^ PTT:

(The intrinsic pathway is initiated by prekalli-krein and high molecular weight kininogen).

Acquired
- Heparin[1]
- Inhibitors of VIII,IX,XI,XII
- Lupus anticoagulants

(usually pro-thrombotic)

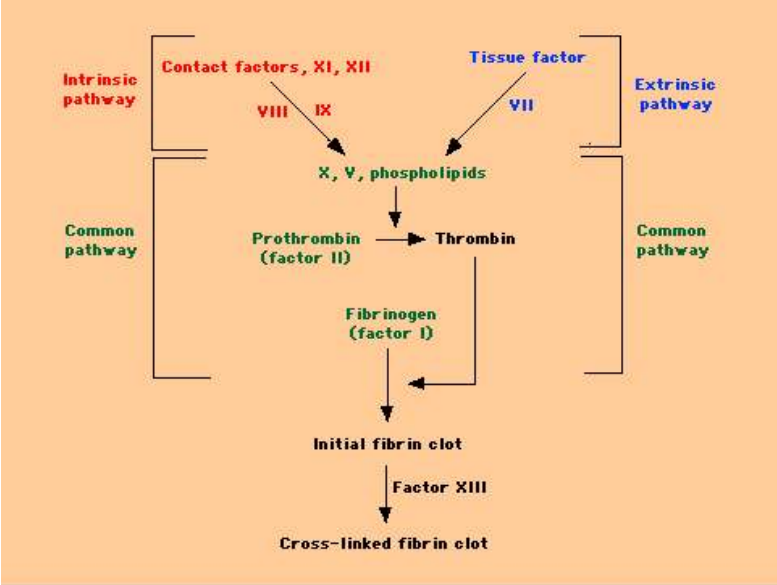
Inherited
- Def of VIII (hemophilia A)
- Def of IX (hemophilia B)
- Def of XI & XII
- Von Willebrand dis

[1]Heparin potentiates the action of antithrombin III and thereby inactivates thrombin (Thrombin factor II ordinarily sustains the coagulation cascade through a positive feedback interaction with XI; it also activates XIII to facilitate formation of crosslinked fibrin polymers.)

Ximelgatrain is a direct thrombin inhibitor.

[2]XI deficiency gives mucocutaneous bleeding.

[3]XII deficiency prolongs PTT but causes no clinical bleeding.



Coagulation pathways Schematic representation of the intrinsic (in red), extrinsic (in blue), and common (in green) coagulation pathways. In the clinical laboratory, the intrinsic (and common) pathway is assessed by the activated partial thromboplastin time (aPTT) and the extrinsic (and common) pathway by the prothrombin time (PT). The thrombin time (TT) assesses the final step in the common pathway, the conversion of fibrinogen to fibrin, following the addition of exogenous thrombin. Fibrin is crosslinked through the action of factor XIII, making the final fibrin clot insoluble in 5 Molar urea or monochloroacetic acid. This latter function is not tested by the PT, aPTT, or TT.

^ PTT and ^ PT

Aquired:
- Inhibitors of prothrombin, fibrinogen, V or X.
- Liver Disease
- DIC
- Very Hi Heparin Dose
- Very Hi Coumadin Dose
- Combined Heparin & Coumadin administration.
- Primary amyloidosis with X defiiency

Genetic:
- Deficient prothrombin, V or X or fibrinogen

Dysfibrinogenemia has ^ PT, PTT and thrombin time. PT and PTT will correct on mixing study.

^TT: v conversion of fibrinogen to fibrin, including heparin. RT is increased too, except with heparin.

Normal PTT & PT

- Platelet deficiency
- Platelet dysfunction (e.g., ASA use; uremia)
- Giant platelet disorders (e.g., Bernard Soulier)
- Von Willebrand's disease (mild)
- XIII deficiency causes a severe bleeding disorder.
- Defects in Plasminogen activation or plasmin degradation.

Decreased PTT and/or PT: Poor collection, lab error, malignancy, exercise or DIC

^ PT

- Coumadin[2]
- Vit K def
- Liver disease
- VII def (rare)
- Inhibitors of VII (rare)

[2]In the liver, coumadin blocks vitamin K as a co-factor in its conversion of glutamic acid residues on II, VII, IX, X, and protein C. Activated Protein C, generated by initial clot formation, inactivates Va and VIIIa and thus limits coagulation. Coumadin's action on protein C leads to a **pro-coagulant** state in two clinical situations: a) Lack of heparin-ization when initiating coumadin and b) Coumadin induced skin necrosis, where there is a prior lack of protein C. Heparin is the answer for both of these. (Factor V Leiden is resistant to activated protein C.)

VITAMIN B 12 DEFICIENCY

"... B 12 levels are often in range of 200 to 300 pg / ml (low but often not below the lower limit of normal). Liver disease and myeloproliferative diesease can also lead to falsely low-normal or normal levels of vitamin B 12 in patients with pernicious anemia. ... In vitamin B 12 deficiency the levels of both homocysteine and methyl-malonic acid are elevated, whereas in most cases of folate deficiency only the homocysteine level is increased." (Renal insufficiency can also elevate homocysteine levels.)

	homocysteine	methyl-malonic acid
Folate deficiency	^	Normal
B 12 deficiency	^	^

PERNICIOUS ANEMIA: Antibodies to intrinsic factor are 70% sensitive and 100% specific. Antibodies to parietal cell are 90% sensitive and are 50% specific.

Also, note: Treatment with B12 in severe PA can result in dramatic proliferation of bone marrow cells which take up potassium, and patients can become hypo-kalemic very quickly. Sudden death may occur. Monitor potassium and give potassium as needed.

THREE COLD PATIENT SYNDROMES

Disease	Setting	CM's	Lab	Mechanism	Rx
Cold Agglu-tinin Disease	Elderly Raynaud's dis Lymphoma (i antigen) Waldenstrom's. CLL (I antigen) Mycoplasma Infectious mono	**Acral cyanosis** Confirm dx by putting pt's hands in tepid water and slowly adding ice. Dyspnea Ddx: Raynaud's PCH, Cryoglobulinemia. *	May have Hemolysis. Spurious macrocytosis is due to RBC agglutination. DCT detects C3. Cold Agglutinins are detected in plasma when kept at 37 degrees.	IgM Antibodies against polyscacchar-ides on RBCs.	**Warm patient.** Plasmapheresis Rituximab. Cyclophaspham ide NOT prednisone or splenectomy.
PCH: Paroxys-mal cold hemoglob-inuria	Syphillis (1st in 1872!) Mycoplasma Klebsiella Post measles vaccine	**Red-brown urine with cold** exposure. (Intra-vascular hemo-lysis. Sometimes: Raynaud's & urticaria. *	DCT detects C3 at reduced temperature but not at 37 degrees. May have to use radio-labeled anti-IgG test.	IgG reacts with p Ag on RBCs*** Intra-vascular hemolysis.	**Warm patient.** Prednisone if needed. NOT splenectomy.
Cryoglobu-linemia.	Type I: MM, Waldenstrom's will cause glomerulopathy. Distinguish from amyloidosis. Type II: Chronic infection with Hep C or HIV (previously thought to be IM and Hep B). Both monoclonal IgM directed against a polyclonal IgG == MIXED CRYOGLOBULINEMIA Type III: Mixed cryoglob but both IGM and IgG are polyclonal. Associated with Lupus and other autoimmune disease.	Most are asymptomatic Palpable purpura. In Type I: livido reticularis & Raynauds hepatitis, cirrhosis H S megaly, Peripheral neuropathy, Low grade Hodgkin's dis Glomerular disease in 1/2 of patients with Type II 12% in Type III	**Normal hemogram.**	Cyroglobulins are Immunoglobu-lins that precipitate in serum in the cold but dissolve on warming. Decreased C4.	**Warm patient**. Prednisone, cyclophospham ide, and plasmapheresis in combo. OR Rituximab (80% response) RX of underlying Hep C etc.

Blood in periphery cools and AB & 1st 2 complement components are fixed to RBCs. On warming, the complement cascade is completed causing hemolysis.

