**Anemia**

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| **Disease/Abnormality** | **Pathophysiology** | **Clinical Presentation** | **Lab Findings** | **Treatment** |
| **Hemolytic Anemias (Intrinsic)** |
| Spherocytosis | Autosomal dom/rec defects in ankyrin, spectrin, band 3, and band 4.1 proteins that cause loss of RBC membrane stability with formation of a spherical shape (rather than a biconcave disc). Abnormal RBC’s are removed by splenic macrophages. Spleen enlarges due to “work hyperplasia” | Chronic anemia, splenomegaly, jaundice of varied severity. Cholelithiasis sometimes seen. | Smear: Spherocytosis, reticulocytosis.Elevated EPO, indirect bilirubinDecreased haptoglobin, HB, and HCT | Splenectomy |
| G6PD Deficiency | X-linked recessive G6PD deficiency. Without G6PD, NADPH is not formed by the pentose phosphate shunt, and the antioxidant glutathione cannot be reduced. ROS build up in the RBC under oxidative stress and cause denaturing of proteins that stick to the RBC membrane causing hemolysis. Splenic Mθ remove abnormal proteins from mildly affected cells. | Mild hemolytic anemia and jaundice that is preceded by oxidant stress (infection, ingestion of fava beans, certain drugs). | Smear: Heinz bodies, spherocytes, bite cells.Elevated EPO, indirect bilirubinDecreased haptoglobin, HB, and HCT | None |
| Sickle Cell Anemia | Point mutation in β-globin (HbS) chain causes sickling (abnormal function) under low O2 tension or oxidative stress that is initially reversible, but eventually becomes permanent. Reversible sickled cells are sticky and occlude small vascular beds while irreversibly sickled cells occlude the spleen and cause inflammation🡪fibrosis. | Chronic anemia, splenomegaly🡪 autosplenectomy, jaundice, occlusive/pain crises (common in bones), acute chest syndrome, aplastic crisis (with Parvo18 infection) organ infarction, seizures/stroke, skin ulceration | Smear: Sickled cells, reticulocytosisElevated EPO, indirect bilirubinDecreased haptoglobin, HB, and HCT | Hydroxyurea |
| Warm Autoimmune Hemolytic Anemia (WAIHA) | IgG antibody to the RBC membrane causes extravascular and minor intravascular hemolysis. | Chronic low-grade anemia | Smear: Spherocytes, reticulocytesDAT: + | None |
| Cold Autoimmune Hemolytic Anemia (CAIHA) | IgM antibody to the RBC membrane causes chronic low grade hemolysis mediated by complement activation. Vascular obstruction may occur in extremities where RBC’s bound to IgM can aggregate at lower temperatures. | Chronic low-grade anemia. Reynaud’s phenomenon. | Smear: Spherocytes, reticulocytesDAT: + | None |
| Drug-Induced Hemolytic Anemia | Antibody to RBC-drug or drug alone causes both extravascular and intravascular hemolysis. | Anemia and jaundice develop 2-4 days after drug administration (usually IV-ie Penicillin) |  |  |
| **Microcytic Anemias** |
| Β-Thalassemia | Autosomal recessive disease that causes decreased synthesis of β-globin chains in RBC’s. Excess α chains (insoluble) aggregate in the RBC and cause hemolysis or removal by splenic macrophages. B/B+ or B/B0-Thalassemia MinorB0-B+ or B0/B0Thalassemia MajorThalassemia intermedia consists of intermediate forms. | Thalassemia minor: Mild hemolytic anemia, usually asymptomatic. (Hb>9)Thalassemia Intermedia: Moderate hemolytic anemia HB 5-6 rarely requiring interventionThalassemia major (Cooley’s anemia): Severe hemolytic anemia requiring transfusion (Hb<3), cortical bone thinning with facial and skull deformity, HSM. | Smear: Microcytic hypochromic anemia with target cells and poikilocytes.Hb Electropheresis: All will show presence of HbA2 and HbF in different quantities depending on severityElevated EPO, indirect bilirubinDecreased HB and HCT | Minor/Intermedia: No treatment necessary unless symptomatic.Cooley’s Anemia: Transfusion & Fe chelators (Deferoxamine or Deferasirox) to prevent hemochromatosis. Bone marrow transplant is curative. |
| α-Thalassemia | Autosomal recessive disorder that causes decreased synthesis of α-globin chains. Depending on severity, there may be excess β and γ chains that form tetramers (HbH and Hb Barts respectively) which have a very high affinity for O2 and are ineffective in transport.α/α/α/α0-Silent carrierα/α/α0/α0-Thalassemia trait/minorα/α0/α0/α0-Thalassemia Intermedia/HbHα0/α0/α0/α0-Thalassemia Major | Thalassemia minor: Mild microcytic hypochromic anemia. Usually asymptomatic.HbH disease: Moderate-severe microcytic hypochromic anemia with presence of HbH and HB Barts. (HbH-containing cells are removed by the spleen). HSM.Thalassemia Major: Causes hydrops fetalis (fatal in utero). | Smear: Microcytic hypochromic anemia. HbH will show Heinz bodies.Hb Electropheresis: Thal Major will show HbH and Hb Barts.Decreased HB | T Minor: NoneHbH Disease: Occasional blood transfusionsBone marrow transplant is curative. |
| Iron Deficiency Anemia | Decreased iron prevents synthesis of hemoglobin. Causes of low FE:MalnutritionImpaired absorptionIncreased requirementBlood loss (chronic/acute) | Pallor, whitened conjunctivae, alopecia, DOE, tachycardia, diaphoresis, anxiety, koilonychia  | ↓ Free Fe, ferritin, HB, HCT (microcytic, hypochromic anemia)↑ Transferrin and TIBC | Iron supplementation |
| Anemia of Chronic Disease | Elevation in inflammatory cytokines prevents EPO secretion by the kidney, and by unknown mechanisms, stored iron is inaccessible to the body. This causes a pseudo Fe deficient state. | Anemia (see above) in the face of a chronic condition (cancer, autoimmune disease, sepsis, etc) | ↓ Free Fe, transferrin, TIBC, HB, HCT (microcytic hypochromic anemia)↑ Ferritin | Correction of underlying cause.Iron supplementation.EPO. |
| **Macrocytic Anemias** |
| Vitamin B12 Deficiency |  |  |  |  |
| Folate Deficiency |  |  |  |  |
| **Normocytic Anemias** |
| Aplastic Anemia |  |  |  |  |

