure Christmas factor/IX deficiency, sex-linked recessive
- PT normal, PTT prolonged
- Rx: IX concentrate; 1/2 life 24h; pre-op raise level to 60%, 60u/kg, 30% postop

VonWillibrands:
- VonWillibrand's factor/protein binds to platelets and factor VIII, causes cohesion of clot
- VWF gene on chromosome 12 mutation

autosomal dominant, abnormal VWF protein synthesis
VonWillibrand more common than hemophilia
70% abnormal platelet adhesion, count may be normal
affects males and females (v. hemophilia males only)
platelet dysfunction (v. normal platelet function in hemophilia)
increased bleeding time, petecheae, purpura, menorrhagia
Rx: cryoprecipitate (FFP if cryo not available), achieve level >30%
DDAVP/desmopressin: hormone which causes release of VonWillibrand's factor from endothelial cell storage sites

thrombocytopenia: most common acquired bleeding disorder
most common hematological abnormality in critically ill patients
seen in 20% of ICU patients
hypothermia prevents clotting, normal platelet life 2-3d
etiology: decreased production, sequestration, destruction (valve, DIC, HITT), sepsis, shock, ASA, NSAIDS, drugs, VWb
clinical bleeding @ 30K
bank blood has few platelets, and decreased function of remaining
1 unit fresh whole blood -> 50k pl in 50cc, no X-match necessary
platelet pack 5K/u @ 1h, 10pk -> 50K
FFP contains near normal levels of most clotting factors except platelets (3% increase in factors/u FFP)
plasmapheresis results in 30-60K increase

heparin-induced thrombocytopenia (**HIT**), 5% incidence with any form/route of heparin
venous thrombosis most common presentation
pl <150K or 50% of baseline
onset 4-14 days after start heparin therapy, two types
mild form (HIT-I):
transient sequestration of platelets with heparin Rx, 15% incidence
4d, minimal decrease platelets, direct effect of heparin on platelets
not immunological, no thrombosis, resolves without discontinuing heparin
severe/immune HIT (HIT-II): 4-14d, (within hrs if prior exposure to heparin)
usually due to IV unfractionated heparin
suspect if > 30% decrease in platelets or level < 100K, thromboembolic events, resistance to anticoagulation
delayed recognition poor outcome
heparin-associated antiplatelet IGg antibody (HAA) + pl factor 4 -> pl activation/aggregation, XS thrombin generation, venous and arterial thrombosis
test for HAA: if negative, can resume heparin
Rx: stop unfractionated heparin, replace with direct thrombin ihibitor (argatroban, lepirudin)
fondaparinux: similar action to LMWH, does not cause immune mediated thrombocytopenia (HIT)

recombinant VIIa (**rVIIa**) hemostatic:
combines w tissue factor to act on thrombin and activate platelet factor V & VIII
stimulates thrombosis and platelet thrombus generation

activates IX & X causing thrombin burst, fibrin clot
bypasses intrinsic cascade and shortens time to clot formation
prothrombotic for hemophilia A & B
greatest effect at injury site, not systemic
use in emergency reversal of coumidin especially with intracerebral hemorrhage, bleeding trauma patients (after surgical hemostasis) with coagulopathy, perioperative hemorrhage, platelet related bleeds, bone marrow transplant, hepatic dysfunction, hepatic transplant, neonatal/pediatric bleeding
10% incidence of hypertension

Hypercoagulable states, **congenital**

Factor V Leiden: autosomal dominant (altered amino acid sequence on V)
20% of patients with thrombosis, 5% of Caucasians, less African, Asian
heterozygous 7X increased clotting risk, homozygous 80X

G20210A: another amino acid in the V chain; autosomal dominant, 4X thrombosis risk
7% of patients with thrombosis, 3% of caucasians

antithrombin III deficiency: **ATIII** inhibits coagulation proteases that inhibit thrombosis, inactivates thrombin, Xa, XII, XI & IX; enhanced by heparin; increased risk DVT/PE
congenital form: autosomal dominant, 0.03% of pop, in 5% of pts with DVT
suspicious: young DVT, idiopathic, FH, recurrent, thrombosis resistant to heparin, unusual locations, during pregnancy
high risk patients: OR, infection, trauma; give prophylaxis
if AT activity <70% give heparin or coumidin
if contraindicated, give AT to 80-120% level
enoxaparin, dextran, heparin not sufficient
IVC filter if none of the above possible
acquired: massive thrombosis, DIC, heparin Rx, liver disease, GI/GU protein loss
Dx: ATIII assay
Rx: heparin followed by warfarin, antiplatelet Rx

protein C deficiency: inhibits the procoagulant system, lack normal ability to prevent clot degrades V, VIII; hepatic synthesis requires vit K
autosomal dominant, variable penetrance; homozygous inheritance early death
recurrent DVT/PE, test for decreased concentration protein C
Rx lifelong heparin to warfarin

protein S deficiency: cofactor of protein C; vitamin K dependent hepatic synthesis
autosomal dominant, effects and Rx same as protein C

increased XII > 90^{th} percentile 2X risk of thrombosis; may account for 11% of venous thrombotic events