AUTOIMMUNE HEMOLYTIC ANEMIA DIRECT COOMBS POSITIVE. July 31, 2006

	Setting	CM's *	Laboratory *	Mechanism	RX
Warm Antibody	Idiopathic (50%) OR CLL, NHL, SLE, Ulc Collitis, HIV, Penicillin, methyldopa	Extravascular hemolysis. Abd pain, fever, jaundice. May progress to lymphoproliferative dis or DVT with LAC *	DCT** IgG Ab detects IgG, NOT C3, in PEN & AMD. IgG Ab detects IgG AND C3 in SLE.	IgG and C3d on surface of patient's RBCs.	Steroids Azothioprine, Cyclophosphamide, Rituximab Danazol IVIG Splenectomy
Cold Agglutinin Disease	Mycoplasma Infectious mono Raynaud's dis Lymphoma (i antigen) Waldenstrom's. CLL (I antigen)	**Acral cyanosis** extremities, ears, nose during cooling. Confirm dx by putting pt's hands in tepid water and slowly adding ice. Dyspnea Ddx: Raynaud's PCH, Cryoglobulinemia.	Spurious macrocytosis. DCT detects on RBC IgM Ab against C3. Cold Agglutinins in plasma (keep at 37 degrees). i antigen may react best with fetal RBCs	IgM Antibodies against polyscaccharides on RBCs. RBCs removed by liver. **DAT +I've (better in cold).	**Warm patient.** Plasmapheresis Rituximab. Cyclophasphamide NOT prednisone or splenectomy.
PCH: Paroxysmal cold hemoglobinuria	Syphillis (1st in 1872!) Mycoplasma Klebsiella Post measles vaccine	**Red-brown urine with cold** exposure. (Intra-vascular hemolysis. Sometimes: Raynaud's & urticaria. *	DCT for IgG against C3 at reduced temperature but not at 37 degrees. May have to use radio-labeled anti-IgG test.	IgG & C on RBCs*** Intra-vascular hemolysis. **DAT +I've (better in cold)	**Warm patient.** Prednisone if needed. NOT splenectomy.
Drug induced: Against Rh	Methyldopa	Hemolysis in weeks to months after initiation. *	DCT for IgG, NOT C3.		Steroids
More common Drug induced: Against drug-RBC complex (hapten)	Penicillin Sulfa Phenacetin Quinidine	*	DCT for IgG, NOT C3. No Ab in patient's serum. Eluate from patient's RBCs does not react with normal RBCs.	Drug is firmly bound to RBC	
Drug induced: Against drug-protein complex (innocent bystander misnomer)	Fuadin chlropropamide (wide variety of drugs)	Hemolysis within days of initiation. *	DCT NOT for IgG, positive for C3.	Drug is loosely bound to RBC (analogue to drug induced immune thromboytopenia.)	

*All conditions may have pallor, ^ HR, hepatomegaly, and/or splenomegaly. Spherocytes, ^ LDH, V Haptoglobin, nucleated RBCs

**Direct CT = Direct Coomb's Test: The Direct antiglobulin (Coombs') test: the RBCs of the patient are washed free of adherent proteins and reacted with antiserum or monoclonal antibodies prepared against the various immunoglobulins, particularly against IgG and/or against a fragment of the third component of complement, C3d. These Complement and IgG (or in Cold Agglutinin Disease, IgM) immunoglobulins cause the AIHA.

*** IgG fixes 1st 2 components of complement to RBCs in cold extremities then the complement cascade occurs when the blood circulates to warmer core. In vitro, IgG is attached to RBCs in cold but dissociates from the RBCs when warmed.

G6PD DEFICIENCY

Suspect G6PD deficiency in males who are Afro Americans (11% prevalence), Kurdish Jews, and Greeks.

Suspect G6PD deficiency in men taking TMP/SMX (the SMX is the problem; this is used to prevent and treat pneumocystis and for traveler's diarrhea) and primaquine (used to prevent and treat malaria and used to treat pneumocystis carinii).

In red blood cells, the hexose monophosphate shunt protects against oxidation, and G6PD is a key enzyme, which converts NADP to NADPH, which then combines with oxidized glutathione to form reduced glutathione, which is then available to react with H2O2 produced by oxidant stress.

When the G6PD enzyme is defective, oxidative stress by infection or drugs can lead to **oxidation of sulfhydryl groups in hemoglobin, which precipitates in the RBCs forming Heinz bodies which are seen on supravital staining. The sulfhydryl groups in hemoglobin leads to hemolysis.**

Bite Cells are formed on peripheral smear. **The reduction in the abnormal RBCs can mean that the G6PD assay will be normal in the remaining cells**. Therefore, you must repeat the assay if there are bite cells and appropriate oxidizing circumstances. The best assay directly measures the ability of G6PD in the cells to form NADPH from NADP.

Infectious triggers can be viral or bacterial.

The drugs are:

A ntimalarials: Primaquine/ pamaquine/ dapsone

Sulfa antibiotics:

Sulfa antibiotics:
trimethoprim sulfamethoxazole.
Nitrofurantoin

Other:

Vitamin K in water soluble form
Doxorubicin
nalidixic a cd
furazolidone.

METHEMOGLOBINEMIA

Ferrous (Fe2+) is converted to Ferric (Fe3+) daily for about 1% of hemoglobin. Methemoglobin is unable to bind oxygen, and the remaining Ferrous heme in the hemoglobin tetramer binds oxygen more tightly, the O2 dissocation curve is left shifted, and there is decreased O2 delivery to tissues (double whammy). Congenital absence of the reducing, NADH dependent cytochrome b5 reductase enzyme, leads to methemoglobinemia. In heterozygous form, there is no adaptation via increase in RBC mass, and this can be life threatening. In Type II methemoglobinemia, the enzymatic abnormality effects both RBCs and brain cells, and there is associated mental retardation early in life.

The diagnosis is suspected by cyanosis in the presence of a normal PO2a, or it can be suspected by a somewhat low pulse-oximetry in the presence of a high normal PO2a. It is confirmed by assay of methemoglobin via co-oximetry and then by a method involving the addition of cyanide. Assay of the enzymatic activity can also be done. Sulfhemoglobinemia is part of the differential diagnosis.

Treatment is with Methylene blue, which has electron acceptors, **except** in the presence of G6PD deficiency where the methylene blue can cause excessive oxidation and hemolysis that would be potentially life threatening. In this case, ascorbic acid is given.

Agents to avoid are all of those for which G6PD deficiency must be avoided. In addition, nitrates and lidocaine must also be avoided..

DIC: Although heparin was formerly recommended for the treatment of DIC, it is now used rarely and only in unusual circumstances (such as acute promyelocytic leukemia). Focus on treatment of the underlying condition. For the patient who continues to bleed, supplementation of platelets and clotting factors (with fresh frozen plasma or cryoprecipitate) may help control life-threatening bleeding.

Drugs such as nonsteroidal anti-inflammatories can compete with warfarin for albumin-binding sites and will lead to an increased prothrombin time.

THALASSEMIAS July 31, 2006

	Normal	Iron Deficiency	alpha thal minor alpha thal trait ("A" is for African)	alpha thal Hemoglobin H disease	beta thal minor or trait (3) (much more common)	beta thal inter-media (much more common)
Ethnicity			AfroAmericans 30% SE Asian, Africa-West Coast	SE Asian, Africa-West Coast	Italy, Greece, Asia, Africa-Sub Saharan	Italy, Greece, Asia, Africa Sub-Saharan
Clinical Setting			Fatigue	^ spleen, leg ulcers, HA, CHF, ^LDH. Prooxidants: e.g., Sulfa, like G6PD v		^spleen, osteo-porosis, Fe in heart, liver, pan-creas, pituitary etc
PE				^ spleen	NL	^spleen,DM,etc(7)
HgB	15 gm/dL	Decreased (4)	10 gm/dL to Normal	8 gm/DL	Mild v (Hgb > 10)	< 10
MCV	90	75 or normal(4)	75	65	65	<65
Retic count	NL	NL	Increased	Increased	Increased	Increased
Peripheral Smear		Rare inclusions, hypochromia	mild hypochromia	Target Cells (5)	Target Cells hypochromia	Target Cells hypochromia
Fe, Ferritin	NL	Decreased	NL	NL	NL	NL
Hemoglo-bin electropho-resis	Hgb A 97% Hgb H 0% HgbA2 2.5% Hgb F 0%		**Can be normal** because there is no substitution gene for the a gene. But Hgb A ~ 90% (6)	Hgb A 82% Hgb H 5 - 30% Hgb A2 0%	Hgb A2 > 3% +_ Hgb F ^	Hgb A2 elevated
Pathogen-esis	(1)		Deletions. - - / a a OR - a / - a (2) Decrease in alpha chains.	Deletions. - - /- a. Decrease in alpha chains.	b / b+ (3) Decrease in beta chain synthesis or abnormal beta chain function.	b^+/b^0 b^+/b^+
Treatment		Ferrous Sulfate 325 mg TID	None	Survive to mid adult Folate+Splenectomy	None	Like Hemoglobin H disease.

(1) Designations are as follows: Hgb A: $a_2 b_2$, Hgb H: b_4. Hgb A2: $a_2 d_2$. Hgb F: $a_2 g_2$. Most Hgb is Hgb A, which has 2 apha chains and 2 beta chains. Here, a is alpha, b is beta, d is delta, and g is gamma. Alpha globin has 2 alleles so 4 loci can be effected; beta globin has one allele so only 2 loci can be effected. [(Hgb F is fetal hemoglobin. Hydroxyurea causes it to be produced. Also, there are small amounts of Hgb A1C, which have glucose attached to the terminal valin in each beta chain. Each of the 4 subunits contains a heme moity. Alpha has 141 AA's, and beta has 146 AA's. Each heme moiety normally has most iron in ferrous (Fe 2+) form, but when exposed to oxidants, it becomes ferric (Fe 3+), which is normally converted back to Fe2+ by NADH-methemoglobin reductase; if this is absent, there is congenital methemoglobinemia.] Thalassemias are diagnosed by 1st identifying a **microcytic** anemia, 2nd **a retic count >100,000/uL**, (**target cells & Normal Fe & TIBC** further support a thalassemia diagnosis), 3rd an **hemoglobin electrophoresis**: increased A2 &/or F = beta thal, Hgb H = alpha thal Hgb H dis, while normal electrophoresis gives alpha thal minor, which is confirmed by family studies and globin chain analysis.

