EMERGENCY HEMOSTASIS!

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Laboratory Testing

Common Causes of Abnormal Laboratory Tests

Elevated PT/INR, Normal aPTT
Direct oral anticoagulants (DOACs)
Factor VII deficiency
Sepsis
Vitamin K deficiency
Warfarin

Normal PT/INR, Elevated aPTT
Isolated factor deficiency (VIII, IX, XI, XII, Contact Pathway proteins)
DOAC
Heparin
High Hematocrit (>60% - spurious)
Lupus Inhibitor
Specific Factor Inhibitor

Elevated PT/INR, Elevated aPTT
Multiple Coagulation Factor Deficiencies
    Liver Disease
    Disseminated Intravascular Coagulation
Dilutional
DOACS
Dysfibrinogemia
Factor V inhibitors
High heparin levels
Isolated Factor X, V or II deficiency
Low Fibrinogen (< 50 mg/dL)
Warfarin excess

IMMEDIATE THERAPY - TRANSFUSION THERAPY

The Five Basic Tests:

1. **Hematocrit**
2. **Platelet count**
3. **Prothrombin time**
4. **Activated partial thromboplastin time**
5. **Fibrinogen level**

Management of Coagulation Defects

A. Platelets <50-75,000/ul in a bleeding patient or <10,000/ul in a stable patient: Give Platelet Concentrates or 6 Pack of Single Donor Platelets.
B. Fibrinogen <150mg/dl: Give 10 Units of Cryoprecipitate
C. Hematocrit below 21% in a bleeding patient: Give Red Cells
D. Protime >INR 2.0 and aPTT >1.3x control: Give 2-4 Units of FFP.

Massive Transfusions
Massively transfusion is defined as one who receives greater transfused blood than one blood volume in 24 hours or more practically defined as receiving one blood volume in two hours or less.
Coagulation defects are common in the massively transfused patients due to dilution or underlying medical or surgical conditions.
* Give RBC and FFP in 1:1 ratio with platelets for every 6 units of RBC
* Consider Tranexamic acid 1 gram load and 1 gram continuous infusions over 8 hours – especially in trauma and post-partum hemorrhage
* Five basic labs to "tune-up" coagulation defects

Two common problems in massive transfusions:
1) Isolated elevations of the PT/INR
* Factor VII labile
* If aPTT normal should not effect coagulation
2) Greatly prolonged INR
* Low fibrinogen
* Heparin contamination

Thromboelastography (TEG) based therapy

TEG parameter	Interpretation	Direction - Products
R Time	Reaction time – time to fibrin formation	Increased - FFP
K time	Kinetics – time 2 to 20 mm of amplitude	Increased – cryoprecipitate
Alpha angle	r/k slope of tracing– increase in thrombus strength, fibrinogen concentration	Decreased – cryoprecipitate
Maximal Amplitude	Strength and stability of the thrombus	Decreased – platelets
Whole Blood Lysis Index	Fibrinolysis	Increased - antifibrinolytic

TEG Based Management

If r time prolonged -> FFP
If MA low -> plts/cryoprecipitate (if fibrinogen < 150)
If fibrinogen < 150 -> cryoprecipitate
If platelets < 50 - > platelet transfusions
If LY30 increased -> 1000mg tranexamic acid

Correcting Coagulation Defects before Procedures
Risk correlated more with skill of operator than coag defects
Elective procedures:
Platelets 20-30,000/ul
aPTT < 1.5 times normal
Emergency: most skilled person to do procedures

Thrombocytopenia

Differential Diagnosis of Thrombocytopenia

Disseminated Intravascular Coagulation
Drug induce thrombocytopenia
HELLP Syndrome

Hemophagocytic Syndrome
Heparin Induced thrombocytopenia
Immune Thrombocytopenia
Liver Disease
Post-Transfusion Purpura
Pseudothrombocytopenia
Thrombotic Thrombocytopenia Purpura

Typical Platelet Counts in Various Disease States

Moderate Thrombocytopenia (50,-100,000/ul)
Disseminated Intravascular Coagulation
Hemophagocytic Syndrome
Heparin induce thrombocytopenia
Liver disease
Sepsis
Thrombotic Thrombocytopenic Purpura

Severe Thrombocytopenia (<20,000/ul)
Drug induced Thrombocytopenia
Immune Thrombocytopenia
Post-Transfusion Purpura
Severe Sepsis

Two key questions for thrombocytopenia:
1) How low is the platelet count (low vs really low [<10,000])
2) Is the patient sick?

