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MYELOPROLIFERATIVE DISORDERS

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Normal Blood Cell Development

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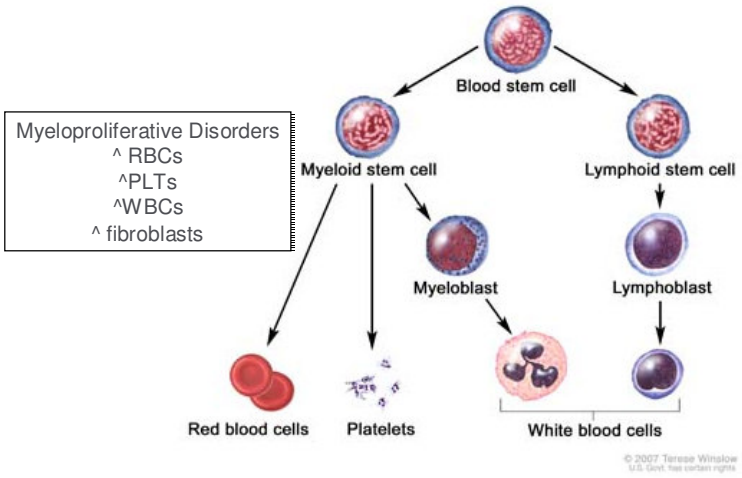

Myeloproliferative Disorders
^ RBCs
^PLTs
^WBCs
^ fibroblasts

Myeloproliferative vs. Myelodysplastic

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- Myelo*proliferative* disorders (MPDs) or neoplasms (MPNs)
  - A group of blood diseases characterized by abnormal over-proliferation of morphologically "normal" blood cells in the bone marrow
  - Erythro*cytosis*/polycythemia, thrombo*cytosis*, leuko*cytosis*
- Myelo*dysplastic* syndromes (MDSs)
  - A group of blood diseases characterized by dysplastic bone marrow hyperplasia
  - Poorly formed or dysfunctional cells
  - Variable degrees of peripheral *cytopenia*

"Classic" vs. "Atypical" Myeloproliferative Disorders (MPDs)

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Comparison of FAB and WHO Classifications of Chronic Myeloproliferative Diseases.

FAB	WHO
Chronic myelogenous leukemia	Chronic myelogenous leukemia
Polycythemia vera	Polycythemia vera
Essential thrombocythemia	Essential thrombocythemia
Agnogenic myeloid metaplasia/myelofibrosis	Chronic idiopathic myelofibrosis
...	Chronic neutrophilic leukemia
...	Chronic eosinophilic leukemia/hypereosinophilic syndrome

French-American-British Classification

2002 World Health Organization

Atypical MPNs: chronic myelomonocytic leukemia, juvenile myelomonocytic leukemia, atypical CML, unclassifiable MDS/MPN

Features Common to all MPDs

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- Origin in a pluripotent hematopoietic stem cell
- ABNORMAL UNSTIMULATED OVERPRODUCTION of one or more of the formed elements of the blood
- HYPERCELLULAR bone marrow
- ^ Risk for Thrombosis and Bleeding (esp. with PV and ET)
- ^ Risk for Transformation to acute leukemia (AML) and/or marrow fibrosis/myelodysplastic syndrome (MDS)
- Associated genetic mutations of many different tyrosine kinases

Presenting Signs and Symptoms

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- Incidental finding in an asymptomatic person with an abnormal CBC
- Fatigue (81%), Pruritis (52%), Night sweats (49%)
- Secondary causes for abnormal elevations much more common than MPDs
  - Erythrocytosis
    - Only 5% of patients with persistant erythrocytosis will have PV
    - Dehydration, hypoxia (smoker, altitude, OSA), renal disease
    - Steroids (testosterone for hypogonadism)
  - Reactive thrombocytosis much more common than ET
    - Acute phase reactant, infections, inflammatory disease, *anemia

Value of Erythropoietin (EPO)

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- Hormone produced by the kidney that promotes the formation of red blood cells (RBCs) in the bone marrow
- Prime regulator of RBC production
- Measurement of serum EPO can be useful in differentiating RBC disorders
  - **Normal or ^ in secondary causes of polycythemia**
  - **Normal or Decreased in Polycythemia Vera**
- Normal levels 0 – 19 mU/mL