**Coagulopathies**

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| **Type** | **Inherited/Acquired** | **Pathogenesis** | **Clinical Features** | **Lab Diagnosis** |
| Factor V Leiden (MOST COMMON COAGULOPATHY) | Autosomal dominant (point mutation) | Mutation of factor V renders it resistant to inactivation by protein C and S leading to a hypercoagulable state. | Recurrent thrombosis at both common and uncommon sites usually with first event occurring <50 years of age.  | DNA studies to make diagnosis |
| Protein C/S Deficiency | Autosomal dominant | Mutation causes decreased function or lack of production of protein C/S leaving factor 5 unopposed. This induces a hypercoagulable state. | Recurrent thrombosis at both common and uncommon sites usually with first event occurring <50 years of age.  | Protein C/S antigen and APC/S activity testing |
| Prothrombin Gene Mutation | Inherited | Point mutation causes increased production of prothrombin leading to a hypercoagulable state. | “ ”  | DNA studies |
| Antithrombin deficiency | Inherited | Antithrombin normally inhibits thrombin activation as well as factors 2,9,10,11 and 12. Deficiency induces a hypercoagulable state. | “ “ | Antithrombin levels and activity testing |
| Antiphospholipid Antibody (APA)/Lupus Anticoagulant | Acquired (secondary to autoimmune dz, drug interaction, or can be primary) | APA causes in vivo hypercoagulability due to effects on protein C, platelets, and plasmin (unknown pathogenesis) and in vitro anticoagulation. | One of the clinical features MUST BE PRESENT to make diagnosis: Thrombocytopenia, recurrent fetal loss, or thrombosis | APA MUST BE PRESENT to make the diagnosis.Decreased aPTT with positive mixing studies |
| DIC |  |  |  |  |