Very low but not sick
Immune thrombocytopenia (ITP)
Drug induced thrombocytopenia

Very low and sick
Thrombotic thrombocytopenic purpura (TTP)
Overwhelming sepsis

Low and sick
TTP
Liver disease and other problem
Sepsis
Disseminated intravascular coagulation

Addition features
ITP/Drug ITP: other blood counts normal, usual rapid onset
TTP: schistocytes, organ dysfunction, high LDH
DIC: very high D-dimers, low fibrinogen, usually 2nd to other illness

Diagnostic Clues to Thrombocytopenia

CLINICAL SETTING	DIFFERENTIAL DIAGNOSES
Cardiac Surgery	Cardiopulmonary bypass, HIT, dilutional thrombocytopenia
Interventional Cardiac Procedure	Glycoprotein IIb/IIIa blockers, HIT
Sepsis Syndrome	DIC, Ehrlichiosis, Sepsis hemophagocytosis syndrome, drug-induced, misdiagnosed TTP,

	mechanical ventilation, pulmonary artery catheters
Pulmonary Failure	DIC, Hantavirus pulmonary syndrome, mechanical ventilation, pulmonary artery catheters
Mental Status Changes/Seizures	TTP, Ehrlichiosis
Renal Failure	TTP, Dengue, HIT, DIC
Cardiac Failure	HIT, drug induced, pulmonary artery catheter
Post-surgery	Dilutional, drug-induced, HIT
Pregnancy	HELLP syndrome, fatty liver of pregnancy, TTP/HUS
Acute Liver failure	Splenic sequestration, HIT, drug induced, DIC

HIT = Heparin induced thrombocytopenia, DIC = disseminated intravascular coagulation, TTP = thrombotic thrombocytopenic purpura, HELLP = Hemolysis, Elevated Liver function tests, and Low Platelets

Diagnostic Clues to Coagulation Defects

CLINICAL SETTING	DIFFERENTIAL DIAGNOSES
Cardiac Surgery	Factor V inhibitor, heparin excess or rebound, protamine excess, fibrinolysis
Sepsis Syndrome	Isolated factor VII deficiency, DIC, vitamin K deficiency,
Recent use of Quinine, Second or Third generation cephalosporin	Drug induced Hemolysis/DIC syndrome
Post-surgery	Dilutional, DIC, thrombin inhibitors
Pregnancy	HELLP syndrome, fatty liver of pregnancy, vitamin K deficiency
Acute Liver failure	Consumption, DIC, fibrinolysis, vitamin K deficiency (biliary obstruction)

DIC = disseminated intravascular coagulation, HELLP = Hemolysis

ITP

Counts can be < 10,000
Otherwise healthy
Normal CBC except for low platelets (can see anemia due to bleeding)
Therapy: Dexamethasone 40 mg/d x 4 days
If very low (< 5,000) or older (> 65) or severe bleeding:
IVIG 1 gram/kg
Refractory ITP “Platelet Boilermaker”
IVIG 1 gram/kg over 24 hours with one unit of platelets every 6 hours all continuous infused
Do NOT transfuse platelets unless life-threatening bleeding.
Response to platelet transfusion is NOT a diagnostic test for ITP

Drug Induced Thrombocytopenia

Counts can be < 10,000
Otherwise healthy
Normal CBC except for low platelets (can see anemia due to bleeding)
Recent exposure (two weeks) to suspect drug
Therapy: stop offending drug

Drug Induced Hemolytic-DIC Syndromes

Patients with severe hemolytic anemia and thrombotic DIC
* One form seen with 2nd and 3rd generation cephalosporins (cefotetan, ceftriaxone most common).

Starts 7-10 days after getting ATB. Patient present with severe Coombs positive hemolytic anemia, hypotension and DIC.
* Second form seen with quinine. 24-96 hours after ingesting present with DIC, anemia, and renal failure. Can also have immune neutropenia.
Therapy is uncertain and process has high mortality - consider plasma exchange

Disseminated Intravascular Coagulation
DIC is the clinical manifestation of inappropriate thrombin activation
Patients with DIC can present in one of four ways:

1) Asymptomatic
2) Bleeding
3) Thrombosis
4) Purpura fulminans

Tests - routine coag tests may be normal. D-dimer has the highest predictive value for DIC. Low fibrinogen most specific

Therapy
* Treat primary cause
* Replace coagulation factors guided by the 5 basic tests
* Heparin only if patient having thrombosis - will need to use heparin levels to guide therapy

Purpura Fulminans is DIC association with symmetrical limb ecchymosis and necrosis of the skin.
1) Primary purpura fulminans
    * Often after viral infections
    * Often with acquire protein S antibodies
    * Therapy is with plasma to keep protein S > 25%, heparin, and IVIG
2) Secondary purpura fulminans
    * Overwhelming infections esp meningealococcemia
    * Therapy: transfusion therapy guided by 5 basic tests.