JAK2 (V617F) Mutation

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- JAK2 (identified in 1993) is the tyrosine kinase protein involved in normal blood cell development
- JAK2 mutation – JAK2 (V617F) – point mutation (discovered in 2005) allows continuous activation of cell proliferation and resistance to cell death – the most important advance in MPD in 30 years!
- Highly sensitive for MPDs since NOT found in healthy persons, secondary polycythemia, or a reactive blood count elevation
- Diagnostic only for the presence of a MPD, not its type
  - 97% of patients with polycythemia vera (PV)
  - 57% of patients with essential thrombocythemia (ET)
  - 50% of patients with primary myelofibrosis (PMF)

Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. Lancet. 2005;365(9464):1054.

Other Molecular Defects in MPDs

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A negative JAK2 (V617F) does not rule out a MDS

10% false negative

Annals of Internal Medicine
ESTABLISHED IN 1927 BY THE AMERICAN COLLEGE OF PHYSICIANS

Table. **The Chronic Myeloproliferative Disorders**

Disease	Molecular Defect*
Chronic myelogenous leukemia	*BCR-ABL*
Chronic eosinophilic leukemia and the hypereosinophilic syndrome	*FIP1L1-PDGFRA*
Chronic neutrophilic leukemia	*BCR-ABL* p230
Chronic myelomonocytic leukemia	*TEL-PDGFRB*
Systemic mastocytosis	*KIT* D816V
Polycythemia vera	*JAK2* V617F (~92% positive) *JAK2* exon 12 mutations (3% positive)
Essential thrombocytosis	*JAK2* V617F (~50% positive) *MPL* W515L/K (~3% positive) *MPL* K39N
Primary myelofibrosis	*JAK2* V617F (~50% positive) *MPL* W515L/K (~14% positive)

* Representative molecular defects caused by balanced translocations or point mutations in the chronic myeloproliferative disorders.

Ann Intern Med. 2010;152(5):300-306. doi:10.7326/0003-4819-152-5-201003020-00008

Polycythemia Vera (PV)

Primary Polycythemia, Polycythemia Rubra Vera

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- Most common Myeloproliferative Disorder
- Elevated RBC parameter (RBC, Hgb, Hct, or RBC mass)
- The number of WBCs and Platelets may also increase
- Relatively rare – 5 to 20 cases/100,000 in US
  - PCP will make the dx once or twice during his/her career
- Peak incidence 50-70 years old, but may occur at any age
- M:F ratio 2:1
- 97% JAK2 mutation+
- 75% have splenomegaly; pruritis is common

Diagnostic criteria for Polycythemia Vera (PV)

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Major criteria	• **Hemoglobin >18.5g/dl** in men or >16.5g/dl in women (or other evidence of ^ RBC volume) • **+ JAK2(V617F) mutation** or other functionally similar mutation such as JAK2 exon 12 mutation
Minor criteria	• Bone marrow biopsy showing hypercellularity with trilineage growth (prominent erythroid, granulocytic and megakaryocytic proliferation) • **Low serum erythropoietin level** • Endogenous erythroid colony formation (in vitro)
PV Diagnosis	• Both major criteria and one minor criterion or • First major and two minor criteria

Revised WHO Criteria 2008 (from 2001)
Hematology/Oncology Clinics Aug 2009

High Risk PV

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- Age > 60
- Previous h/o thrombotic events
- CV risk factors – Smoking, HTN, Diabetes
- Leukocytosis – WBC > 12,000/uL (60%) at diagnosis
- Platelets > 400,000/uL (50%) at diagnosis

Treatment of PV

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- Regular **Phlebotomy** to lower blood viscosity
  - Goal HCT < 45% in men, < 42% in women
    - ^ risk of thromboses and vascular events with HCT > 44%
  - Yields the best overall survival
- **Low dose Aspirin**
- **CV Risk Factor Modification** – stop smoking!
- **Cytoreductive therapy** for High Risk RV (hydroxyurea, etc) can decrease the incidence of thromboses

- Goal of therapy – normalize CBC and prevent thrombohemorrhagic complications

PV – Mortality/Morbidity

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- Median survival for untreated symptomatic patients is 6 to 18 months
- **Thomboses account for the majority of morbidity/mortality**
- Thrombotic complications – 15-60 % - depends on control of disease
  - Major cause of death in 10-40% of patients
  - Both venous and arterial thromboses
  - DVT/PE, Stroke, MI, Renal artery/vein thromboses, intestinal ischemia
- Transformation to AML/MDS ~1.5%
- Bleeding complications – 15-35%
- With treatment, medial survival is more than 10 years