**Thrombocytopenia**

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| **Pathology** | **Pathogenesis** | **Clinical Features** | **Lab Features** | **Treatment** |
| Artifactual thrombocytopenia | EDTA (in certain specimen tubes) + anti-platelet antibodies cause platelets to aggregate satellite. Gives falsely low platelet count.  | None | Thrombocytopenia | None |
| Idiopathic (Immune) thrombocytopenic purpura (ITP)-Diagnosis of exclusion. | Anti-platelet antibody attaches to platelets and causes destruction by the splenic macrophages  | Acute/childhood ITP (spontaneously resolves) VS chronic/adulthood ITP. Mucocutaneous bleeding (epistaxis, menorrhagia), difficulty stopping minor traumatic bleeds, petechiae | Thrombocytopenia, presence of anti-platelet antibody, normal to large platelets | Restriction of activity, steroids, IVIG, splenectomy (depends on severity) |
| Heparin induced thrombocytopenia (HIT) | Heparin-PAF4 antibody binds and causes aggregation of platelets with formation of thrombi | PE, DVT, other thromboembolic evidence. Rarely bleeding will be seen. | Thrombocytopenia, + schistocytes, +D-dimer | Stop heparin and use other anticoagulant (NOT WARFARIN, this may decrease protein C and increase coagulation) |
| HUS (Hemolytic Uremic Syndrome) | Endothelial damage and platelet activation by bacterial-produced shiga-toxin (Ex. O157H7) causes platelet clots to form in the microvasculature. RBC’s traversing these clots are destroyed. There is absence of coagulation cascade involvement. | Overt renal failure, jaundice (hemolysis), anemia, purpura. | Thrombocytopenia, elevated BUN/CR, + schistocytes, elevated un-conjugated/indirect bilirubin | Supportive therapy, dialysis, or plasma exchange |
| Thrombotic thrombocytopenic purpura (TTP) | Defect in ADAMTS13 (or presence of an inhibitor) leaves large vWF proteins in circulation which causes platelet aggregation in the microcirculation. RBC’s traversing these clots are destroyed. There is absence of coagulation cascade involvement. | Purpura, mild renal failure, fever, neurologic symptoms, anemia, jaundice (hemolysis). | Thrombocytopenia, mildly elevated BUN/CR, elevated un-conjugated/indirect bilirubin, schistocytes,If an inhibitor is the cause of deficiency, mixing studies will be positive. | Plasma Exchange (90% effective) |

**Bleeding Disorders**

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| **Disorder** | **Inheritance Pattern** | **Pathogenesis** | **Clinical Presentation** | **Labs** | **Treatment** |
| Bernard-Soulier Syndrome | Autosomal recessive | Gp Ib defect prevents platelet binding to vWF in the instance of endothelial damage | Mucocutaneous bleeding | Variable platelet count with large platelets. Dx by platelet aggregation studies. | Platelet transfusion If severe |
| Glanzmann’s Thrombasthenia | Autosomal recessive | Gp IIb/IIIa defect prevents platelets from adhering to one another in a clot | Mucocutaneous bleeding (early) | Normal platelet count and morphology. Dx by platelet activation studies. | Platelet transfusion if severe |
| Hemophilia A | X-linked recessive | Mutation in the factor 8 gene leads to deficiency. Prevents activation of the intrinsic pathway when a platelet clot forms. Prevents formation of fibrin clots. | Spontaneous hemarthroses, late massive surgical bleeding, large ecchymoses. Can be mild-severe depending on the functionality of factor 8. | Absence of factor 8 on assay. Increased PTT w/normal PT and bleeding time. | Factor 8 replacement (CAUTION, in severe hemophilia antibodies to factor 8 can form rendering PT untreatable) |
| Hemophilia B | X-linked recessive | Mutation in the factor 9 gene leads to deficiency. Prevents activation of the intrinsic pathway when a platelet clot forms. Prevents formation of fibrin clots. | Spontaneous hemarthroses, late massive surgical bleeding, large ecchymoses. Can be mild-severe depending on the functionality of factor 8. | Absence of factor 9 on assay. Increased PTT w/normal PT and bleeding time. | Factor 9 replacement |
| Von Willebrand Disease (MOST COMMON BLEEDING DISORDER) | Autosomal dominant | vWF is either abnormal or has decreased production. Because vWF stabilizes factor 8, it becomes deficient as well. This leads to inefficient formation of fibrin clots in the face of endothelial damage. | Mucocutaneous bleeding, easy bruising, spontaneous soft tissue bleeding from minor trauma. | Normal platelet count, abnormal bleeding time and prolonged PTT. Electrophoresis shows decreased or abnormal vWF. | DDAVP (causes release of vWF from endothelial cells). Extrinsic vWF. |
| Vitamin K Deficiency | Acquired | Vitamin K is necessary for synthesis of factors 2,7,9 and 10 as well as protein C and S | Easy bruising, GI bleeds, hematomas | Prolonged PT and PTT time | Give vitamin K. If severe infuse plasma. |
| Severe Liver Disease | Acquired | The liver is the site of production for the clotting factors. Liver failure has two complications, decrease in clotting factors and splenomegaly (sequestration = thrombocytopenia) | Ecchymoses, hemarthroses, mucocutaneous bleeds, severe bleeding of ruptured varices (life threatening) | Prolongation of PT, PTT, and bleeding time. Thrombocytopenia. | Plasma, platelets, and/or vitamin K |