Thrombotic Thrombocytopenic Purpura
TTP should be suspected when any patient presents with any combination of renal insufficiency, thrombocytopenia, and end organ damage.

There is currently no rapid diagnostic test for TTP - diagnosis is based on the clinical presentation. TTP should be consider in any patients who presents with multi-system illness and thrombocytopenia.

* Microangiopathic hemolytic anemia - schistocytes on the blood smear
* Thrombocytopenia - usually 20-60,000/ul range
* Renal insufficiency - often mild, frank renal failure rare. UA usually abnormal with red cells and proteinuria
* Fevers - seen in less than half of TTP
* Mental status changes - can range from confusion to coma. Seizures can also be seen.
* Pulmonary - patients can infiltrates and hypoxia
* Cardiac - coronary microthrombi common - can lead to ischemia and dysrhythmias
* GI - pancreatitis is a common complication.

One helpful clue is the presence of a raised LDH. LDH levels are often over 2 times normal in TTP and on fractionation is from all isoenzymes representing widespread tissue damage

Although inhibitors to ADAMTS13 are responsible for many if not most cases of TTP, rapid assays are not widely available so the diagnosis remains clinical. Activity < 10% specific but not sensitive for TTP. Levels above 10% can be seen in any ill patient.

Therapy:

Untreated TTP is rapidly fatal. Mortality in the pre-plasma exchange era ranged from 95-100%.

Today plasma exchange therapy is the cornerstone of TTP treatment and has reduced mortality to less than 30%.

** Plasma exchange (1.5 plasma volumes) is essential and has been shown to be superiors to simple plasma infusion. Patients should get 5 days of therapy and then exchange is tapered based on LDH and platelet counts. If there is delay in plasma exchange plasma (units/4-6 hours) should be given.

* Glucocorticosteroid therapy, equivalent to 60-120 mg of prednisone is often used.
* Platelet transfusions are contraindicated in most patients with TTP and in most patients there is little justification for platelet transfusion.

* For patients not responding rapidly to therapy vincristine 1 mg/meter squared days 1, 4, 7, 10 can be tried.
* For patients with anti-ADAMTS13 antibodies rituximab 375mg/m2 weekly x 4 should be started to reduce relapses and speed resolution
* Caplacizumab may be indicted in severe or refractory cases: 11mg IV before plasmaexchange then 11mg sub-q daily for at least 30 days after last exchange and if ADAMTS13 is > 10% - if not then therapy needs to be extended until > 10%

Three patterns for ADAMTS13 will be found:
* Very low levels (<10%), positive inhibitor: classic TTP, autoimmune; consider adding rituximab
* Very low levels (<10%), no inhibitor: congenital TTP, will need long term plasma infusions to prevent relapses – can get genetic testing to confirm
* Not low levels (>10%), positive inhibitor: can be TTP, consider other diagnosis or atypical HUS

Hemolytic Uremic Syndrome
Consider: rapid onset renal insufficiency with thrombocytopenia, high LDH, and hypertension. If there is severe renal disease smear may not show schistocytes

Typical: post infection (Shiga toxin producing e coli) – preceded by bloody diarrhea, no role for plasmaexchange

Atypical HUS
Primary: presents like HUS but no infection or other provoking factors
Secondary: drugs: gemcitabine, tyrosine kinase inhibitors, VEGF inhibitors; stem cell and solid organ transplant
Therapy: Eculizumab 900mg IV weekly then 1200mg every other week. Hematological response is rapid but can take months to see renal response especial if severe renal disease/failure is present. Duration is controversial – can stop once drug induced resolves but in other situation unclear when to stop

Hemophagocytic syndrome
Multisystem disease with fevers, organomegaly, and cytopenias. Can be primary or complication infections and hematological malignancies

Diagnosis: HLH-94 criteria need 5/8 criteria
• Fevers
• Splenomegaly
• Cytopenia
  • Hgb < 9.0
  • Platelets < 100
  • ANC < 1
•Hypertriglyceridemia or hypofibrinogenemia
  •Fasting triglycerides > 265
  •Fibrinogen < 150
• Ferritin > 500 (3000)

• sCD25 > 2400
• Decrease NK cell activity
• Hemophagocytosis on biopsy

Therapy: HLH-94 with dexamethasone/etoposide still standard, for EBV related add rituximab.