(2) - - / a a is termed alpha thal 1 trait, or alpha thalassemia minor, which is more severe than - a/- a, which is termed alpha thal 2 trait.

(3) Notation: b is normal, b^+ is decreased synthesis (a mild mutation), and b^0 is no synthesis. Beta thalassemia major has b^0/b^0, which requires early stem cell transplantation.

(4) In iron deficiency anemia, anemia precedes microcytosis, which does not occur until Hgb decreases below 10. In mild thalasesemias, the Hgb is normal while there is microcytosis, or microcytosis is severe relative to the anemia.

(5) RBC fragments and RBC occlusions are seen when stained with supravital dye.

(6) Since, in alpha thalassemia minor, the hemoglobin electrophoresis is often normal, the diagnosis is made presumptively by ruling out other causes of mild anemia or normal Hgb with microcytosis. The only diagnostic method is a globin chain synthesis study which is not generally available. Alpha thalassemia occurs in 20% of blacks. These patients are often given iron supplementation to no avail.

(7) Beta thal intermedia can be asymptomatic to severely symptomatic with variable degrees of iron overload, cardiomyopathy, bronze diabetes, hypopituitarism, hypogonadism, and osteoporosis with bony fractures bone dysplasias due to several mechanisms: ineffective erythropoesis, endocrinopathy, and excessive iron chelation therapy. (For beta thalasemia see NEJM 2005;353:1135-46)

TRANSFUSION REACTIONS July 31, 2006

Reaction	Product/ Onset/Inc	CMS (**hallmarks in bold**)	Mechanism of Action	Treatment
Acute Hemolytic (1)	RBC/ Immediate/ 1:25,000	^T,Chills,N,V,Pain in flank, abd, head, Dysp, Renal Failure, **RED PLASMA & URINE (hemoglobinuria),** direct coombs positive, **Massive ^ K**. Mortality 17-60%.	ABO incompatibility. Group O recipient gets A or B. IgM Ab fixes C	**Normal Saline**. Alert Blood bank for error. **Heparinize**, acute dialysis, monitor EKG for increase K.
Anaphylaxis (2)	Almost any except albumin. Immediate. 1:20,000	**Rash**, hives, SHOCK, ANGIOEDEMA, Dysp, N, abd cramps, diarrhea Especially in East Asians.	IgG or IgA Ab in an IgA deficient patient.	Epinephrine, Steroids, normal saline, IV diphenhydramine. Airway. Block with blood from IgA deficient donor
Urticarial or allergic (1) (2)	FFP, Platetlets (1%), RBCs Immediate	**RASH**, hives, urticaria. Pre-existing IgA deficiency.	Patient's pre-existing IgE Ab's on mast cells and basophils are released.	IV diphenhydramine 50 mg. **If sx's stop, this rules out anaphylaxis and can continue transfusion.**
Sepsis (2)	RBCs, Platelet concentrates (not stored in cold)/ imm. to <1hr 1:1,000	^ T, chills, V BP, ^HR, back, chest, abd pain, dyspnea, oliguria Gram stain & culture donor blood & patient's blood. Yersinia grows in refrigerated RBCs.	Bacteria (yersinia)in not cold stored product or skin plug (salmonella) from patient.	Broad Spectrum Ab'c
Febrile non-hemolytic (THE MOST COMMON) (1) (2) (3)	**Platelets (30%),** RBCs(1%) 1-6 hours. If use leukocyte reduced, rate is 15%.	**^ FEVER**, ^HR, ^ BP. HA,N,V. BENIGN.	Either 1) cytokines from WBCs or 2) recipient Ab to donor Ag's. HLA reaction.	Rule out Acute Hemolytic via blood sample. Prevent by leukocyte reduction pre storage. Avoid when preparing for transplant.
TRALI: transfusion related acute lung injury (1)	FFP. 2 to 4 hours. 1:2,000	Dyspnea, pulmonary edema, **HYPOXEMIA NOT FROM FLUID OVERLOAD !!!!** CVP is normal. ARDS picture.	Donor HLA specific or PMN specific Ab reaction with patient's WBCs causing WBC trapping	Respiratory support. **Stop diuretics.** Fluid excess is not causal !!!
Delayed Hemolytic (1)	RBC/ 2-10 ds, 1:7,000	**Unexplained drop in HGB**. Less severe than acute hemolytic transfusion rxn. ^ Ind Bili, ^LDH, v Haptoglobin, Spherocytosis. ^ T	Alloantibody to Rh, Kidd, Duffy, Kell due to prior sensitization.	Diagnosed by blood bank. Prevent by I.D. the Ag and informing the patient.
Post transfusion purpura	RBC, platelets, WBCs/ 5-10ds	Women 95%. ITP picture: Marked V platelets	Same as ITP. Sensitized by pregnancy or prior transfusion. HPA 1a on platelets	IV IG 1gm/kg 2 days. Steroids. Exchange transfusion Use wash or HPA-1a deficient cells in future.
ACE I x Transfusion interaction (3)	Transfusion of WBCs via Leukocyte reduction	Acute decrease in BP. Patient on an ACE Inhibitor !!	leukocyte reduction activates kinninogen or F XII	DISCONTINUE THE ACEI THIS IS NOT TRUE ANA-PHYLAXIS !!
GVHD	4 to 30 days following transfusion.	Pancytopenia, infection, hemorrhage.	Engraftment of donor T lymphocytes in immunocompromised and sometimes in normal persons.	Radiate blood prior to transfusion, particularly where donor is HLA compatible relative.
CMV		CMV	CMV	
Iron Overload		hemochromatosis	hemochromatosis	

(1) Acute Hemolytic, Urticarial-Allergic, Febrile Non-hemolytic, TRALI, and Delayed Hemolytic transfusion reactions were emphasized in MKSAP XIII with cardinal signs of red plasma & urine, rash, fever, hypoxemia, and unexplained drop in hemoglobin, respectively.

(2) Isn't it interesting: Anaphylaxis is to Urticarial as Sepsis is to Febrile non-hemolytic.

(3) Bedside leukocyte filtration or prestorage leukoreduction will prevent HLA allo-immunation while awaiting organ transplant and b) febrile non-hemolytic transfusion reactions.

HYPONATREMIA OF MALIGNANCY:
Differential Diagnosis of SIADH
Drugs: Carbamazepine, cyclophosphamide, SSRIs

Small Cell Lung CA

Pulmonary infections
Positive Pressure Breathing
Pneumothorax
Asthma

CNS disorders

Major surgery

RX:
*If moderate,
Restrict fluid intake to 500 to 1000 l/d
Demeclocycline

*If Sx'c hyponatremia with altered Mental status,
Compute amount of sodium required to raise serum concentration to 125 meq/L:
0.6*Weight in KG*(125 meq/L - Na observed) ??????????????

*Correct at no more than 0.5 meq/L hour.

Na in 3% is 513 mmol/L
Na in 0.9% is 154 mmol/L

SPINAL CORD METS
Sx's: muscle weakness, change in bowel or bladder habits, sensory loss, autonomic dysfunction.
Stat:
*IV 10 mg Dexamethasone IV followed by 4 mg Q6Hr..
If impaired ambulation, give 100 mg initially and then 4-24 mg Q6H and taper.
High dose has associated hyperglycemia, GI bleed, GI perforation, and Avascular necrosis of hip.
*Hospitalize
*MRI – gadonlinium enhanced.
*Radiotherapy

In Trouseau's syndrome – thrombosis in malignancy – the treatment of choice is fractionated heparin which has lower thrombosis rate than coumadin in RCT: NEJM 2003;349:146.
Heparin may also increase survival in advanced malignancy even where there is no thrombosis: J Clin Onc 2004;22:1944 !!

Hemachromatosis: Sensitivity of Fe/TIBC >45% for hemachromatosis is 98%. Among Northern Europeans, 0.5% are homozygoous. C282Y (most severe) and H63D. (NEJM2006;355:1812).

SVC SYNDROME:

Sx's: SOB, head fullness, facial edema, plethora, cough, arm swelling.
EMERGENCY: Stridor, HA, visual changes, altered mental status.
CXR, CT, Biopsy of supraclavicular node, thoracentesis, mediastinoscopy, thoracotomy.
Do NOT biopsy axillary node as there is poor wound healing.
MGT: Diurese, O2, Elevate head, Steroids (not shown to work), Tracheal stent if needed.
Small dose contrast venogram to r/o THROMBUS.

PERICARDIAL TAMPONADE
*DOE, Orthopnea, hepatic vein engorgement, JVP increased, tachycardia, hypotension, **narrow pulse pressure**, **distant heart sounds, elevated pulsus paradoxus**.

