Anemia is **not a final diagnosis**

IRON DEFICIENCY ANEMIA **IS NOT** A DIAGNOSIS PER SAY.
ALWAYS PUT A LABEL TO IT:
IDA DUE TO UPPER GI BLEEDING DUE TO GASTRIC CANCER

Clinical copper deficiency can cause microcytic, normocytic, or macrocytic anemia and neutropenia.

Copper deficiency also causes myelopathy and peripheral neuropathy.

Bone marrow evaluation can reveal myelodysplasia and megaloblastic anemia.

Treatment with copper replacement promptly reverses hematologic manifestations of the disease, although neurologic manifestation may take longer.

- Folic acid is mainly absorbed in the jejunum and the body stores around 5 mg of folate in the liver, which is enough for 3 to 4 months.
- Folic acid deficiency may be related to decreased intake in the case of alcohol use disorder or malnutrition (elderly patients, institutionalized patients, poverty, special diets, etc.), increased demand particularly in case of pregnancy, hemolysis, hemodialysis, and malabsorption (tropical sprue, celiac disease, jejunal resection, Crohn disease, etc.). In some cases, medications like anticonvulsants and anticancer agents cause megaloblastic anemia related to folate deficiency by affecting folate metabolism.

most common cause for B12 def. : Pernicious anemia.

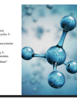
- The cells arrest in the DNA synthesis (S) phase and make DNA replication errors, which eventually leads to apoptotic cell death

MEGALOBLASTIC ANEMIA

Drug induced — * can be inherited

- Bone Marrow Effect (DNA Synthesis): thyamine receptor
- Allopurinol, Azathioprine, Capecitabine, Cladribine, Fludarabine, Fluorouracil, Gadolinium, Gemcitabine, Hydroxyurea, Lamivudine, Leflunomide, Mercaptopurine, Methotrexate, Mycophenolate mofetil, Trimethoprim, Zidovudine.
- Reduce the intestinal absorption or metabolism of these vitamins:
- Aminosalicylic acid, Antacids and proton pump inhibitors, Penicillin antibiotics, Chloramphenicol, Erythromycin, Oral contraceptives, Metformin, Phenytoin, Tetracyclines, Valproic acid.

PATHOPHYSIOLOGY



CLINICAL PRESENTATION

CLINICAL PRESENTATION

Pathogenesis of ITP

- Increased platelet destruction mediated by autoantibodies
- Auto-antibodies that react with major membrane glycoproteins can be identified in ~80% of patients
- Antibody concentrations diminish with effective treatment and increase with relapse
- Decreased production despite the increase in megakaryocytes in BM

WHO Bleeding Grade and Characteristics

Grade 1	Grade 2	Grade 3	Grade 4
Mucocutaneous bleed Petechiae Ecchymosis <10 cm Orophayngeal Conjunctival Epistaxis No intervention Vaginal spotting (<2 pads/day)	Ecchymosis >10cm Hematoma Epistaxis packing Retinal hemorrhage w/o visual Bleeding w/o RBC transfusion	Melena* Hematemesis* Hemoptysis* Hematuria* Vaginal bleeding* Epistaxis* Oropharyngeal* Musculoskeletal/ Soft tissue * With transfusion	Debilitating Non-fatal CNS Any fatal bleeding

Miller et al. Cancer 1981; 47:207-214

Initial Treatment or No treatment of ITP

Platelet Count (per µl)	Symptoms	Treatment
> 50,000	None	None
30-50,000	Not bleeding Bleeding	None Glucocorticoids
< 30,000	Not bleeding Bleeding	Glucocorticoids ? Glucocorticoids Hospitalization

Approach to the Treatment of ITP

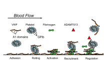
Initial treatment	Glucocorticoids IVIG
Curative therapy	Glucocorticoids Splenectomy Rituximab
Rescue therapy	High dose glucocorticoids IVIG
Chronic therapy	Many agents Thrombopoietin receptor agonists