Heparin Induced Thrombocytopenia (HIT)

Natural History: Occurs at least 4 days after starting heparin in any form. Thrombocytopenia is modest - 60,000/ul is average - rare for counts to be under 20,000/ul. 20-50% of patients will have thrombosis. Can occur rapidly if patient has had heparin in past 100 days. Some patients can present with HIT up to 2 weeks after heparin exposure.

Pathogenesis: Formation of antibodies directed against the complex of heparin that bind to platelet factor 4 (PF4)
Frequency of HIT: Standard heparin 1-5% (bovine > porcine), LMWH <1%.

Diagnosis: Suspect if any of these occur:
* Platelet counts drops by 50% - most sensitive
* Platelet counts fall under 100,000/ul
* New thrombosis on heparin

Laboratory testing:
* Platelet activation assays - sensitive and specific but technically difficult and not always available
* Anti-PF4 ELISA - Very sensitive but not specific especially in cardiac surgery patients
Testing most useful for patients with multiple causes for their thrombocytopenia and low to moderate pretest probability for HIT

Therapy
The first step in therapy of HIT consists of stopping all heparin. Given high rate of thrombosis all patients with HIT should receive antithrombotic therapy. LMWH CANNOT be used due to cross-reactivity. Of agents available best choice for ICU patients is argatroban.

Argatroban: Direct thrombin inhibitor. Hepatically cleared. Dose at 2 ug/kg/min infusion with dose adjustments to keep aPTT 1.5 - 3 times normal. No dose adjustment for renal disease but for severe liver disease dose is 0.5 ug/kg/min. Also for patients with MOSF use 1ug/kg/min. Will also raise INR to 2-4.

Other agents:
Fondaparinux: Appears not to react with HIT antibodies. Long half-life and renal clearance makes ICU difficult - useful later in course
Direct oral anticoagulants – Increasing use in HIT but most expert prefer to start with argatroban in severe cases
Bivalirudin: Limited data - most useful in HIT patients needing cardiac procedures

Suggested HIT Protocol

Points	**2**	**1**	**0**
Thrombocytopenia	>50% fall or nadir 20-100,000/ul	30-50% fall or nadir 10-19,000/ul	Fall < 30% or nadir <10,000/ul
Timing of platelet fall	Onset day 5-10 of heparin or < 1 day if patient recently exposed	Consistent but not clear records or count falls after day	Platelets falls < 5 days and no recent (100

	to heparin	10	days) heparin
Thrombosis	New thrombosis or skin necrosis or systemic reaction with heparin	Progressive or recurrent thrombosis or suspected but not proven thrombosis	None
o**T**her cause for thrombocytopenia	No	Possible	Definite
Pretest Score 6-8=high, 4-5 intermediate, 0-3 low			

Warkentin, Heddle Current Hematology Reports 2:148 2003

If HIT score is >6 *or*
Patient has documented new thrombosis on heparin *or*
Platelets fall by over 50% for no other reason than heparin exposure
Then stop heparin and substitute argatroban

If HIT score is 4-5 than obtain HIT test. If test positive then stop heparin and substitute argatroban
If HIT score is 0-3 no need to obtain HIT test

Thrombocytopenia and Pregnancy
Three syndromes in the critically ill pregnant woman who presents with coagulation defects.

1) HELLP (**H**emolysis, **E**levated **L**iver tests, **L**ow **P**latelets)
* Variant of pre-eclampsia
* High LDH, schistocytes, DIC
* Responds to delivery of child
* Severe cases may require plasma exchange

2) Fatty liver of pregnancy
* Severe coagulation defects and liver failure
* Responds to delivery of child

3) TTP
* Occurs most often in 2nd trimester
* Can support mother through pregnancy with plasma exchange

Pregnancy Related Diseases -TTP/HUS, HELLP Syndrome, and Acute Fatty Liver of Pregnancy (FLP)

	HELLP	**TTP/HUS**	**AFLP**
Hypertension	Always present	Sometimes present	Sometimes present
Proteinuria	Always present	Sometimes present	Sometimes present
Thrombocytopenia	Always	Always	Always
LDH Elevation	Present	Marked	Present
Fibrinogen	Normal to Low	Normal	Normal to Very Low
Schistocytes	Present	Present	Absent
Liver Tests	Elevated	Normal	Elevated
Ammonia	Normal	Normal	Elevated
Glucose	Normal	Normal	Low

HELLP = Hemolysis, Elevated Liver tests, and Low Platelets
TTP/HUS = Thrombotic Thrombocytopenic Purpura/Hemolytic Uremia Syndrome
AFLP = Acute Fatty Liver of Pregnancy