RX OF HYPERCALCEMIA OF MALIGNANCY (NEJM 2005;352 (4): 373.)
Mech'm: ^osteoclast activity; increased production of PTHrP in 80% of cases, rather than direct bone resportion as thought previously.
^1 25 dihydroxy vit D in Hodgkin's disease
Calcium, corrected upward in hypoalbuminemia, = Ca mg/dL observed + 0.8(4-albumin g/dL).
***Replace phosphate orally** (not IV); hypophosphatemia increases the difficulty of treating the hypercalcemia.
***Give IV normal saline** 300 cc/hr as tolerated. Patients with ^Ca associated with cancer are dehydrate due to nephrogenic DI from ^Ca and due to n & v. Increase the GFR and inhibit calcium absorption by calciuretic effect of saline.
***Give Lasix** (calciuretic) not HCTZ (inhibits calciuresis). After re-hydration, furosemide 20 - 40 mg IV Q 3 Hr to balance fluid in/out and promote renal excretion of CA.
***Give bisphosphonates** I.V. — either pamidronate or zoledronate. Although these cause renal dysfunction, the decrease in calcium can have a net improvement in renal function. Pamidronate 90 mg IV over 4 hours or Zoledronic acig 4 to 8 mg iv over 15 minutes.
*Steroids as short term management in sensitive tumors (MM, lymphoma, hormone sensitive breast cancer) at a dose of 1 to 2 mg/kg prednisone / day.
*Dialysis of patients with renal dysfunction may be required.

Coumadin:
^ INR effect: acetominophen, NSAIDs, metronidazole, anti-fungals, TMP/SMX, erythromycin, herbs with a G (Garlic, Gingko).
v INR effect: Avocado, phenobarbitol, rifampin, green tea, ginseng.
RESPONSE TO HIGH INR

	INR	GI or GU bleed	CNS bleed
Hold coumadin	< 9	-	-
2 - 4 mg vitamin K	> 9	-	-
FFP or Factor VIIIa	-	X	X

Coumadin 1/2 life is 36 hrs.... PT/INR done in the evening can be checked at 6AM.
coumadin and heparain are overlapped for 4 days because 1/2 live of factor 2 is 100 hrs.

THROMBOCYTOPENIA: DDX.

	ITP	TTP	HUS	HELLP
Etiology	Infection in children Quinidine Sulfonamides Heparin	Pregnancy OCPs, Quinine, adencocarcinomas, Chemo: mitomycin C, cyclosporine, Inf'n: HIV, Drugs: Clopidogrel, Ticlopidine	E Coli 157:H7, or post partum	Pregnancy 10% have pre-eclampsia
General	W>M, Usually age < 40 Follows inf'n in children			
skin	Lower extremities. Non-palpable petechia, purpura, easy bruising.	Palpable purpura	Palpable purpura	
other bleeding	epistaxis, menorrhagia			
Anemia		microangiopathic: helmut cells.	microangiopathic	microangiopathic
Renal			Anuria.	
Other	ITP has NO clumping on smear.*	Neuro – Severe	Neuro – mild	ALT > 70
pathogenesis	autoantibody to platelets.	Platelets in endothelium caused by a functional deficiency in ADMATS13, a Von WF cleaving protease, caused either by an acquired antibody or, more rarely, congenitally.	Platelets in endeothelium, but not caused by deficiency in ADAMTS13.	
DDX	Common: Gestational thrombocytopenia, Drugs: heparin, quinidine, Viruses: HIV, mono, hepatitis, Other: hyperslpenism. DIC Rare: myelodysplasia, vonWillebrand 2B, TTP Dx of exclusion.	DIC HUS, ITP	TTP, DIC, ITP	TT
RX	Prednisone AntiDglobulin if RH+ (85%) & spleen IVIG Retuximab (anti-CD20 Ab) Give vaccines, then splenectomy. Helicobacter eradication immuno-suppressive rx.	Discontinue offending drugs. Plasma exchange. Prednisone & immunosuprressive agents have been tried. Platelet transfusion is contraindicated.	Discontinue offending exposures. Plasma exchange may not work as well.	Delivery

*One might have expected clumping on blood smear in ITP because there are probably antibodies to the platelets, and this would sort of be analogous to rouleau formation in coomb's + hemolytic anemia. However, the ITP smear is normal; Platelet clumping occurs in pseudo-thrombocytopenia.

Hypercoagulable states: Protein C or S deficiency, anti-thrombin III deficiency, dysfibrinogenemia, elevated factor VII or VIII, FV Leiden, F II 20210, LAC, homocysteinemia, sickle cell disease.

Chronic uremia causes increased bleeding time due to abnormal platelet function. Treatment is desmopressin given before planned dental extraction. Other treatments take longer to be effective but are estrogens and erythropoietin.

Aminocaproic acid, a fibrinolysis inhibitor can be used in primary mennorhagia, g-u tract bleeding post prostate surgery, mild hemophilia, in profound thrombocytopenia, or after cardiac or joint surgery.

Lymphoplasmacytic lymphoma (Waldenstrom's macroglobulinemia) does not produce lytic bone lesions. It has IgM protein, HS megaly, viscosity syndrome. Viscosity is measured and if elevated, they are treated urgently with plasmapheresis and chemotherapy. There is often a positive direct coomb's test and an autoimmune hemolytic anemia. Treat with plasmapheresis and then nucleoside analogues fludarabine and cladrabine or rituximab. (MKSAP 14, hem-onc, Q68)

Treat parvo virus bone marrow failure with **IVIG** and therefore it is worth documenting this infection by obtaining titers.

Syngeneic transplantation, although not creating a risk of GVHD, paradoxically offers less chance of a cure for a number of hematologic malignancies. This is thought to relate to a "graft-versus-tumor" effect of the allogeneic transplant.

In radiation treatment, the mean time to onset of "acute" pericarditis is 9 months after treatment, and so caretakers must be vigilant.

For tumor lysis syndrome, give allopurinol, sevelamer for phosphate binding, monitor EKG for ^ K and v Ca (due to ^ phosphate), give NS, and alkalinize the urine.

Iron is lost from the body is by blood loss and desquamation of epidermal cells from skin and gut. Vitamin C assists in the absorption of iron and also in the mobilization of iron for utilization and to overcome EPO resistance in ESRD (MKSAP 14. Hematology. Q 35).

Daunorubicin: CHF

Bleomycin: interstitial pulmonary fibrosis

cyclophosphamide: Hematuria

cisplatin: renal toxicity

ifosfamide: fanconi's syndrome and neurotoxicity

Causes of thrombocythemia: essential thrombocythemia, iron deficiency anemia, myelodysplastic syndrome, CML, inflammation.

Use steroids in lymphomas where excess Hydroxylation of vit D may be involved, but not in most other malignancies.

Adult T cell lymphoma is seen particularly in southern Japan and the Caribbean, in association with infection with **human T cell lymphotropic virus (HTLV) I**. Patients with HIV infection are predisposed to the development of an aggressive B cell non-Hodgkin's lymphoma.

APPROACH TO BLEEDING PATIENT:

PT, PTT: Abnormal >>> Do mixing study. If PT/PTT correct, this indicates a low clotting factor. If not it indicates an inhibitor.

PT,PTT: Normal >> Test for vWillebrand factor. And do test for platelet aggregation. (E.G., “The platelet function analyzer” is a global screening test of overall platelet function, including adhesion to collagen, activation (change shape, put out pseudopodia), and aggregation.)

In **AML, hyperleukocytosis** is an emergency. It involves **hyperviscosity**, which includes stupor, headache, dizziness, tinnitus, visual disturbances, confusion, and frank coma. Pulmonary leukostasis may present as respiratory distress, hypoxemia, and progressive respiratory failure. Do a leukophoresis, HLA typing for allogenic transplant, chemotherapy, but DO NOT GIVE BLOOD PRODUCTS.... E.G., RBCS BECAUSE THIS MAY RAISE BLOOD VISCOSITY.

In hemophilia A, multiple transfusions of clotting factor VIII can cause IgG antibody to this factor. This is diagnosed by a mixing study which initially corrects but then is uncorrected on 2 hour incubation. Treatment is to by-pass VIII via use of recombinant VIIa or prothrombinase complex. Purified porcine factor VIII may not be effected by the antibodies. Steroids can also help.

Down's syndrome: acute leukemia

Fanconi's anemia involves defects in DNA repair, including leukemia.

Von Hippel——Lindau syndrome is associated with hemangioblastomas, renal cysts, pancreatic cysts and carcinomas, and renal cell cancer.

Neurofibramotosis (NF) type I and type II are both associated with increased tumor formation.

Diffuse large B cell lymphoma (DLBCL) is the most common NHL. Prognosticators are LDH level, stage, extranodal involvement, and age. (Tumor grade is not considered.)

If DVT is expected, following the patient twice weekly for 2 weeks with ultrasound to determine if there is going to be DVT. Protein C, Protein S, and anti-thrombin are decreased in acute DVT.

These tests can NOT be done when a patient has an active DVT or is on warfarin: Anti-thrombin, protein C and protein S.

Tylosis is a genetic disease characterized by thickening of the skin on the hands and feet and is associated with squamous cell cancer of the esophagus.

