PTT:
(The intrinsic pathway is initiated by prekallikrein and high molecular weight kinogen).

Acquired

- Heparin
- 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

1Heparin 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.)

Ximelagatrain is a direct thrombin inhibitor.

2XI deficiency gives mucocutaneous bleeding.

3XII deficiency prolongs PTT but causes no clinical bleeding.

^ PT

Counadin^2
Vit K def
Liver disease
VII def (rare)
Inhibitors of VII (rare)

^ PTT and ^ PT

Acquired:

- 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 defiency

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
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 disease 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.)

<table>
<thead>
<tr>
<th></th>
<th>homocysteine</th>
<th>methyl-malonic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folate deficiency</td>
<td>^</td>
<td>Normal</td>
</tr>
<tr>
<td>B 12 deficiency</td>
<td>^</td>
<td>^</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Disease</th>
<th>Setting</th>
<th>CM’s</th>
<th>Lab</th>
<th>Mechanism</th>
<th>Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cold Agglutinin Disease</td>
<td>Elderly</td>
<td><strong>Acral cyanosis</strong></td>
<td>May have Hemolysis. Spurious macrocytosis is due to RBC agglutination. DCT detects C3. Cold Agglutinins are detected in plasma when kept at 37 degrees.</td>
<td>IgM Antibodies against polysaccharides on RBCs.</td>
<td><strong>Warm patient.</strong> Plasmapheresis Rituximab. Cyclophospham ide NOT prednisone or splenectomy.</td>
</tr>
<tr>
<td></td>
<td>Raynaud’s dis</td>
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<tr>
<td></td>
<td>Waldenstrom’s.</td>
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</tr>
<tr>
<td></td>
<td>CLL (1 antigen)</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Mycoplasma</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Infectious mono</td>
<td></td>
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</tr>
<tr>
<td>PCH: Paroxysmal cold hemoglobinuria</td>
<td>Syphilis (1st in 1872!)</td>
<td><strong>Red-brown urine with cold exposure. (Intra-vascular hemo-lysis. Sometimes: Raynaud’s &amp; urticaria.</strong> *</td>
<td>DCT detects C3 at reduced temperature but not at 37 degrees. May have to use radio-labeled anti-IgG test.</td>
<td>IgG reacts with p Ag on RBCs*** Intra-vascular hemolysis.</td>
<td><strong>Warm patient.</strong> Prednisone if needed. NOT splenectomy.</td>
</tr>
<tr>
<td></td>
<td>Mycoplasma</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Klebsiella</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Post measles vaccine</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Cryoglobulinemia.</td>
<td>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 CYROGLOBULINEMIA Type III: Mixed cryoglob but both IgM and IgG are polyclonal. Associated with Lupus and other autoimmune disease.</td>
<td>Most are asymptomatic Palpable purpura. In Type I: livido reticularis &amp; Raynauds hepatitis, cirrhosis H S megalay, Peripheral neuropathy, Low grade Hodgkin’s dis Glomerular disease in 1/2 of patients with Type II 12% in Type III</td>
<td><strong>Normal hemogram.</strong></td>
<td>Cyroglobulins are Immunoglobulins that precipitate in serum in the cold but dissolve on warming. Decreased C4.</td>
<td><strong>Warm patient.</strong> Prednisone, cyclophospham ide, and plasmapheresis in combo. OR Rituximab (80% response) RX of underlying Hep C etc.</td>
</tr>
</tbody>
</table>