Summary: Thrombopoietin-receptor agonists

	Romiplostim	Eltrombopag
Mechanism	TPOR: active site	TPOR: TM domain
Indications	Chronic ITP	Chronic ITP
Route	SQ	PO
Initial dose	1 mcg/kg/wk	50 mg/day
Overall response	~80%	~80%

Six treatment principles of HIT

- **Two Do's**
  *Stop heparin
  *Start alternative A/C
- **Two Don'ts**
  *No warfarin until substantial platelet count recovery
  *No platelet transfusions
- **Two Diagnostics**
  *Test for HIT
  *Duplex for lower limbs



Thrombotic Thrombocytopenic Purpura: Treatment

- Initial treatment:
  - Plasma exchange (plasmapheresis) daily
- Relapsed or refractory disease:
  - Plasmapheresis ± Rituximab immunosuppressive therapy
  - Other (Vincristine; Splenectomy)
- Adjunctive therapy (unproven role)
  - Glucocorticoids
  - Aspirin

Sites of bleeding in thrombocytopenia

- Skin and mucous membranes
  - Petechiae
  - Ecchymosis
  - Hemorrhagic vesicles
  - Gingival bleeding and epistaxis
- Menorrhagia
- Gastrointestinal bleeding
- Intracranial bleeding

Hemophilia: genetic testing for carriers and patients

DNA testing should be done if possible
- Identification of causative mutation in an affected relative helpful, since mutations run in families particularly for families with missense mutations
- Can be applied for females carriers, pre-implantation(PGD), CVS in utero testing

Why do we develop AML as we get older?
Hematopoietic stem cells acquire mutations over their lifetime.
Most are benign (passenger).
Occasionally one leads to clonal hematopoiesis.
Each division within this clone results in further mutations, and facilitate subclonal evolution and progression to MPD/MDS/AML.

M4: Myelomonocytic leukemia

- With inverted 16 and associated eosinophilia this is a good prognostic category
- Associated with leukemia cutis.
- CNS disease may occur.

Treatment aml/m3

- Tretinoin (all tran retinoic acid) is an oral drug that induces the differentiation of leukemic cells bearing the t(15;17); it is not effective in other forms of AML.
- APL is responsive to cytarabine and daunorubicin, but about 10% of patients treated with these drugs die from DIC induced by the release of granule components by dying tumor cells.

ATRA Syndrome

- Tretinoin does not produce DIC but produces another complication called the ***retinoic acid syndrome***.
- *Occurring within the* first 3 weeks of treatment, it is characterized by **fever**, **dyspnea**, **chest pain**, **pulmonary infiltrates**, **pleural** and **pericardial effusions**, and **hypoxia**.
- The syndrome is related to adhesion of differentiated neoplastic cells to the pulmonary vasculature endothelium.
- Glucocorticoids, chemotherapy, and/or supportive measures can be effective.
- The mortality of this syndrome is about **10%**.

Chromosomal/molecular abnormalities with prognostic significance in ALL
Better prognosis
- normal koryotype
- hyperdiploidy
Poor prognosis
- t (8; 14)
- t (4; 11)
Very poor prognosis
- t (9; 22); BCR/ABL (+)

Treatment Approach in ALL

Risk classification in ALL
1. Standard risk
2. High risk
3. Very high risk

Allogeneic BMT for ALL
High risk All
Unacceptable minimal residual disease
Availability of a donor
Good performance status
Aim to cure

CLL treatment criteria:

- Patient has symptoms
- Decline in Hb or Plt.
- Lymphadenopathy
- Hepatosplenomegaly
- Recurrent infections

CLL Treatment Options

1960s	1970s	1980s	1990s	2000
Alkylating Agents - Chlorambucil - Cyclophosphamide		Purine Nucleosides - Fludarabine - Pentostatin - Cladribine	Purine Nucleosides Plus Alkylators	Chemoimmunotherapy