Melanomas are radioresistant. Therefore, if they metastasize to the spine, surgery is indicated and not RT.

Vitamin B 12 deficiency: Causes of vitamin B 12 deficiency include a fish tapeworm ingestion from Canada (diphyllobothrium), pernicious anemia with associated autoimmune disease, (e.g., hypothyroidism), Zollinger Ellison syndrome due to inability to alkalinize the small intestine, and bacterial overgrowth from GI surgery.

Folate deficiency is uncommon because grains are usually fortified with folate, which also occurs in bananas, melons, asparagus, brocoli, and leafy vegetables.

Methemoglobinemia: Certain drugs such as nitroprusside, sulfonamides, local anesthetic, and acetaminophen have been found to cause methemoglobinemia.

Her oropharynx demonstrates purpuric lesions. Case of MDS. Petechiae can be anywhere!

Megaloblastic refers to a morphologic abnormality of cell nuclei caused by various defects in DNA synthesis, most commly cobalamin deficiency, folate deficiency, metabolic inhibitor-type chemotherapeutic agents, and less commonly inborn errors and other unexplained disorders. **Macrocytic** is a specific term that refers only to the increased size of RBCs. Megaloblastic anemia is a subset of macrocytic anemia.

The neuropsychiatric abnormalities caused by cobalamin deficiency are not seen in folate deficiency, even though methionine synthesis appears to be equally impaired in both vitamin deficiencies. The cytopenias and bone marrow hypercellularity that results from either cobalamin or folate deficiency can be so severe that patients are rarely misdiagnosed with myelodysplasia or even leukemia. Because cobalamin and folate deficiencies are so easy to correct with replacement therapy, it is imperative that these disorders be ruled out. Serum LDH levels can be excessively elevated in cobalamin- and folate-deficient states.

In Sickle Cell Anemia, the neutrophil count is directly correlated with mortality, hemorrhagic stroke, and acute chest syndrome. Suppression of neutrophil count is the desired result of hydroxyurea administration.

Exchange transfusion in sickle cell anemia treating stroke and acute chest syndrome but is not effective in pregnancy or in preventing priapism.

Sickle cell trait raises the risk of death in military recruits during basic training by 30 fold, and can produce hematuria.

Sickle-alpha-thalassemia is frequent because there is a 20% of alpha thalassemia trait in US blacks and an 8% prevalence of sickle cell trait. Sickle-alpha-thalassemia is associated with higher rate of painful crises, mortality, CVA, osteonecrosis, decreased incidence of leg ulcers, and **decreased hemolysis and a milder anemia**, as compared to SS disease.

In acute painful episodes of sickle cell crises, **oxygen administration is now contraindicated because it is realized that it removes the oxygen drive for the production of erythropoetin and thus for production of new RBCs.**

Sickle cell anemia is treated with kertorolac, tramadol, butyric acid (to attempt to induce Hgb F), and hydroxyurea. In some patients, bone marrow transplant is used .in children.

CLL has coexpression of CD19, CD20, and CD5 in 95% of cases. Unless there are other unusual features, demonstration of this cell surface marker pattern is generally diagnostic for CLL, and marrow exams, node biopsies, and other procedures can be avoided initially.

CLL patients commonly have hypogammaglobulinemia, opportunistic infections, autoimmune disorders (pernicious anemia, thyroiditis, ITP, autoimmune hemolytic anemia), and second malignant tumors, including skin cancers, colorectal cancers, lung cancers, and sarcomas.

In acute promyelocytic leukemia, all-trans retinoic acid (a vitamin A derivative) induces complete remissions and is related to the known cytogenetic translocation (t15;17).

Contrary to popular belief, many (50%) patients with acute leukemia actually present with a total WBC count that is in the normal range. The differential will be abnormal, which points out the importance of checking the entire CBC in anyone suspected of having hematologic problems. About 25% of patients with acute leukemia will present with a low total WBC count, and only 25% will present with the more commonly described elevated WBC count.

ALL can relapse in gonads, CNS, or joints.

Presence of Philadelphia chromosome translocation t(9,22) is associated with the worst prognosis in ALL.

Lymphomas are associated with a) EBV in Burkitt's lymphoma, b) EBV in HIV infection, and b) H pylori in malt lymphoma.

In NHL, the monoclonal antibody, rituximab, is directed against CD20 surface marker.

In MM, two new therapies are autologous marrow transplantation, which results in longer survival, and pamidronate, which leads to fewer skeletal complications.

AL amyloid, either the primary or the localized form, is associated with κ or λ light chain as the major protein component.

Severe bleeding, intracranial bleeding, easy bruising and repeated spontaneous abortions are hallmarks of factor XIII deficiency. The diagnosis must be suspected on clinical grounds because screening coagulation assays are most often normal. The euglobulin clot lysis assay can be used for detection in suspected cases. (Lee

FAP is the most common autosomal-dominant polyposis syndrome. Polyps are noted by late adolescence throughout the colon, and the risk of colorectal cancer is greater than 90%.

Gardner's syndrome is a similar autosomal-dominant syndrome associated with desmoid tumors, lipomas, sebaceous cysts, and osteomas.

Turcot's syndrome is an autosomal-recessive syndrome associated with CNS malignancy and bowel polyposis.

HNPCC is a hereditary process with a high frequency of colon cancer without adenomatous polyposis and occurs in 1 to 6% of all colorectal cancers. The syndromes are divided into Lynch I and II; Lynch I is characterized by an autosomal-dominant pattern.

A high CEA correlates with poor prognosis in colorectal ca.

Standard therapy (e.g., 5 fu) is not curative for metastatic colon cancer and extends survival only negligibly.

For Non-Small Cell Lung Cancer, in stage I and stage II disease (which represent tumor within the lung without extension, 2 cm or more from the carina, and at most involving the hilar or bronchopulmonary lymph nodes <N1>), complete excision gives a chance of cure. Therefore, in a patient without mediastinal lymphadenopathy (N2) and with a <3 cm (T1) tumor, the proper management should be surgery, with a 5-year survival rate of greater than 50%. Genomic analysis refines the prognosis of early stage NSC Lung Ca (NEJM 2006;355:570).

Stage IIIA is a gray zone in which treatment could consist of surgery, neoadjuvant chemotherapy followed by surgery, or radiation combined with chemotherapy. Stage IIIA includes either a T3 tumor (tumor extending to the pleura, chest wall, or pericardium) or N2 nodes (nodes in the ipsilateral mediastinum).

Stage IIIB is defined by a T4 tumor (tumor involving the mediastinal organs or the pleural fluid) or N3 nodes (nodes on the contralateral side, as choice B in question 9 describes).

Aromatase inhibitors (anastrozole, letrozole, and exemestane) reduce 2nd primary contralateral breast cancer more than SERMs (tamoxifen) in ER positive women and these have become the recommended intervention in ER positive women.

If a patient has only in situ breast cancer, axillary lymph node dissection is not indicated.

Breast neoplasia type		
DCIS	in the breast ducts; does not penetrate the basement mb.	Good prognosis if resected. Lumpectomy plus RT or mastectomy alone. No lymph node resection.
LCIS	High risk marker for breast ca. (Similar to contralateral breast cancer.)	Resection Tamoxifen
Invasive breast ca		Axillary lymph node resection. lumpectomy+RT

(1) No bone scan is necessary in those with stage I or II disease (only 5% positive); In stage III disease (>5cm), get the bone scan (positive in 25%)

For locally advanced breast cancer, preoperative chemotherapy is administered to improve the resectability of the tumor.

Although uncommon, patients can have familial renal cell carcinoma inherited in an autosomal-dominant fashion or associated with von Hippel-Lindau disease, which results from mutations at a tumor-suppressor locus on chromosome 3p25-p26. In the latter, renal cell carcinoma develops in as many as 35% of patients, and some have associated pheochromocytoma, cerebellar hemangioblastoma, and retinal angiomas. In inherited renal cell carcinoma, the tumor is often bilateral.

Patients with a solitary metastasis of renal cell carcinoma can have a good 5-year survival rate after surgical resection.

In renal cell ca, chemotherapy has, at best, a 20% response rate

For bladder ca, patients with metastatic disease are treated with combination chemotherapy agents such as MVAC (methotrexate, vincristine, Adriamycin, and cisplatin), paclitaxel, and carboplatin or more recently regimens with gemcitabine combinations.

Lymphoma: Low Grade: Approach is to observe

Follicular small cleaved

Small lymphocytic

Follicular mixed

Prostate cancer: Patients with urinary symptoms and elevated serum PSA have a 60% percent likelihood of having prostate cancer.

A serum PSA between 4 and 10 ng/mL indicates that cancer is 25% likely, whereas values >10 ng/mL increase the likelihood of cancer to about 60%.

The vast majority of cancers that are detected by screening for PSA are localized clinically and therefore have an excellent chance of being cured with either radiation or surgery. Moreover, few tumors detected by PSA screening are incidental as most have a high volume or a worrisome Gleason score (indicating a poor prognosis based on histologic grade).