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**

<table>
<thead>
<tr>
<th>Setting</th>
<th>CM’s *</th>
<th>Laboratory *</th>
<th>Mechanism</th>
<th>RX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warm Antibody</td>
<td>Idiopathic (50%) OR CLL, NHL, SLE, Ulc Collitis, HIV, Penicillin, methyldopa</td>
<td>Extravascular hemolysis. Abd pain, fever, jaundice. May progress to lymphoproliferative dis or DVT *</td>
<td>DCT** IgG Ab detects IgG, NOT C3, in PEN &amp; AMD. IgG Ab detects IgG AND C3 in SLE.</td>
<td>IgG and C3d on surface of patient’s RBCs. Steroids Azothioprine, Cyclophosphamide, Rituximab Danazol IVIG Splenectomy</td>
</tr>
<tr>
<td>Cold Agglutinin Disease</td>
<td>Mycoplasma Infectious mono Raynaud’s dis Lymphoma (i antigen) Waldenstrom’s. CLL (I antigen)</td>
<td>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.</td>
<td>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</td>
<td>IgM Antibodies against polysacchrides on RBCs. RBCs removed by liver. **DAT +I’ve (better in cold).</td>
</tr>
<tr>
<td>PCH: Paroxysmal cold hemoglobinuria</td>
<td>Syphilis (1st in 1872!) Mycoplasma Klebsiella Post measles vaccine</td>
<td>Red-brown urine with cold exposure. (Intra-vascular hemolysis. Sometimes: Raynaud’s &amp; urticaria. *</td>
<td>DCT for IgG against C3 at reduced temperature but not at 37 degrees. May have to use radio-labeled anti-IgG test.</td>
<td>IgG &amp; C on RBCs*** Intra-vascular hemolysis. **DAT +I’ve (better in cold)</td>
</tr>
<tr>
<td>More common Drug induced: Against drug-RBC complex (hapten)</td>
<td>Penicillin Sulfaphenacetin Quinidine</td>
<td>*</td>
<td>DCT for IgG, NOT C3. No Ab in patient’s serum. Eluate from patient’s RBCs does not react with normal RBCs.</td>
<td>Drug is firmly bound to RBC</td>
</tr>
<tr>
<td>Drug induced: Against drug-protein complex (innocent bystander misnomer)</td>
<td>Fuadin chlorproamidine (wide variety of drugs)</td>
<td>Hemolysis within days of initiation. *</td>
<td>DCT NOT for IgG, positive for C3.</td>
<td>Drug is loosely bound to RBC (analogue to drug induced immune thromboytopenia.)</td>
</tr>
</tbody>
</table>

*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:
- **Antimalarials:** Primaquine/ pamaquine/ dapsone
- **Sulfamethoxazole:**
  - trimethoprim sulfamethoxazole.
  - Nitrofurantoin
- **Other:**
  - Vitamin K in water soluble form
  - Doxorubicin
  - nalidixic acid
  - 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 dissociation 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. Sulphhemoglobinemia 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

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Normal</th>
<th>Iron Deficiency</th>
<th>Alpha Thal Minor</th>
<th>Beta Thal Minor</th>
<th>Beta Thal Intermediate</th>
</tr>
</thead>
<tbody>
<tr>
<td>AfroAmericans 30% SE Asian, Africa-West Coast</td>
<td>SE Asian, Africa-West Coast</td>
<td>Italy, Greece, Asia, Africa-Sub Saharan</td>
<td>Italy, Greece, Asia, Africa Sub-Saharan</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Clinical Setting | Fatigue | ^spleen, leg ulcers, HA, CHF, ^LDH, Prooxidants: e.g., Sufa, like G6PD v | ^spleen, osteoporosis, Fe in heart, liver, pancreas, pituitary etc |

<table>
<thead>
<tr>
<th>PE</th>
<th>HgB</th>
<th>MCV</th>
<th>Retic count</th>
<th>Peripheral Smear</th>
<th>Fe, Ferritin</th>
<th>Hemoglobin electrophoresis</th>
<th>Pathogenesis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15 gm/dL</td>
<td>Decreased (4)</td>
<td>8 gm/dL</td>
<td>Mild v (Hgb &gt; 10)</td>
<td>&lt; 10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>90</td>
<td>75 or normal(4)</td>
<td>65</td>
<td>65</td>
<td>&lt;65</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NL</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Rare inclusions, hypochromia</td>
<td>Target Cells (5)</td>
<td>Target Cells hypochromia</td>
<td>Target Cells hypochromia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreased</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hgb A</td>
<td>97%</td>
<td>82%</td>
<td>3% &gt; Hgb F ^</td>
<td>Hgb A2 elevated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hgb H</td>
<td>0%</td>
<td>5 - 30%</td>
<td>0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hgb A2</td>
<td>2.5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hgb F</td>
<td>0%</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Can be normal** because there is no substitution gene for the a gene. But Hgb A ~ 90% (6)  
Hgb A & Hgb H: Hgb F ~ Hgb A2 (3)  
Decrease in beta chain synthesis or abnormal beta chain function.  
Hgb A2 > 3% + Hgb F ^  
Decrease in alpha chains.  
(a) Deletions. - /- a OR - a / - a (2)  
(b) / b+ (3)  
(b')/b+