Lymphomas

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| **Type** | **Histology** | **Cell of Origin** | **Biology** | **Genetics** | **Clinical Presentation** |
| Follicular Lymphoma (90% 5 year survival) | Preponderance of follicles present in the lymph node. Irregular appearing B-cells. | B-cell | BCL-2 gene which is involved in prevention of apoptosis is translocated next to a promoter area leaving the cell invulnerable to apoptosis. | T(14:18), BCL-2 translocation. | Usually asymptomatic, can present with enlarged painless lymph node(s) that diminish in size as the immune response controls the B-cell population (early). Indolent progression. |
| Diffuse Large B-Cell Lymphoma (DLBCL)(65% 5 year survival) | Sheets of abnormal B-cells found in the lymph node (they are higher grade and have lost the ability to form germinal centers). | B-cell | BCL-6 gene is involved in signal transduction. Alterations elevate its activity causing hyperproliferation of the clonal cell. | BCL-6 alteration. BCL-2 translocation is also seen, and is thought to indicate transformation of a follicular lymphoma. | Rapidly enlarging (aggressive) hard nontender lymph nodes. May have B symptoms. Treatment involves monoclonal antibody and chemotherapy. |
| MALToma/Marginal Zone Lymphoma | Expansion of MALT lymphoid follicle(s) in the GI tract with invasion into the epithelium of lymphocytes | B-cell in mucosal lymphoid follicles | Inflammation (IE H. pylori, Crohn’s, etc) increases B-cell activity and proliferation and a likelihood for chromosomal translocations/ mutations exists | None identified | Can present as ulceration or formation of thickened areas within the mucosa. Treatment can include: antibiotics, radiation, and chemotherapy. Can transform into DLBCL. |
| Hodgkin’s Lymphoma | Reed-Sternberg cells (owl eyes) can be seen amongst what appears to be reactive lymphocytes, eosinophils, and histiocytes. Destroys normal lymph node architecture. | B-cell (cells do not express normal B-cell surface markers) | HL is unique from other lymphomas:Often only involves a single node/chain of nodes. Spread is predictable (nodes, spleen, liver, bone marrow). Rarely involves mesenteric nodes or extranodal lymphoid tissue. | None identified | Painless enlargement of lymph nodes with predictable tumor spread. Often found in younger persons (20-30’s). Curable with multi-agent chemotherapy. |
| Burkitt’s Lymphoma | “Starry sky” pattern of proliferation | B-cell  | EBV infected cells can become immortalized and are at high risk for developing genetic mutations. C-myc is a single transduction molecule that is overexpressed in Burkitt’s lymphoma. It induces rapid and uncontrolled cell proliferation. | t(8:14)-C-myc. | Rapid painless enlargement of lymph nodes. 2 forms-endemic (jaw, kidney, ovary nodal involvement) and sporadic (abdominal node involvement). Intense chemo/radiation therapy is curative in 60-90% of cases. |
| Mycosis Fungoides | Clusters of T-cells within the epidermis that have convoluted nuclei (seen well on EM) | CD4 helper T-cell | Unknown | None Identified | Begins as a flat erythematous patch and evolves into a raised plaque then a tumor nodule. If it becomes widespread, erythroderma develops. |