Case Ten: Diagnosis and Management
1- Decide the type of lymphocyte
2- Determine the stage
Stage IV Rai, C Binet
3- Cytogenetics
+ 12
3- Decide therapy
5- Decide Prognosis
6- Determine follow-up

sIg	+
CD19	++
CD20	++
CD5	+

CLL Clinical Presentation

- Lymphocytosis
  - Morphologically mature
  - Immunologically immature
  - Accumulation in PB, BM and lymphatic tissues
- Enlarged Lymph nodes
- Splenomegaly
- Hypogammaglobulinaemia

Disorders of haemostasis
- Thrombotic disorders
  - Congenital: -Factor V Leiden mutation -Prothrombin mutation -ATIII deficiency -Protein C and protein S deficiencies -Homocysteinemia
  - Acquired: -Aging -APS -Malignancy -Immobilisation -Pregnancy and estrogen use -Nephrotic syndrome -Liver disease -DIC -HIT
- Mixed: -Liver disease -DIC -HIT -TTP
- Bleeding disorders
  - Primary Haemostatic defects
    - Quantitative disorders: -Immune mediated (idiopathic or secondary to infections, drugs, autoimmune disease) -Hypersplenism -TMAs -DIC -Prosthetic heart valves -Bone marrow depression (aplastic anaemia, chemotherapy, infections, infiltration)
    - Qualitative disorders: -VWD -Congenital plateltes disrders (e.g. Glanzmann's) -Medications -Acquired VWD -Uraemia
  - Secondary Haemostatic defects
    - Congenital: -Haemophilia A -Haemopophilia B -Other rare bleeding disroders
    - Acquired: -Liver disease -Vitamin K deficiency -Medications -Severe VWD -Acquried haemophilia

Symptoms

- Insidious onset: accidental discovery
- Fatigue, malaise, weight loss
- Symptoms due to splenomegaly
  - LUQ pain, early satiety,mass
- Infections, thrombosis, bleeding.
- ?Gout
- Worsening of symptoms heralds progression (fever, weight loss, decreased response to therapy, bone pain).
- Some patients may present in the accelerated or blastic phase.

CML

Hematologic Findings

- Elevated WBC, <5% blasts and <10% blasts and promyelocytes
- Elevated platelets
- Normochromic normocytic anemia
- Basophilia
- The cytogenetic hallmark of CML, found in 95% of patients, is the t(9;22)(q34;q11.2).
- Originally designated as the Philadelphia chromosome.
- All patients should have evidence of the translocation either by cytogenetics, FISH, or molecularly to make a diagnosis of CML.

Physical Findings

- Minimal to moderate splenomegaly
- Mild hepatomegaly
- Lymphadenopathy and myeloid sarcomas rare except in terminal stages of the disease.

Hematologic Findings

Accelerated Phase is characterized by:
- Anemia, Blood or BM basophils ≥20%, Platelet count <100,000/µl
- Cytogenetic clonal evolution, Blood or BM blasts between 10 and 20%

Blastic Phase (Crisis)
- Acute leukemia, with blood or marrow blasts ≥ 20%.
- Hyposegmented neutrophils may appear (Pelger-Huet anomaly).
- Blast cells can be classified as myeloid, lymphoid, erythroid, or undifferentiated.

Treatment

- Aim of treatment is to reduce WBC, prevent gout and **target the molecular cause** of the disease
- The treament has been revolutionized by imatinib mesylate, a targeted treatment.
- Stem cell transplant (SCT) is the only definitive therapy and treatment of choice in some

Side effects

- The main side effects are fluid retention, nausea, muscle cramps, diarrhea, and skin rashes.
- Myelosuppression is the most common hematologic side effect.