**Target Cells**  
None  
Like Hemoglobin H disease.

1. Designations are as follows: Hgb A: a2 b2 , Hgb H: b4 , Hgb A2: a2 d2 , Hgb F: a2 g2. Most Hgb is Hgb A, which has 2 alpha 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 moiety. 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. **Pathogenesis**  
(a) Deletions. - /- a OR - a / - a (2)  
(b) / b+ (3)  
(b')/b+

3. (Normal) b is normal, b' is decreased synthesis (a mild mutation), and b0 is no synthesis. Beta thalassemia major has b0/b0, 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 thalassemias, 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 thalassemia 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 thalassemia see NEJM 2005;353:1135-46)
<table>
<thead>
<tr>
<th>Reaction</th>
<th>Product/ Onset/Inc</th>
<th>CMS (hallmarks in bold)</th>
<th>Mechanism of Action</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Hemolytic</strong> (1)</td>
<td>RBC/ Immediate/ 1:25,000</td>
<td>'^T, Chills, N, V, Pain in flank, abd, head, Dysp, Renal Failure, RED PLASMA &amp; URINE (hemoglobinuria), direct coombs positive, Massive ^K.** Mortality 17-60%.</td>
<td>ABO incompatibility. Group O recipient gets A or B. IgM Ab fixes C.</td>
<td>Normal Saline. Alert Blood bank for error. Heparinize. acute dialysis, monitor EKG for increase K.</td>
</tr>
<tr>
<td><strong>Anaphylaxis</strong> (2)</td>
<td>Almost any except albumin. Immediate. 1:20,000</td>
<td>Rash, hives, SHOCK, ANGIOEDEMA, Dysp, N, abd cramps, diarrhea Especially in East Asians.</td>
<td>IgG or IgA Ab in an IgA deficient patient.</td>
<td>Epinephrine, Steroids, normal saline. IV diphenhydramine. Airway. Block with blood from IgA deficient donor</td>
</tr>
<tr>
<td><strong>Urticarial or allergic</strong> (1) (2)</td>
<td>FFP, Platelets (1%), RBCs Immediate</td>
<td>RASH, hives, urticaria. Pre-existing IgA deficiency.</td>
<td>Patient’s pre-existing IgE Ab’s on mast cells and basophils are released.</td>
<td>IV diphenhydramine 50 mg. If sx’s stop, this rules out anaphylaxis and can continue transfusion.</td>
</tr>
<tr>
<td><strong>Sepsis</strong> (2)</td>
<td>RBCs, Platelet concentrates (not stored in cold)/ imm. to &lt;1hr 1:1:000</td>
<td>^ T, chills, V BP, ^HR, back, chest, abd pain, dyspnea, oliguria Gram stain &amp; culture donor blood &amp; patient’s blood. Yersinia grows in refrigerated RBCs.</td>
<td>Bacteria (yersinia)in not cold stored product or skin plug (salmonella) from patient.</td>
<td>Broad Spectrum Ab’s</td>
</tr>
<tr>
<td><strong>Febrile non-hemolytic</strong> (THE MOST COMMON) (1) (2) (3)</td>
<td>Platelets (30%), RBCs(1%) 1-6 hours. If use leukocyte reduced, rate is 15%.</td>
<td>^ FEVER, ^HR, ^ BP. HA,N,V. BENIGN.</td>
<td>Either 1) cytokines from WBCs or 2) recipient Ab to donor Ag’s. HLA reaction.</td>
<td>Respiratory support. Stop diuretics. Fluid excess is not causal !!!</td>
</tr>
<tr>
<td><strong>TRALI</strong> transfusion related acute lung injury (1)</td>
<td>FFP. 2 to 4 hours. 1:2,000</td>
<td>Dyspnea, pulmonary edema. HYPOXEMIA NOT FROM FLUID OVERLOAD !!! CVP is normal. ARDS picture.</td>
<td>Donor HLA specific or PMN specific Ab reaction with patient’s WBCs causing WBC trapping</td>
<td>Rule out Acute Hemolytic via blood sample. Prevent by leukocyte reduction pre storage. Avoid when preparing for transplant.</td>
</tr>
<tr>
<td><strong>Delayed Hemolytic</strong> (1)</td>
<td>RBC/ 2-10 ds, 1:7,000</td>
<td>Unexplained drop in HGB. Less severe than acute hemolytic transfusion rxn. ^ Ind Bili. ^LDH, v Haptoglobin, Spherocytosis, ^ T</td>
<td>Allantybody to Rh, Kidd, Duffy, Kell due to prior sensitization.</td>
<td>Diagnosed by blood bank. Prevent by I.D. the Ag and informing the patient.</td>
</tr>
<tr>
<td><strong>Post transfusion purpura</strong></td>
<td>RBC, platelets, WBCs/ 5-10ds</td>
<td>Women 95%. ITP picture: Marked V platelets</td>
<td>Same as ITP. Sensitized by pregnancy or prior transfusion. HPA 1a on platelets</td>
<td>IV IG 1gm/kg 2 days. Steroids. Exchange transfusion Use wash or HPA-1a deficient cells in future.</td>
</tr>
<tr>
<td><strong>ACE I x Transfusion interaction (3)</strong></td>
<td>Transfusion of WBCs via Leukocyte reduction</td>
<td>Acute decrease in BP. Patient on an ACE Inhibitor !!</td>
<td>leukocyte reduction activates kinninogen or F XII</td>
<td>DISCONTINUE THE ACEI THIS IS NOT TRUE ANAPHYLAXIS !!</td>
</tr>
<tr>
<td><strong>GVHD</strong></td>
<td>4 to 30 days following transfusion.</td>
<td>Pancytopenia, infection, hemorrhage.</td>
<td>Engraftment of donor T lymphocytes in immunocompromised and sometimes in normal persons.</td>
<td>Radiate blood prior to transfusion, particularly where donor is HLA compatible relative.</td>
</tr>
<tr>
<td><strong>CMV</strong></td>
<td></td>
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<tr>
<td><strong>Iron Overload</strong></td>
<td></td>
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</tr>
</tbody>
</table>