Hypercoagulable states, **acquired** (more common than congenital)

disseminated intravascular coagulation (DIC): thromboplastic material in circulation
general: surgery (1/2 of DVTs start in the OR), trauma, immobility, age, malignancy, pregnancy, prior hx DVT/PE

antiphospholipid antibodies: most common of the acquired protein defects
most commonly seen with autoimmune diseases (initially found with SLE)
associated with 25% of unexplained thrombotic events
Rx heparin

thrombocytosis: myeloproliferative disorders, post-splenectomy (problems when reach 1M), inflammatory disease, malignancy
rarely symptomatic; Rx ASA, rarely plasmapheresis necessary
platelet inhibitors:

ASA: weak inhibitor, blocks only one pathway, arichidonic to thromboxane; blocks cyclooxygenase activity of prostaglandin synthetase (COX1) and COX2 for the 3-5d life of the platelet

plavix/clopidogrel: selective inhibition of ADP receptor-mediated aggregation; associated with increased bleeding, transfusion requirement, stop 5-7d before OR; in emergency give platelet transfusion

reopro/abciximab (-ab indicates monoclonal antibody): inhibit platelet glycoprotein IIb/IIIa receptor; most potent
for high risk for coronary event who undergo intervention (e.g. angioplasty) within 2d of hospitalization; severe drop in platelets; 9d to normal platelet count

pletal/cilostozol: reversible phosphodiesterase III inhibition, increases availability of camp, causes vasodilatation, platelet inhibition; may improve walking distance in claudication; weak inhibitor of platelet aggregation; 5-7d

NSAIDS: inhibit thromboxane-dependent platelet function by reversibly inhibiting COX1 at high dose, not clinically therapeutic, 24h reversal

DVT/PE

anticoagulation: INR 2.5-3 usually adequate, intensive up to 3.5

High risk for DVT/PE: closed head injury (GCS <8), pelvic & long bone fx, multiple long bone, spinal cord injury, hx DVT/PE, age, obesity, immobility >3d, femoral V catheter >24h, multiple transfusions, abnormal coags on admission

mechanical prophylaxis: foot pump, sequential pressure devices (increase femoral vein flow, fibrinolytic activity); pts remove pressure devices because hot, especially when sitting and need them most

low dose heparin: 5K units 2-3X/d
reduces DVT from 25% to 9%, PE from 1.2% to 0.5%
increase minor bleeding 4-6%
no significant difference in major bleeding
not effective prophylaxis in trauma patients
lo dose anticoagulation decreases cath thrombosis

low molecular weight heparin: better than low dose in trauma, 10X cost of unfractionated
binds to antithrombin III increasing its anti factor Xa activity
activated PTT not useful for monitoring
cleared by kidney, adjust dose in renal impaired
trauma, ortho, general surgery, pelvic fx pts. treated with bed rest

spinal cord injury; continue several weeks if patient remains high risk

DVT/PE Rx: 1st episode anticoagulate 6mo; stop at 3mo 25% risk of reclotting

lifetime anticoagulation: ATIII deffic, Protein C, S, homozygous V Leiden, combined thrombophilias, antiplatelet antibody syndrome, G20210

therapeutic IVC interruption: PE, progressive DVT in spite of adequate anticoagulation, ongoing DVT/PE risk, not candidate for anticoagulation (head bleed)

prophylactic IVC interruption: controversial

free floating clot in IVC or iliac
after major PE, high risk of death from another PE
in conjunction with venous embolectomy
high risk for DVT and bleeding complications
non-operative treatment of solid organ injury
pelvic fx, hematoma
retroperitoneal hematoma
intraocular hemorrhage

IVC filter: does not increase or prevent DVT (continue prophylaxis)

reduces but does not eliminate PE risk
IVC thrombosis in 10%, 50% recanalize, rest chronic venous stasis
long term IVC patency 95%
retrievable filters put in from below, retrieved from above, remove up to 1y

methemoglobinemia

ferrous form of iron capable of combining with oxygen, not when oxidized to ferric
exposure to chemical oxidizing agent most common etiology
genetic defect NADH dependent reductase enzyme production
genetic abnormality of Hb making it susceptible to oxidation
methylene blue accelerates the enzymatic reduction of methemoglobin by NADP-methemoglobin reductase and its reduction product leukomethylene blue
directly reduces methemoglobin

Transfusion

bank blood has low 2,3DPG, high O_2 affinity (curve shift to L)

hemolytic transfusion reaction most commonly from ABO

first intraop sign diffuse ooze
fever common