Resistance

Mechanisms include
- Gene amplification
- **Mutations at the kinase site**
- Enhanced expression of multidrug exporter proteins
- Alternative signaling pathways functionally compensating for the imatinib-sensitive

Pathogenesis of DIC

Plasma/Red Cell Separation

Centrifugation — Plasma expression

PULMONARY EMBOLISM and DVT TREATMENT

TREATMENT OF VTE
*HEPARIN(UFH)??:80u/kg loading>18u/kg/hr PTT 1.5-2.5
OR
*HEPARIN(LMW):
1mg/kgx2 enoxaparin
175u/kgx1 tinzaparin
*WARFARIN: start with 5mgx1 keep INR 2-3
OVERLAP HEPARIN+WARFARIN
* OR NEW ORAL ANTICOAGULANTS

Duration of Therapy

VTE:OTHER TREATMENT MODALITIES
THROMBOLYTIC THERAPY
* V.Thrombectomy
* IVC Filters
* Pulmonary embolectomy
* Post DVT syndrome

Contraindications to NOAC therapy include:

NOAC adverse effects

NOAC indications include:
- Reduces risk of stroke in non-valvular atrial fibrillation
- Prevention of VTE following hip or knee replacement
- Treatment and ongoing prevention of VTE

Etiology of NHL

- Idiopathic
- Immune suppression
  - congenital (Wiskott-Aldrich)
  - organ transplant (cyclosporine)
  - AIDS
  - increasing age
- DNA repair defects
  - ataxia telangiectasia
  - xeroderma pigmentosum

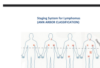
Etiology of NHL

- Chronic inflammation and antigenic stimulation
  - *Helicobacter pylori* inflammation, stomach
  - *Chlamydia psittaci* inflammation, ocular adnexal tissues
  - Sjögren's syndrome
- Viral causes
  - EBV and Burkitt's lymphoma
  - HTLV-I and T cell leukemia-lymphoma
  - HTLV-V and cutaneous T cell lymphoma
  - Hepatitis C

Staging: Ann Arbor

I. 1 lymph node region or structure
II. >1 lymph node region or structure, same side of diaphragm
III. Both sides of diaphragm
IV. Extranodal sites diffuse, beyond "E" designation

Staging System for Lymphomas (ANN ARBOR CLASSIFICATION)



Revised European-American Lymphoma (REAL) Classification: B-Cell Neoplasms

Indolent	Aggressive	Very Aggressive
•CLL/SLL •Lymphoplasmacytic/ IMC/WM •HCL •Splenic marginal zone lymphoma •Marginal zone lymphoma – Extranodal (MALT) – Nodal •Follicle center lymphoma, follicular, grade I-II	•PLL •Plasmacytoma/ Multiple myeloma •MCL •Follicle center lymphoma, follicular, grade III •DLCL •Primary mediastinal large B-cell lymphoma •High-grade B-cell lymphoma/Burkitt's-like	•Precursor B-lymphoblastic lymphoma/Leukemia •Burkitt's lymphoma/ B-cell acute leukemia •Plasma cell leukemia

Prognostic factors in non-Hodgkin's lymphoma
- *Adverse factors:*
- *Age > 60 years*
- *Stage III or IV, i.e. advanced disease*
- *High serum lactate dehydrogenase level*
- *Performance status (ECOG 2 or more)*
- *More than one extranodal site involved*

Treatment Options in Advanced Indolent Lymphomas
- ***Observation only.***
- ***Radiotherapy to site of problem.***
- ***Systemic chemotherapy***
  - ***oral agents: chlorambucil and prednisone***
  - ***IV agents: CHOP, COP-R, FC-R***
- ***Antibody against CD20: rituximab***
- ***Stem cell or bone marrow transplant.***
- *New monoclonal antibodies*

Reasons to Treat in Advanced Indolent Lymphomas
- Constitutional symptoms
- Anatomic obstruction
- Organ dysfunction
- Cosmetic considerations
- Painful lymph nodes
- Cytopenias

Standard Treatment for Aggressive Lymphomas
- Systemic chemotherapy
  - CHOP-R
- ± Intrathecal chemotherapy
  - AIDS patients and CNS involvement
- ± Radiotherapy
  - Spinal cord compression, bulky disease
  ??BMT

Burkitt's Lymphoma
- Treated with multidrug regimen similar to pediatric leukemia/lymphoma regimens.
- BMT

Treatment Options: Aggressive Lymphomas

Aggressive
- Diffuse large cell lymphoma, large cell anaplastic lymphoma, peripheral T cell lymphoma.