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.

Roushmedicine.com
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 – gadolinium 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 homozygous. 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 TAMPOANDE
*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 calciumetic 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: acetaminophen, 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**

<table>
<thead>
<tr>
<th>INR</th>
<th>GI or GU bleed</th>
<th>CNS bleed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hold coumadin</td>
<td>&lt; 9</td>
<td>-</td>
</tr>
<tr>
<td>2 - 4 mg vitamin K</td>
<td>&gt; 9</td>
<td>-</td>
</tr>
<tr>
<td>FFP or Factor VIIIa</td>
<td>-</td>
<td>X</td>
</tr>
</tbody>
</table>

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 life of factor 2 is 100 hrs.
<table>
<thead>
<tr>
<th>Etiology</th>
<th>ITP</th>
<th>TTP</th>
<th>HUS</th>
<th>HELLP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection in children</td>
<td>Quinidine</td>
<td>Pregnancy</td>
<td>E Coli 157:H7, or post partum</td>
<td>Pregnancy 10% have pre-eclampsia</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>Heparin</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 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 ADAMTS13, a Von WF cleaving protease, caused either by an acquired antibody or, more rarely, congenitally. | Platelets in endothelium, but not caused by deficiency in ADAMTS13. |                                     |
| DDX              | Common: Gestational thrombocytopenia, Drugs: heparin, quinidine, Viruses: HIV, mono, hepatitis, Other: hypersplenism. 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 & immuno-suppressive 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 menorrhagia, 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 cladribine 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 thrombocytopenia: 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 leukopheresis, 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.

Neurofibromatosis (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 alkalize 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, broccoli, 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 commonly 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 erythropoietin 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.