Evaluation Summary for Polycythemia

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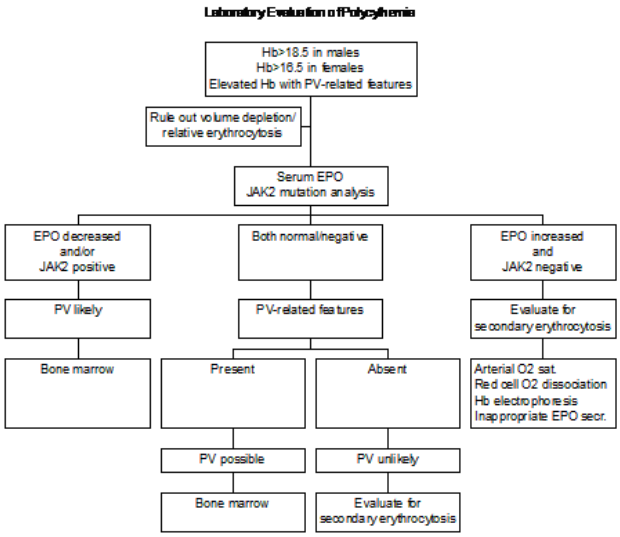

Essential Thrombocythemia (ET)

Essential Thrombocytosis, Primary Thrombocytosis

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- A diagnosis of exclusion, first described in 1934
- Chronic *nonreactive* elevated platelets without evidence of any other MPD
- Megakaryocyte hyperplasia in the bone marrow
- Prevalence 24 cases/100,000 in US
- Median age at diagnosis 60, up to 20% < 40 years old, extremely rare in kids
- F:M ratio 2:1
- 50% JAK-2 mutation+
- ~50% totally asymptomatic at presentation

Diagnostic Criteria for ET

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- A diagnosis of EXCLUSION
  - Sustained Platelet Count ≥ of 450 X 10^9/L
  - Megakaryoctyic Hyperplasia on Bone Marrow Biopsy
  - Does not meet WHO criteria for PV, PMF, CML, MDS, or any other myeloid neoplasm (Diagnosis of exclusion)
  - +JAK-2 mutation OR no evidence for reactive thrombocytosis
- All four criteria must be met

Revised WHO Criteria 2008 (from 2001)
Hematology/Oncology Clinics Aug 2009

High Risk ET

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- Age of onset ≥ 60 years old
- History of thromboses
- Platelet count ≥ 1.5 million x 10^9/L
  - Paradoxically ^ risk of bleeding
- WBC count > 15 x10^3/uL at diagnosis
- Low hemoglobin level (<12 g/dL in females; < 13.5 g/dL in males)
- CV risk factors: Smoking, Hypertension, Hyperlipidemia, Obesity, Diabetes
- Markers for Hypercoagulability (e.g. Factor V Leiden, Antiphospholipid Ab)

- Increased risk of thromboses, poorer survival

Low Risk ET

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- Age at dx < 60 years old
- No history of bleeding or thrombotic events
- WBC < 15,000/microL
- Well followed with stable platelet counts < 1 million/microL
- Good CV profile

Treatment for ET

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- Consider observation for low risk patients
- Low dose aspirin
- CV risk factor modification - Stop smoking!
- Coumadin for venous thromboses
- Cytoreductive therapy (hydroxyurea, etc) for high risk ET
  - Hydroxyurea vs Anagrelide
    - HU +ASA superior to Anagrelide +ASA (^rate of arterial thromboses, bleeding, transformation, but decreased venous thromboses) (NEJM 2005;353:33-45)
- In emergencies, plateletpheresis for acute thrombosis and/or marked thrombocytosis

Goal Platelet Count

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- There is no established target platelet count
- No correlation between platelet count and thrombosis risk
- Goal platelet count:
  - Level where the patient is FREE from symptoms or from the risk of bleeding
  - Generally, less than 900K