Finasteride decreases risk for prostate ca but not prostate mortality in men 55+.

Alpha tocopherol or selenium decreases risk for prostate cancer in RCT.

Stage	description	RX
A T1C	No palpable nodule, Elevated PSA	
B		RT or radical prostatectomy.
C	Invasion of seminal vessicles, bladder neck, prostatic apex	RT
D1	Lymph node involvement.	
D2	Metastatic disease	

For Localized prostate cancer, Low PSA Density (<0.1; PSA divided by prostate volume) and Gleason <7 do active surveillance Q6 months. In comparison for symptomatic men, the NNT with radical prostatectomy = 300 to prevent one prostate cancer death.

In good hands, for radical prostatetomy, an anatomical approach gtives incontinence of 3% and impotence of 30%.

Erythroplakia is characterized by red superficial patches. It is more commonly associated with dysplasia and carcinoma in situ or malignancy than is leukoplakia. Leukoplakia is found in up to 50% of people who chew tobacco.

Estrogen in herbs can lower testosterone level and act as anti-androgen therapy.

Melanoma: The S-100 and HMB-45 markers can be used to confirm the diagnosis; HMB-45 is more specific than S-100.

RX of melanoma: Therapy for metastatic disease may consist of combination chemotherapy with agents such as dacarbazine, cisplatin, BCNU, and tamoxifen, and possibly IL-2 and interferon.

The 14:18 translocation is frequently detected in follicular lymphomas.

M3, promelocytic leukemia, often has DIC as presentation. Treat with platelets, FFP, and, possibly heparin. Treat with allopurinol to prevent tumor lysis syndrome and with alkalinization of urine to prevent uric acid stones. Treat hyperviscosity syndrome with leukophoresis. The 15:17 translocation is seen in APL and causes the fusion of the retinoic acid receptor-αa with promyelocytic leukemia protein (a transcription factor).

Case

34 yo woman

3 months post partum (or pregnant or with a diagnosis of cancer or immune conditions)

Vaginal bleeding, easy bruisability.

Hematuria

Increased PTT

Mixing study: No change in PTT.

Dx: Factor 8 inhibitor

TESTICULAR CANCER

	Seminoma	Non-seminoma
beta HCG (½ life 1 day) (1,2)	elevated in ½ of pateints (Mneumonic: HCG tied to reproduction; AFP is not!)	in 85% either bHCG or AFP or both are elevated.
AFP (½ life 6 days)	(never elevated)	in 85% either bHCG or AFP or both are elevated.
Stage features	80% are stage 1	
Radiosensitivity	Very High. Mneumonic: R is closer to S than N.	Not radiosensitive.
Stage 1	Treat with prophylactic RT to regional lymphatics.	
retroperitoneal lympadenectomy		Standard in stage 1.
Bleo, etoposide, cisplatin	Used	Used

(1) One cause of a false-positive beta HCG assay is an increased LH level. This can be distinguished by repeating the hCG assay after an injection of testosterone.

Eaton Lambert (small cell ca): Decreased DTRs, proximal muscle weakness involvement and autonomic dysfunction, such as incontinence; no ocular and bulbar muscles. Tensilon test is not useful.

Myasthenia gravis: Preserved DTRs, and involves ocular or bulbar manifestations. Tensilon test is useful.

Risk factors for esophageal carcinoma include tylosis (a condition involving hyperkeratosis of the palms and soles, inherited as an autosomal-dominant disorder) and achalasia.

A phase I trial evaluates the toxicity of a new agent or combination and often enrolls patients with any malignancy if a reasonable standard treatment is unavailable. The trial is usually constructed to continue dose escalation until a maximum tolerated dose is obtained. The starting dose is usually based on the maximal tolerated dose found in the animal model. A phase II trial usually evaluates the tumor response in a specific tumor type. In a phase II trial, therefore, measurable disease is important to assess response. A phase III trial evaluates, in a randomized fashion, the efficacy of an agent compared directly with the standard agent or agents. Usually, large numbers of patients are required. Until these phases are complete, it is difficult to determine whether a particular drug or regimen should be used as a standard agent off of a clinical trial.

CA125 is elevated in ovarian cancer but is also elevated in any peritoneal malignancy.

CA 125 and US can detect early stage ovarian cancer.

The sign of Leser-Tréélat is characterized by the development of large numbers of seborrheic keratoses and is associated with adenocarcinoma of the stomach, lymphoma, and breast cancer.

Fever in neutropenic patients is a medical emergency. Risk of infection increases with a neutrophil count of <1000 (the absolute neutrophil count is calculated as the percentage of neutrophils and bands times the total WBC). A culture should be performed immediately and patients started on broad-spectrum antibiotics. The coverage must include *Pseudomonas* and other gram-negative organisms. Additionally, if infection of a catheter is suspected or fever persists after initiation of antibiotics, coverage for gram-positive cocci should be added with drugs such as vancomycin. If fever persists after 5 to 7 days and the patient is still neutropenic, coverage for fungi should be added. The use of GCSF (granulocyte colony-stimulating factor) is best after the next cycle of treatment in patients who have had fever

and neutropenia. In this setting, it has been shown to decrease duration of hospitalization and number of infections. It should not be given during the administration of chemotherapy because it could increase myelotoxicity. Its use at the time of neutropenia is not generally recommended.

In melanoma, 65% will have mets to brain.

RADIOGRAPHY, BONE SCANS & MALIGNANCY

	radiograph	bone scan
multiple myeloma	lytic lesions	normal (normal alk phos)
lung cancer and lung cancer	mixed lytic and slcerotic lesions	postive in some areas
prostrate cancer	sclerotic (blastic) lesions	strongly positive bone scan
lymphoma	normal	normal

Hodgkin's disease has two age peaks, in the 30s and the 50s, risk factors include a same sex sibling (10x risk), few siblings, single family house, early birth order, and fewer playmates. HD has fever, nite sweats, > 10% body weight in weight loss, and more than 80% present with lymphadenopathy above the diaphragm, often in the anterior mediastinum.

In Hodgkin's disease, patients with stage IA or IIA disease can be treated with radiation therapy only. Patients with classification B symptoms consisting of fever or weight loss should be treated with chemotherapy because there is a higher rate of recurrence with radiation alone. Patients with stage III or IV disease are generally treated with chemotherapy. Patients with large mediastinal masses, defined as greater than one third of the thoracic width, are treated with chemotherapy followed by mediastinal radiation.

Med Study:

Breast cancer > 4cm and node negative in a premenopausal woman gets modified radical + chemo. (I think lumpectomy + RT + chemo could also be done.)

For breast cancer in a postmenopausal woman, a cancer that is > 4cm but patient is node negative, is treated with radical mastectomy without RT (not that she does not get lumpectomy plus RT ??? look up !!!) and either tamoxifen alone if she is ER + or chemotherapy alone if she is ER -.

For prostate cancer, the first staging work up is a bone scan. If it is abnormal, plain films of the positive areas are done to rule out other causes (?).

The following drugs have peripheral neuropathy:

vincristine

vinorelbine

paclitaxel

cisplatin

Cisplatin causes renal v serum K and Mg, and secondarily, Ca.

Cisplatin also induces nausea and vomiting.

In neutropenic patients, some doctors begin empiric antibacterial coverage plus amphotericin.

Multiple Myeloma: Remember A BIRCH: anemia, bone pain (bone lytic lesions, bleeding), infection, renal ins, ^Ca, hypervisc. Criteria from International Myeloma Foundation (MKSAP 13 update):

Major: a) plasmacytoma on tissue biopsy. B) >30% monoclonal plasma cells in bone marrow. C) High M protein: IgG >3.5 gm/dL. IgA > 2.0 gm/dL. D) Bence Jones Protein > 1 Gm/ 24Hr.

Minor: a) 10-30% plasma cells on BM. B) M protein but less than above. C) IgG <600, IgM < 50, IgA <100. D) Lytic lesions on x-ray.

Diagnosis: 1 Major and 1 Minor. Or 3 Minor.

Rx: thalidomide.

MGUS:

Low M Protein: IgG <3.5 gm/dL. IgA < 2.0 gm/dL. Bence Jones Proteinuria < 1.0 gm/24hr.

Bone Marrow clonal plasma cells < 10%.

No end organ damage.

Gynecomastia in a male suggests a germ cell tumor (? Other endocrine tumor??)