HNPPC 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., 5fu) 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 NSCLlung 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

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Treatment/Staging Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCIS</td>
<td>in the breast ducts; does not penetrate the basement mb.</td>
<td>Good prognosis if resected. Lumpectomy plus RT or mastectomy alone. No lymph node resection</td>
</tr>
<tr>
<td>LCIS</td>
<td>High risk marker for breast ca. (Similar to contralateral breast cancer.)</td>
<td>Resection</td>
</tr>
<tr>
<td>Invasive breast ca</td>
<td></td>
<td>Axillary lymph node resection. Lumpectomy+RT</td>
</tr>
</tbody>
</table>

(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.
<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>RX</th>
</tr>
</thead>
<tbody>
<tr>
<td>A T1C</td>
<td>No palpable nodule, Elevated PSA</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Invasion of seminal vesicles, bladder neck, prostatic apex</td>
<td>RT or radical prostatectomy.</td>
</tr>
<tr>
<td>C</td>
<td>Invasion of seminal vesicles, bladder neck, prostatic apex</td>
<td>RT</td>
</tr>
<tr>
<td>D1</td>
<td>Lymph node involvement.</td>
<td></td>
</tr>
<tr>
<td>D2</td>
<td>Metastatic disease</td>
<td></td>
</tr>
</tbody>
</table>

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 prostatectomy, an anatomical approach gives 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 alkalization of urine to prevent uric acid stones. Treat hyperviscosity syndrome with leukopheresis. The 15:17 translocation is seen in APL and causes the fusion of the retinoic acid receptor-α 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 bruising.
Hematuria
Increased PTT
Mixing study: No change in PTT.
Dx: Factor 8 inhibitor
TESTICULAR CANCER

<table>
<thead>
<tr>
<th></th>
<th>Seminoma</th>
<th>Non-seminoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>beta HCG (½ life 1 day)</td>
<td>elevated in ½ of patients</td>
<td>in 85% either bHCG or AFP or both are elevated.</td>
</tr>
<tr>
<td></td>
<td>(Mnemonic: HCG tied to reproduction; AFP is not!)</td>
<td></td>
</tr>
<tr>
<td>AFP (½ life 6 days)</td>
<td>(never elevated)</td>
<td>in 85% either bHCG or AFP or both are elevated.</td>
</tr>
<tr>
<td>Stage features</td>
<td>80% are stage 1</td>
<td></td>
</tr>
<tr>
<td>Radiosensitivity</td>
<td>Very High. Mnemonic: R is closer to S than N.</td>
<td>Not radiosensitive.</td>
</tr>
<tr>
<td>Stage 1</td>
<td>Treat with prophylactic RT to regional lymphatics.</td>
<td></td>
</tr>
<tr>
<td>retroperitoneal lymphadenectomy</td>
<td></td>
<td>Standard in stage 1.</td>
</tr>
<tr>
<td>Bleo, etoposide, cisplatin</td>
<td>Used</td>
<td>Used</td>
</tr>
</tbody>
</table>

(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.

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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

<table>
<thead>
<tr>
<th></th>
<th>radiograph</th>
<th>bone scan</th>
</tr>
</thead>
<tbody>
<tr>
<td>multiple myeloma</td>
<td>lytic lesions</td>
<td>normal (normal alk phos)</td>
</tr>
<tr>
<td>lung cancer and lung cancer</td>
<td>mixed lytic and sclerotic lesions</td>
<td>positive in some areas</td>
</tr>
<tr>
<td>prostate cancer</td>
<td>sclerotic (blastic) lesions</td>
<td>strongly positive bone scan</td>
</tr>
<tr>
<td>lymphoma</td>
<td>normal</td>
<td>normal</td>
</tr>
</tbody>
</table>

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

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

(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? 
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