Leukemias

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| **Type** | **Pathogenesis** | **Histology** | **Clinical/Lab Features** | **Immunophenotype** | **Karyotype** | **Treatment** |
| B-Cell Acute Lymphoid Leukemia (Most common childhood hematologic malignancy) | Proliferation of immature pre-B cells causes suppression of hematopoesis due to “crowding out”, competition for growth factors, and other nonspecified causes. Abnormal cells can infiltrate the spleen and liver. Bone marrow expansion occurs. Variable peripheral blood involvement. | Bone Marrow: Overwhelming of normal precursors by lymphocytes with a large nucleus, condensed blue chromatin, scant cytoplasm and inconspicuous nucleoli. Identical to pre-T cell. | Fatigue, pallor mucocutaneous bleeding/petechiae, recurrent infection, HSM, bone pain, headaches/N/V.Marrow: Overwhelmed by lymphocytic blastsLab: +/- blasts, thrombocytopenia, anemia, neutropenia.  | CD 19CD20, TdT, +/- Ig | Good prognosis: Tel-AML1Bad Prognosis: Philadelphia chromosome t(9:22), MLL t(4:11) | **Induction**: Vincristine, prednisone, PA.**Compression**: 6 mos methotrexate**Continuation**: daily VP + weekly methotrexate.**CNS Prophylaxis**: IT Methotrexate |
| T-Cell Acute Lymphoid Leukemia/ lymphoma (young males) | Proliferation of pre-T cells (immature) in the lymph nodes causes enlargement (frequently mediastinal). Can also present as leukemia. | Large nucleus w/condensed blue chromatin with scant cytoplasm and inconspicuous nucleoli. Identical to pre-B cell. | Nontender lymph node enlargement, frequently with mediastinal involvement with mass effects (dyspnea, IVC syndrome, etc). Can present like B-cell ALL. | Early pre-T: CD 1,2,5,6,7Late pre-T: CD 3,4,8ALL: TdT | **Good prognosis**: Tel-AML1**Bad Prognosi**s: Philadelphia chromosome t(9:22), MLL t(4:11) | See Above. |
| Chronic lymphocytic leukemia/ small lymphocytic lymphoma (most common adult leukemia) | Proliferation of mature non-functional B-cells in the peripheral circulation (moving to the BM) affects immune function for unknown reasons. Can infiltrate the spleen, nodes, and liver. Some develop autoreactive antibodies and have thrombocytopenia and hemolytic anemia. Can transform into APL or DLBCL (Richter’s syndrome). | Small mature B-cells with condensed chromatin and scant cytoplasm found in periphery or bone marrow | Most are asymptomatic. Recurrent infection. HSM. Lymphadenopathy. Jaundice. Mucocutaneous bleeding. Lab: Anemia, elevated indirect bilirubin, hypogammaglobulinemia, thrombocytopenia, marked lymphocytosis. | 50% have normal karyotype. Not associated with translocations. Commonly, deletions of 11q, 17p, and trisomy 12. | CD 19CD20CD 23CD5 | If asymptomatic, monitoring.Indications for Tx:B-SymptomsAnemiaBleedingRecurring InfectionSymptomatic HSM or lymphadenopathy.Tx: Chemotherapy with alkylating agents, purine analogs, and monoclonal antibodies (rituximab).  |
| Acute myelocytic leukemia (25-35 y/o) | Proliferation of immature myeloblasts that overwhelm the bone marrow (>20%) and “squeeze out” normal hematopoesis. | Bone Marrow: Overwhelming of normal precursors by lymphocytes w/Delicate chromatin with 2-4 nucleoli and more cytoplasm than lymphoblasts. Presence of Auer rods is pathognomic for AML. | Presentation very similar to that of ALL. Tiredness, pallor, weakness, mucocutaneous bleeding, recurrent infectionsRARELY HSM, lymphadenopathy, and CNS involvement.Lab: +/- blasts. ↓HB/HCT, thrombocytopenia, neutropenia.  | Most common: t(8:21), inv(16)APL: t(14:18) | CD13, 14, 15, 33, 34 | Primary Disease/ Translocation: ChemotherapySecondary to treatment/ deletions and monosomies/ relapse: Stem cell transplant. |