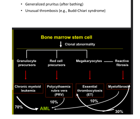
Very Aggressive
- Burkitt's lymphoma and lymphoblastic lymphoma.

Treatment Options for Aggressive Lymphomas
*potentially curable
*disseminates through bloodstream early
*must use systemic chemotherapy
❖CHOP-R x ?8 cycles
❖CHOP-R x 3 cycles followed by radiotherapy
*Bone marrow transplantation for some cases
*New monoclonal antibodies

Myeloproliferative Neoplasms

Common features
- Specific clincopathologic criteria for diagnosis and distinct diseases, have common features
- Increased number of one or more myeloid cells
- splenomegaly
- Hypercatabolism: wt loss, gout
- Clonal marrow hyperplasia without dysplasia
- Predisposition to evolve

- Generalized pruritus (after bathing)
- Unusual thrombosis (e.g., Budd-Chiari syndrome)



Polycythemia Vera Diagnostic Criteria

Table 4. WHO diagnostic criteria for P-vera

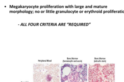
Major Criteria
1. Elevated RBC mass > 25% above mean normal predicted value or hemoglobin > 18.5 gm/dL (male) or 16.5 gm/dL (female)
2. Presence of JAK2 V617F
Minor Criteria
1. BM trilineage myeloproliferation
2. Low serum erythropoietin levels
3. Endogenous erythroid colony formation

Diagnosis requires both major criteria or one major and two minor criteria

Essential Thrombocythemia: Diagnostic Criteria

- **Platelet count ≥ 450,000**
- **JAK2 V617F* OR no evidence of reactive thrombocytosis**
- **Not meeting WHO criteria for other MPNs (e.g PV, CML)**
- **Megakaryocyte proliferation with large and mature morphology; no or little granulocyte or erythroid proliferation**

- ALL FOUR CRITERIA ARE "REQUIRED"



➢ **Bone marrow: Hypercellularity with marked megakaryocytic hyperplasia**

Ruxolitinib in the treatment of MPN
Selective JAK I & II inhibitor
Second line after hydroxyurea
Offers improvement of systemic symptoms, trx requirements.
No survival benefit as yet

Hodgkin's Disease/Lymphoma Treatment

With appropriate treatment about 85% of patients with Hodgkin's disease are curable
- **I A,B — chemo.Radiation Therapy in selected cases**
- **II A — Chemo.XRT in selected cases**
- **IIB; IIIA,B; IVA,B — Chemo (+/- radiotherapy in selected cases)**

Chemotherapy Regimens for Hodgkins disease
- MOPP
  - Mechlorethamine, Oncovin, Procarbazine, Prednisone
- ABVD
  - Adriamycin, Bleomycin, Vinblastine, Dacarbazine
- BEACOPP
- BMT for relapse or resistance

Workup

- Bone marrow biopsy and aspirate
- Serum protein electrophoresis and immunofixation
- Skeletal survey/ MRI/PET Scan
  - Plain x-rays are better than bone scan.
  - Lytic lesions do not show up well on bone scan.
- Quantitative immunoglobulins

→ multiple myeloma

Prognostic Factors

International staging system
I (good prognosis)
Serum albumin > 3.5 g/dl
Serum β2 microglobulin < 3.5 mg/dl
II
Not I or III
III
β2 microglobulin: >5.5 mg/dl

Treatment of Multiple Myeloma

Standard Chemotherapy
- Dexa and Thalidomide
- Dexa and Bortezomib(Velcade)/ Lenalidomide
- Melphalan and prednisone
- High Dose Chemotherapy with Bone marrow transplant (auto)

Management - TRALI
- No specific treatment
- Largely supportive
- Respiratory support with O_2
- Most cases require mechanical ventilation
- Steroids
- Clinical staff who administer transfusions must be aware how to diagnose & manage promptly