Roushmedicine.com
<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Inheritance</th>
<th>vWF Activity</th>
<th>RIPAN*</th>
<th>Multimer Pattern</th>
<th>1st Choice</th>
<th>2nd Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>AD</td>
<td>v</td>
<td>v</td>
<td>Uniform v</td>
<td>Desmopressin</td>
<td>F VIII- vWillebrand Conc</td>
</tr>
<tr>
<td>2A</td>
<td>AD or AR</td>
<td>v</td>
<td>v</td>
<td>Large &amp; intermediate v</td>
<td>F VIII-vWillebrand Conc</td>
<td>Desmopressin</td>
</tr>
<tr>
<td>2B</td>
<td>AD</td>
<td>v</td>
<td>^</td>
<td>Large v</td>
<td>&quot;</td>
<td>none</td>
</tr>
<tr>
<td>2M</td>
<td>AD</td>
<td>v</td>
<td>v</td>
<td>nl multimers</td>
<td>&quot;</td>
<td>Desmopressin</td>
</tr>
<tr>
<td>2N</td>
<td>AR</td>
<td>nl</td>
<td>nl</td>
<td>nl multimers</td>
<td>&quot;</td>
<td>Desmopressin</td>
</tr>
<tr>
<td>3</td>
<td>AR</td>
<td>vv</td>
<td>vv</td>
<td>Undetectable</td>
<td>&quot;</td>
<td>Platelet conc.</td>
</tr>
</tbody>
</table>

*RIPA, Ristocetin Induced Platelet Aggregation, is used primarily to identify the type 2B variant.
For severely reduced levels, give FVIII and von Willebrand 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 anticardiolipin 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, seizure meds: DPH, carbamazepine, antibiotics: TMP-SMX, semisynthetic penicillins, NSAIDs, anti-thyroid meds.
*Autoimmune:SLE.
*Postinfectious: ehrlichiosis, HIV, sepsis.
<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Estimated Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inherited conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td>25</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>10</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>10</td>
</tr>
<tr>
<td>Factor V Leiden mutation</td>
<td></td>
</tr>
<tr>
<td>Heterozygous</td>
<td>5</td>
</tr>
<tr>
<td>Homozygous</td>
<td>30</td>
</tr>
<tr>
<td>G20210A prothrombin-gene mutation (heterozygous)</td>
<td>2.5</td>
</tr>
<tr>
<td>Dysfibrogenemia</td>
<td>18</td>
</tr>
<tr>
<td><strong>Acquired conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Major surgery or major trauma</td>
<td>5–200</td>
</tr>
<tr>
<td>History of venous thromboembolism</td>
<td>50</td>
</tr>
<tr>
<td>Antiphospholipid antibodies</td>
<td></td>
</tr>
<tr>
<td>Elevated anticardiolipin antibody level</td>
<td>2</td>
</tr>
<tr>
<td>Nonspecific inhibitor (e.g., lupus anticoagulant)</td>
<td>10</td>
</tr>
<tr>
<td>Cancer</td>
<td>5</td>
</tr>
<tr>
<td>Major medical illness with hospitalization</td>
<td>5</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&gt;50 years</td>
<td>5</td>
</tr>
<tr>
<td>&gt;70 years</td>
<td>10</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>7</td>
</tr>
<tr>
<td>Estrogen therapy</td>
<td></td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>5</td>
</tr>
<tr>
<td>Hormone-replacement therapy</td>
<td>2</td>
</tr>
<tr>
<td>Selective estrogen-receptor modulators</td>
<td></td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>5</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>3</td>
</tr>
<tr>
<td>Obesity</td>
<td>1–3</td>
</tr>
<tr>
<td><strong>Hereditary, environmental, or idiopathic conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>3</td>
</tr>
<tr>
<td>Elevated levels of factor VIII (&gt;90th percentile)</td>
<td>3</td>
</tr>
<tr>
<td>Elevated levels of factor IX (&gt;90th percentile)</td>
<td>2.3</td>
</tr>
<tr>
<td>Elevated levels of factor XI (&gt;90th percentile)</td>
<td>2.2</td>
</tr>
</tbody>
</table>

* Data are from Rosendaal and Kearon. 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.
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 lymphoma.
HTLV I adult t cell eleukemia-lymphoma.
HHV8 with HIV: Kaposi's.
Hep C: lymphoplasmocytic lymphoma (Waldenstrom'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: Aplastic 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 aplastic 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, sizer 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.

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

*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.)
Roushmedicine.com
Alternative anticoagulants: 1. Direct 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 \leq 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-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.