| Chronic myelogenous leukemia (25-50 y/o) | Clonal expansion of myeloid precursor cells that retain differentiating abilities leads to ↑neutrophils, basophils, eosinophils (sometimes MKC’s) in the periphery and hypercellular marrow. Sometimes RBC precursors are “squeezed out” Extramedullary neoplastic hematopoesis occurs. | Bone marrow: Tri-lineage hyperplasia with 100% cellularity. Moderately abnormal myeloid precursor cells can be found (ie uni-lobular PMN’s without granules). | Insidious onset of B-symptoms. Mild anemia. Dragging sensation in the abdomen or LUQ pain. HSM. Vascular sludging can occur @ WBC> 100,000 (hypoxia, arrhythmias, visual changes, neurologic changes, death). 3 Stages: *Chronic* <5% blasts-asymptomatic, *Accelerated* 5-19% blasts + B symptoms, *Blast* *crisis* >20% blasts looks like AML.Lab: Profound peripheral leukocytosis (mainly PMN/Baso/Eos), ↓HB, HCT, platelet count. | t(9:22) Philadelphia chromosome (BCR-ABL). All hematopoietic cells in CML express the Philly chromosome, but only the granulocyte lineage becomes neoplastic.  | Unknown | Gleevec (fusion protein inhibitor) + allopurinol. Refractory DZ: bone marrow transplant.Sludging: hydroxyurea and leukapheresis with fluids. |
| Polycythemia vera | Proliferation of granulocyte, monocyte, and erythroid lineages occurs causing peripheral elevations in PMN/Eos/Basos/ RBC’s/MKC’s. The disease can progress to a spent phase (unknown mechanism) or to AML. | Bone marrow: Hypercellular with increased normal appearing granulocytes, MKC’s, and erythroid precursors.  | Plethora, pruritus, cyanosis, headache, dizziness, hypertension, GI symptoms. DVT/PE/Stroke can also occur. HSM increases as disease progresses to spent phase. Lab: Leukocytosis, thrombocytosis, elevated HB/HCT. Low EPO. | N/A | JAK-2 Mutations. Allow precursor cells to divide without the influence of growth modulators.  | Aspirin and phlebotomy |
| Essential thrombocytosis (diagnosis of exclusion) | Proliferation of abnormal megakaryocyte clone occurs in the bone marrow due to decreased reliance on growth factors for replication. Increased numbers of dysfunctional platelets circulate in peripheral blood. Neoplastic extramedullary hematopoiesis can occur. Can progress to a spent phase or AML. | Bone Marrow: Abnormally large megakaryocytes. Peripheral: large platelets. | Long periods of absence of symptoms are punctuated by bleeding or thrombotic events occurs (PE, DVT, stroke, MI). HSM. Erythromelalgia.Lab: Thrombocytosis (>600,000) with or without leukocytosis. | N/A | JAK-2 mutation allows MKC’s to replicate without the influence of growth factors.  | Aspirin or alkylating agents used to lower platelet counts. |
| Primary myelofibrosis-least common, worst prognosis | Early stages are hypercellular with expansion of MKC lineages that produce PDGF and TGF-β. These growth factors cause activation of fibroblasts progressive fibrosis of the marrow. This causes pancytopenia and increasing extramedullary hematopoiesis (that is unable to keep up with the body’s needs) with rapid cell turnover. Can transform to AML. | Bone Marrow: Early-hypercellular with large MKC’s.Late- fibrotic.Peripheral: nucleated RBC’s precursor, large platelets, and teardrop cells (dacrocytes) | Fatigue, pallor, impressive HSM, lymphadenopathy, gout, B-symptoms. Lab: normochromic normocytic anemia, nucleated RBC’s, teardrop cells, + blasts, pancytopenia, hyperuricemia/ | N/A | JAK-2 Mutation | Supportive treatment. No curative therapies exist. Consider stem cell transplant in young patients. |
| Myelodysplastic syndrome | Clonal expansion of an abnormal myelocytic stem cell occurs. The clones retain the ability to differentiate into progenitor cells that are dysfunctional. These precursor cells overwhelm the normal marrow and cause hematopoiesis to become dysfunctional which causes peripheral cytopenias. Increased propensity to progress to AML. | Marrow: Hypercellular. Bi-lobed PMN’s, ringed sideroblasts, uni-lobular monocytes, giant MKC’s.Periphery: +/- blasts, nucleated & megaloblastic RBC’s, agranular PMN’s with bi-lobular nucleus. | B-symptoms, fatigue, mucocutaneous bleeding, recurrent infections. May be asymptomatic. Lab: Megaloblastic anemia, thrombocytopenia, neutropenia (pancytopenia). | Genetic alterations can be idiopathic or secondary to chemotherapy: Monosomy 5 or 7.Deletion of 5q or 7q. Trisomy 8. | N/A | In younger patients bone marrow transplants may be effective in prolonging life span. |