Hemolytic anemias and Coombs testing(1) September 21, 2005

IgG	C3	Antigen	Clinical correlate
Pos	Neg	Rh-prot	Drugs: Pen, AMD. D.C. drug (1)
Pos	Pos	Glycopr	SLE (1)
Neg	Pos	Polysach. <>IgM	Peripheral purpura in cold;ulceration. RBC clumping on PBS. Cold Aggl Dis:Mycoplasma, IM, HIV, Measles, Lymphoma. Rx: Rituximab, plasmapheresis(1,2)
Neg	Pos	Polysach <>IgG Ab	Ditto symptoms. Dark urine in cold. Abdominal pain, Raynaud's. PCH:Mycoplasma, Klebsiella pn. (3)
P/N	P/N	Prot-drug	Drug (e.g, cephalosporin). Indirect Coombs + (4)
Neg	Neg	Any	Any: Clinical correlate, indirect Coombs for drug(4)

(1) Direct Coomb's test: Patient's RBCs are washed free of protein and then incubated with Antibodies to IgG and Ce.
(2)In cold agglutinin disease, the IgM antibody is in the serum. The antigens can be characterized further to correlate with different diseases.
(3) PCH is confirmed by incubating patient's serum with RBCs from a PCH patient. in the cold. IgG attaches to RBCs in the cold and fixes complement; when blood circulates to warm extremities, the IgG dissociates from RBCs but the complement cascade is completed.
(4)Indirect Coombs: Patient's serum is tested against normal RBCs without, and with, the normal RBCs pre-treated with high concentration of drug.
(5) Coomb's negative diagnoses: hemolysis is
Intravascular if LDH-ser^, Haptoglobin-ser is V, Hemosiderin-ur, Hgb-ser ^, Hgb-ur^: G6PD def, acute hemolytic transfusion rxn's, mechanical valves, PNH, sepsis, Malaria.
"**Extravascular**": Above LDH, haptoglobin, and hemosiderin, but Hgb in serum and urine is absent: Milder forms of the above causes Acanthocytosis from liver disease with splenomegaly, renal disease, spherocytosis, and SSA.

Case

50 yo man with a history of either aplastic anemia or myelodysplastic syndrome.

Presents with: Esophageal or abdominal pain,

Anemia, Normocytic, reticulocytosis, ^ LDH, v haptoglobin, ^ hemoglobin, hemoglobinuria.

v PMNs or platelets.

Coombs negative.

CT shows: DVT in hepatic, mesenteric, portal or cerebral veins,

Dx: PNH. How do you confirm this?

Flow cytometry: absence of proteins CD55 and CD59.

Rx: (1) prednisone 20 QOD, (2) anticoagulation. (3) Eculizumab is an monoclonal AB that inhibits activation of the terminal complement components causing hemolysis in PNH. (4) Gove Fe, folate.

Plain films: Lytic versus Blastic:

Paget's:	Blastic
Prostate ca:	Blastic
Renal cell ca	Lytic
Amyloidosis:	Lytic
Hungry bone syndrome:	Lytic
Multiple Myeloma	Lytic.
Breast CA:	blastic and lytic

Case:
60 y.o. man
Pruritis, headache, symptoms of PUD.
Splenomegaly
97% on room air
HCT 60, platelets 400,000, WBC 12,000
LAP score 110.
EPOser is low.
BM: ^ cellularity, no iron stores.
Dx: PV

Rx: phlebotomy and low dose aspirin are used to reduce risk of DVT.

In patients with prior DVT, a qualitative abnormality of the D-Dimer (Clearview Simplify D-dimer assay, a qualitative test) 1 month after discontinuation of anticoagulation was found in 37% and these patients had a 2.3 x higher risk DVT than those with normal D-dimer; In those with abnormal D-dimer, resumption of anti-coagulation reduced recurrent DVT from 15% to 2.9% at 1.4 years (Palareti G. NEJM 2006;355:1780).

Case
50 y.o. man with pruritis on taking a shower and erythromyalgia.
Splenomegaly
Swollen right leg. (Uh Oh: DVT).
Hemoglobin is 18.7.
Dx: PV

Criteria for PV are:

Major:
Hgb >18.5 or 16.5 in m & w or ^ RBC mass (by 25%)..
No cause of 2ndary erythrocytosis (Normal PO2 (no COPD etc).)
Splenomegaly
JAK2 mutation (80% of PV patients; also in myelofibrosis and essential thrombocythemia).
ECF

Minor:
^WBC
^platelets
Panmyelosis
Low EP.
Dx= First 2 major criteria plus another major or plus 2 minor criteria.

Causes of Erythrocytosis.

EPO is appropriately elevated: chronic hypoxemia from pulmonary disease, right to left shunts, obesity hypoventilation syndrome, osbstructive sleep apnea, high altitude, carbon monoxide poisoning (COHgb>5%) from cigarette smoking or from poor ventilation of indoor heating, certain cases of methemoglobinemia.

EPO is inappropriately elevated: renal cell ca, hepatocellular ca, hemangioblastoma, uterine fibroids, renal transplant recipients.

EPO is low: PV, methemoglobinemia, other germ line mutations.

In PV, phlebotomy and low dose aspirin are used to reduce risk of DVT.

Case

“Bruising & oozing”. Epistaxis, monorrhagia or prolonged post surgical or post child birth bleed.

0.5% of whites. AD(or rarely recessive) family history. Most common inherited bleeding disorder.

Non-inherited causes: hematopoetic neoplasms, CT disorders, hypothyroidism, cardiac valve defects, uremia, valproic acid.

Lab: v Bleeding time, v or normal VIII, v VonWillebrand Ag, Abnormal ristocetin co-factor activity.

Dx: Von Willebrand’s disease. VWF is an acute phase re-actant and will be increased by estrogens, vasopressin, stress, infection & inflammation. Von WF has 2 critical roles: 1) It attaches platelets to blood vessels and anchors a growing thrombus to site of injury. 2) vWF is a carrier protein for F VIII, which allows F VIII to circulate.

Further testing to classify for treatment:

Multimeric analysis. FVIII binding assay

Phenotype	inher-itance	vWF activity	RIPA*	multimer pattern	1st choice	2nd choice
I	AD	v	v	uniform v	Desmopressin	F VIII-vWillebrand Conc
2A	AD or AR	v	v	Large & intermediate v	F VIII-vWillebrand Conc	Desmopressin
2B	AD	v	^	Large v	"	none
2M	AD	v	v	nl multimers	"	Desmopressin
2N	AR	nl	nl	nl multimers	"	Desmopressin
3	AR	vv	vv	undetectable	"	Platelet conc.

*RIPA, Ristocetin Inducted Platelet Aggregation, is used primarily to identify the type 2B variant.
For severely reduced levels, give FVIII and von Willeb rand Factor at a level of 25 to 50 IU/kg with every other day or daily dose, depending on the type of procedure: Dental extraction, minor surgery or delivery, major surgery... lowest to highest. (NEJM 2004; 351: 683.)

Case
DVT or thrombosis of an artery (e.g., aorta, carotid, femoral or subclavian).
OR
Delivery or death of a normal fetus 10th week thru 34th week
OR
3 or more spontaneous abortions before the 10th week.
^ PTT
Micro-angiopathic hemolysis
Dx: LAC syndrome. Ddx TTP, malignant HTN, HUS, scleroderma.
Special lab:
Moderate or high levels of anticardioplipin Ab or LAC 6 weeks apart.
Rx: heparin & coumadin
Catastrophic antiphospholipid syndrome:
RX: anticoagulants, steroids, and plasmapheresis or IV immune globulin.
(NEJM 2002; 346:752.)

Clotting assays for the LAC can be done when the patient is on warfarin if the INR is less than 3.5.
In LAC DVT, one DVT is sufficient for indefinite anti-coagulation.

Conditions associated with arterial thrombosis are
hyperhomocysteinemia
antiphospholipid antibody syndrome.
Protein C & S deficiencies
Antithrombin III deficiency
HIT, HITT
PNH
TTP
DIC

Progestin only containing OCPs does not increase the risk for DVT... unlike estrogen OCPs.

PNH: Esophageal or abdominal pain, DVT in hepatic, mesenteric, portal or cerebral veins, aplastic anemia, myelodysplastic syndrome, v PMNs or platelets, hemolysis, NL smear, Coombs-, flow cytometry: absence of proteins CD55 and CD59.

Rx: Fe, folate, prednisone 20 QOD, anticoagulation. Monitor for aplastic anemia or acute leukemia.

Causes of Neutropenia:
*Drugs: psychiatric (phenothiazine, clozapine, sizure meds: DPH, carbamazepine, antibiotics: TMP-SMX, semisynthetic penicillins, NSAIDs, anti-thyroid meds.
*Autoimmune:SLE.
*Postinfectious: ehrlichiosis, HIV, sepsis.

Table 1. Risk Factors for Venous Thromboembolism.*

Risk Factor	Estimated Relative Risk
Inherited conditions†	
Antithrombin deficiency	25
Protein C deficiency	10
Protein S deficiency	10
Factor V Leiden mutation	
Heterozygous	5
Homozygous	50
G20210A prothrombin-gene mutation (heterozygous)	2.5
Dysfibrinogenemia	18
Acquired conditions	
Major surgery or major trauma	5–200‡
History of venous thromboembolism	50
Antiphospholipid antibodies	
Elevated anticardiolipin antibody level	2
Nonspecific inhibitor (e.g., lupus anticoagulant)	10
Cancer	5
Major medical illness with hospitalization	5
Age	
>50 years	5
>70 years	10
Pregnancy	7
Estrogen therapy	
Oral contraceptives	5
Hormone-replacement therapy	2
Selective estrogen-receptor modulators	
Tamoxifen	5
Raloxifene	3
Obesity	1–3
Hereditary, environmental, or idiopathic conditions	
Hyperhomocysteinemia§	3
Elevated levels of factor VIII (>90th percentile)	3
Elevated levels of factor IX (>90th percentile)	2.3
Elevated levels of factor XI (>90th percentile)	2.2

* Data are from Rosendaal[14] and Kearon.[15] Relative risks are for patients with the specified risk factor, as compared with those without the risk factor.
† The definition of deficiency of antithrombin, protein C, or protein S varies among studies; it is usually defined as a functional or immunologic value that is less than the 5th percentile of values in the control population.
‡ The risk varies greatly, depending on the type of surgery, the use and type of prophylaxis, and the method of diagnosis.
§ The definition of hyperhomocysteinemia varies among studies; it is usually defined as a persistent elevation of fasting plasma homocysteine levels or plasma homocysteine levels after methionine loading that are greater than the 95th percentile of the control population or more than 2 SD above the mean for the control population.