Very Quick Guide to Reversing Antithrombotic Therapy

Agent	Half-life	Renal Disease	Reversal
Aspirin	15-30 minutes	No change	DDAVP, Platelet Transfusions (?)
Clopidogrel	8 hours	Metabolites renally cleared	DDAVP(?), 2 units of platelet transfusions
Prasugrel	7 hours	Metabolites renally cleared	DDAVP(?), 2 units of platelet transfusions
Ticagrelor	7 hours	No change	DDAVP(?), 2 units of platelet transfusions (may be ineffective)
Abciximab	30 minutes	No change	Platelet Transfusion
Tirofiban	2 hours	Decrease dose by 50% if ClCr < 30 ml/min	Platelet transfusions, DDAVP, cryoprecipitate, dialysis
Eptifibatide	2-3 hours	Decrease dose by 50% if ClCr < 30 ml/min	Platelet transfusions, DDAVP, cryoprecipitate, dialysis
Unfractionated Heparin	30-150 minutes	45-225	Protamine - see table
Low Molecular Weight Heparin	2-8 hours	4-16 hours	Protamine - see table
Fondaparinux	17-21 hours	Clearance decreased by 50% if ClCr < 30 ml/min	PCC 50 units/kg
Argatroban	40 minutes	No change	PCC 50 units/kg
Bivalirudin	25 minutes	60% dose reduction if ClCr < 30 ml/min	PCC 50 units/kg
Dabigatran	12-14 hours	Avoid if ClCr < 30 ml/min	Idarucizumab 5grams
Apixaban	12-14 hours	Can be used in dialysis patients	PCC 50 units/kg or Andexanet
Betrixaban	19-27 hours	50% reduction if CrCl 15-30 ml/min, Avoid if ClCr < 15 ml/min	PCC 50 units/kg

Edoxaban	10-14 hours	50% reduction if CrCl 30-60 ml/min, Avoid if ClCr < 30 ml/min	PCC 50 units/kg
Rivaroxaban	4-9 hours	Avoid if ClCr < 15 ml/min	PCC 50 units/kg or Andexanet
Warfarin	36 hours	50% reduction in CYP C2P9	vitamin K, FFP, PCC, rVIIa - see table
Streptokinase		Hepatically cleared	Plasma, platelet, cryoprecipitate
tPA	3 minutes	Hepatically cleared	Plasma, platelet, cryoprecipitate
Reteplase	13-16 minutes	Hepatically cleared	Plasma, platelet, cryoprecipitate
Tenecteplase	15-20 minutes	Hepatically cleared	Plasma, platelet, cryoprecipitate

PCC = prothrombin complex concentrates, FFP = Fresh Frozen Plasma

Standard Heparin Reversal: Protamine:

Time since last heparin dose	**Dose of Protamine**
< 30 minutes	1 unit/100 units of heparin
30-60 minutes	0.5 - 0.75 units/100 units of heparin
60-120 minutes	0.375 - -0.5 units/100 units of heparin
> 120 minutes	0.25 - 0.375 units/100 units of heparin

Infusion rate should not exceed 5 mg/min. Maximum dose is 50 mg

Low Molecular Weight Heparin

Reversal of Bleeding: Protamine (works just as well with LMWH as heparin) - if with-in 4 hours of dose 1mg of protamine for each 1mg of enoxaparin or 100 units of dalteparin and tinzaparin. Should repeat one-half dose in 4 hours. If 4-8 hours after dose give 0.5 mg for each 1 mg of enoxaparin or 100 units of dalteparin and tinzaparin.

Therapy of the Bleeding Patient on Warfarin

Key point about vitamin K

- sub-Q erratic and should **NOT** be used
- PO effective in most patients
- IV should be given slowly (over one hour)
- A little goes a long way - the RDA is 80 ug/day

Not Bleeding: Goal is INR in 2-3 range

INR	Action
3-3.45	Hold dose until INR decreased
4.5-10	1.25 mg Vitamin K PO
> 10	2.5 -5 mg Vitamin K PO

Should see INR back in therapeutic range in 24-48 hours

Bleeding: Goal is INR under 2

INR	Action
2-4.5	2.5 mg Vitamin K ± FFP (15ml/kg)
4.5-10	5 mg Vitamin K ± FFP (15ml/kg)
>10	5-10 mg Vitamin K ±FFP (15ml/kg)

Consider Intravenous route for Vitamin K if faster effect desired

Use Prothrombin Complex Concentrates for life-threatening bleeding such as intracranial hemorrhage - dosing:
If INR 2-4: 25 units/kg (not to exceed 2500 units)
If INR 4-6: 35 units/kg (not to exceed 3500 units)
If INR > 6: 50 units/kg (not to exceed 5000 units)