Aspirin: Irreversibly inhibits platelet coagulation by blocking thromboxane synthesis which is normally responsible for platelet aggregation.

**Cancer Genetics**

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| **Gene** | **Normal Function of Protein Product** | **Alteration** | **Associated Cancer(s)** | **Affected Chromosome(s)** |
| **Independence in Growth Signals** |
| ERB-B2/HER2/NEU | Epidermal growth factor receptor | Amplification (Herceptin antagonizes the receptor) | Breast Cancer | NA |
| BCR-ABL  | Tyrosine kinase | Fusion protein that is constitutively active (Gleevec targets fusion protein) | CML, ALL | t(9:22) Philadelphia Chromosome |
| RAS | Signal Transducer | Mutation induces constitutive activity | Multiple | N/A |
| C-myc | Transcription factor | Overexpression by translocation to the heavy chain promoter region | Burkitt’s Lymphoma | t(8:14) |
| **Insensitivity to Anti-Growth Signals** |
| PRb | Arrest of cell cycle in G1 | Point mutation causes inactivation | Retinoblastoma, various others | NA |
| P53 | Arrest of cell cycle in G1 and repair of DNA damage | Mutation causes inactivation | Multiple cancers | NA |
| TGF-B | Arrest of cell cycle | Mutation causes inactivation | Pancreatic and colon cancers | NA |
| APC | Suppresses β-catenin (transcription factor) | Deletion or mutation allows β-catenin to become constitutively active | Familial polyposis/ Colorectal cancer | NA |
| Ataxia Telangiectasia Mutation (ATM) | Cell cycle arrest when DNA breaks occur and either repairs or causes apoptosis | Mutation causes inactivation |  | NA |
| **Limitless Replicative Potential** |
| P53 | Initiates apoptosis in senescent cells | Mutation causes inactivation | Multiple cancers | NA |
| **Anti-Apoptotic Mechanisms** |
| P53 | Initiates apoptosis in cells with DNA damage | Mutation causes inactivation | Multiple cancers | NA |
| BCL-2 | Prevents apoptosis | Overexpression by translocation to the heavy chain promoter region  | Follicular lymphoma and some DLBCL’s | t(14:18) |
| **Angiogenesis** |
| VEG-F | Promotes angiogenesis | Self/expression by tumor cells | Multiple cancers (IE given in class: GBM) | NA |
| HIF-1α | Increases production of VEG-F | Elaboration by tumor cells | Multiple cancers | NA |
| Von Hippel Lindau Protein | Degrades HIF-1α+O2 when bound | Deletion or mutation allows HIF-1α to become elevated | Multiple cancers | NA |
| **Invasion/Metastasis** |
| * Proteases
* Decreased Cellular adhesion molecules (CAM)
 |