Table 4. Recommendations for the Duration of Anticoagulant Therapy for Patients with Deep-Vein Thrombosis.*

Characteristics of Patient†	Risk of Recurrence in the Year after Discontinuation (%)	Duration of Therapy
Major transient risk factor	3	3 mo
Minor risk factor; no thrombophilia	<10 if risk factor avoided >10 if risk factor persistent	6 mo Until factor resolves
Idiopathic event; no thrombophilia or low-risk thrombophilia	<10	6 mo‡
Idiopathic event; high-risk thrombophilia	>10	Indefinite
More than one idiopathic event	>10	Indefinite
Cancer; other ongoing risk factor	>10	Indefinite

* Data are from Hirsh and Hoak,[22] Hyers et al.,[36] and Kearon.[44]
† Examples of major transient risk factors are major surgery, a major medical illness, and leg casting. Examples of minor transient risk factors are the use of an oral contraceptive and hormone-replacement therapy. Examples of low-risk thrombophilias are heterozygosity for the factor V Leiden and G20210A prothrombin-gene mutations. Examples of high-risk thrombophilia are antithrombin, protein C, and protein S deficiencies; homozygosity for the factor V Leiden or prothrombin-gene mutation or heterozygosity for both; and the presence of antiphospholipid antibodies.
‡ Therapy may be prolonged if the patient prefers to prolong it or if the risk of bleeding is low.

NEJM 2004;351:268 In inflammation, T cells produce IL6 which stimulates prod'n of hepcidin in the liver which blocks Fe absorption and release of Fe stores from macrophages causing anemia.

Platelet transfusion is contraind in both HIT and TTP.

Finasteride stops hematuria of BPH.

Familial syndromes associated with pancreatic cancer: BRCA2, familial non-polyposis coli, familial atypical multiple mole syndrome, and familial pancreatitis.

EBV: Burkitt's, HIV associated.

HIV: large B cell lymphoma, primary CNS lympohoma.

HTLV I adult t cell eleukemia-lymhpoma.

HHV8 with HIV: Kaposi's.

Hep C: lymphoplasmocytic lynmphoma (Waldenstorm's).

H pylori : Gastric MALT., Stomach cancer.

Campylobacter jejuni: MALT of the small bowel.

Tumor lysis syndrome, when emergent or at high risk for occurrence, is now treated with hydration

and rasburicase IV which degrades uric acid rather than allopurinol.

Case

60 y.o. man with gradual onset of weakness. Palor.

V Hgb, WBC, and platelets.

Marrow: hypocellular.

Dx: Applastic anemia.

Most cases have autoimmune suppression of stem cells by interferon- activated T cells. Hence,

Rx: immunosuppressive therapy with anti-thymocyte globulin and cyclosporine.

Fanconi's anemia is a hereditary form of aplasstic anemia with skeletal malformations of thumb and radius, short stature, and hypogonadism. There is increased chromosomal fragility (a test).

Causes of Neutropenia:

*Drugs: psychiatric (phenothiazine, clozapine, sizure meds: DPH, carbamazepine, antibiotics:

TMP-SMX, semisynthetic penicillins, NSAIDs, anti-thyroid meds.

*Autoimmune:SLE.

*Postinfectious: ehrlichiosis, HIV, sepsis.

HIT (note that TTP can look like this but platelet count is lower, there is fever and neuro signs, and the antibody is to ADAM 14.

Entity	Type I HIT	Type II HIT
Frequency	10 - 20%	1 - 3%
Latency	1 to 4 days	5 to 10 days. (Shorter if prior exposure; occasionally up to 40ds)
Nadir of platelet count	100,000/uL	30,000 to 55,000/uL OR >50% fall
antibody mediated?	NO*	YES Abs to Heparin PF4 complexes (platelet factor 4)
Thromboembolic sequelae	None	30 to 380 % (arterial & venous)
Hemorrhagic sequelae	none	Rarely
Management	Observe	Stop heparin; use alternative anti-coagulation.

*Due to direct effect of heparin on platelet activation.

Diagnosis of HIT:

14 Serotonin Release Assay $50 at St. V's

Heparin platelet factor 4 assay (ELISA) S&S: 97% & 80%. Both of these re send outs and take a few days.

The risk of thrombosis remains 30 x average risk for days to weeks after heparin is discontinued.

Prevention: limit heparin to < 5 days; Use LMWH. (Unfractionated heparin has 10x risk of fractionated heparin.)

Alternative anticoagulants: 1. Directo thrombin inhibitors: lepirudin, argatroban (monitor PTT). Bivalirudin-HIT patients undergoing PCI. If platelets are >100,000, transition to warfarin with an overlap of 5 days. INR 2 - 3. Duration of anticoagulation is 4 weeks minimum, but 3 - 6 months if thrombosis is present.

POST PHLEBITIC SYNDROME

About 1/4 of patients developing venous insufficiency following DVT. The risk of this can be reduced in patients with symptomatic DVT with knee high compression stockings exerting 30-40 mmHg at the ankle and less at the knee. For treatment of chronic venous insufficiency and ulcers, the modalities are leg elevation, compression, horse chestnut seed extract (300 mg, standardized to 50 mg of aescin, applied BID), and ASA 325 mg daily. Silver sulfadiazine and debriding enzymes do not work. For ulcers use occlusive dressings. For stasis dermatitis use zinc oxide paste or topical steroids.

Modified Wells Ann Int Med 2008; 149: ITC3-1

Each gets 1:

Active cancer Rx

Paresis or immobilization

Bedridden ? 3 ds or major surgery

Local tenderness in the deep vein system

Entire Leg swollen

Calf swell > 3cm 10cm below tibial tuberosity

Pitting edema unilateral

Collateral superficial veins not varicose

Previous DVT

This gets minus 2:

Alternative dx as likely as dvt .

Low: score <0/ Intermediate 1-2/ High 3+

DVT score ≤1, Use the d dimer 1st.

If negative, there is no DVT & discharge the patient.

If positive, obtain US.

If negative, repeat US in 1 week.

If positive, treat for DVT

DVT score 2+, use US.

If positive, treat.

If negative, obtain DVT.

If negative, Don't treat and discharge the patient.

If positive, repeat US in 1 week.

Ddx of DVT

Venous insufficiency (e.g., obesity)

Superficial thrombophylebitis

Muscle strain, tear or trauma

Leg swelling in a paralyzed limb

Baker cyst

Cellulitis

Lymphedema

For duration of anti-coagulation, categorize the patient into

Thrombophilia-low risk : FVL-Het or G20210A-Het : 6 mo anti-coagulation.

Throbmophilia-high risk: FVL-Hom or G20210A-Hom or both heterozygotes OR APLAS OR Prot C or Prot S or Anti-thrombin III deficiency. : Indefinite anti-coagulation.

The pathologist assigns a grade to the most common tumor pattern, and a second grade to the next most common tumor pattern. The two grades are added together to get a Gleason score. For example, if the most common tumor pattern was grade 3, and the next most common tumor pattern was grade 4, the Gleason score would be 3+4 = 7.

The Gleason grade is also known as the Gleason pattern and the Gleason score is also known as the Gleason sum.

The Gleason grade ranges from 1 to 5, with 5 having the worst prognosis. The Gleason score ranges from 2 to 10, with 10 having the worst prognosis.

It should be noted that for Gleason score 7, a Gleason 4+3 is a more aggressive cancer than a Gleason 3+4. Also, there is not really any difference between the aggressiveness of a Gleason score 9 or 10 tumour.

Grades 1 through 5

Gleason scores are associated with the following features:

Grade 1 - The cancerous prostate closely resembles normal prostate tissue. The glands are small, well-formed, and closely packed

Grade 2 - The tissue still has well-formed glands, but they are larger and have more tissue between them.

Grade 3 - The tissue still has recognizable glands, but the cells are darker. At high magnification, some of these cells have left the glands and are beginning to invade the surrounding tissue.

Grade 4 - The tissue has few recognizable glands. Many cells are invading the surrounding tissue

Grade 5 - The tissue does not have recognizable glands. There are often just sheets of cells throughout the surrounding tissue.

In the UK, prostate cancer of Gleason pattern 1 and 2 are almost never seen. Gleason pattern 3 is by far the most common.