ET – Mortality/Morbidity

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- Related to thrombotic and bleeding complications
  - Platelet count is elevated but function is impaired
  - ^ Bleeding risk when PLT > 1.5 million
- Transformation Risk < 5% @ 15 years
  - Acute Leukemia (AML) < 5%
  - Myelodysplastic syndrome 4%
  - More common with +JAK 2
- Life expectancy for the low risk group is nearly that of the healthy population

Chronic Myelogenous Leukemia (CML)

Chronic Myeloid Leukemia, Chronic Myelocytic Leukemia

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- Expansion of a clone of cells that carry the Philadelphia Chromosome
- t(9,22) translocation => forms the BCR-ABL cancer gene (discovered 1960)
- 3 phases

Chronic stable	< 5% blasts	Mild sx
Accelerated	5-30%	^ sx
Blast crisis	> 30%	Aggressive

- Goals of therapy
  - Complete *hematologic* response (NL WBCs, PLTs, no splenomegaly)
  - Complete *cytogenetic* response (No Ph-positive cells in BM)

Imatinib mesylate (Gleevec, Novartis)

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- Currently recommended for *first-line therapy* of CML
- Well tolerated oral medication - SPECIFIC *tyrosine kinase inhibitor* of the protein made by the BCR-ABL cancer gene (first approved TKI)
- FDA-approved since May 2001, 400 mg/day for chronic-phase CML ($32K/yr)
- Sustained remissions with impressive response rates
  - 2003 NEJM 76% complete cytogenetic response @ 18 months
  - Overall survival 89% at 5 years, cumulative response 83%
- Responses occur quickly (within 2 weeks, almost all by 6 months)
- CML likely to return if drug treatment stopped, follow-up has been short (7 years)
- Main concerns: relapse, progression of disease, development of drug resistance

Clinical practice guideline of the National Comprehensive Cancer Network, Feb 2007, NCI guidelines Mar 2007, N Engl J Med Mar 2003

Second and Third generation TKIs

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- dasatinib (SPRYCEL®) Initial US Approval 2006
- nilotinib (TASIGNA®) (2007) **WARNING: QT prolongation and sudden deaths
- bosutinib – third generation – undergoing clinical trials

- Valuable treatment options for subgroup of patients intolerant or resistant to imatinib
- In the first line-setting - lower rates of transformation, comparable or superior complete cytogenetic response compared to imatinib by *2-year* f/u.

J Blood Med. 2012:3:51-76.

Allogeneic Stem-Cell Transplantation

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- Only proven curative treatment for CML, potential toxicity, early mortality risk
- Leading causes of premature death
  - Relapse of primary disease (29%)
  - Chronic graft-vs-host disease (22%)
    - Up to 70% transplant patients develop some degree of GVHD
    - Prevention/treatment with immunosuppressives
  - Risk for secondary malignancies (treatment related) lymphomas
  - Endocrine abnomalities (premature menopause, hypothyroid)
  - Organ dysfunction (restrictive lung disease, CHF, infections, anemia)
  - Immunity begins to develop and be fully functional ~ 1-1.5 years in the absence of chronic GVHD

Mortality Risks after BMT

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- Recurrence of primary disease – 29%
  - 67% occurred between 2 to 5 years
  - 27% occurred in the next 5 years
- cGVHD – 22% of deaths
- Late infection (in the absence of cGVHD) – 11%
- Treatment related causes – 25%
  - Second malignancy - 7%
  - Pulmonary complications - 5%
  - Cardiotoxicity - 3%
  - Other treatment related sequelae – 8.4%

Blood 2007; 110: 3784-3792

Primary Myelofibrosis (PMF)

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- Least common MPD, most difficult to diagnose
- ^ collagen in bone marrow => bone marrow fibrosis
- Fever, night sweats, weight loss, fatigue
- 95% with palpable splenomegaly
- Anemia, thrombocytopenia with eventual complete bone marrow failure
- Average survival – 5 years
- Allogeneic stem cell transplant is the only possible curative therapy
- Generally considered an uninsurable condition

MPD Summary
Diagnosis, Risk, and Survival varies

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	Diagnostic Criteria	Thrombotic Bleeding Risk	AML/MDS Transformation Risk	Survival
PV	^RBC parameter +JAK 2 Low EPO	>20%	<3% 10%	Untreated 6-8 months Treated > 10 years
ET	^PLTs Dx of exclusion	>20%	<1% 1%	Near NL
CML	^WBCs Ph-chromosome		Untreated > 90%	Improving
PMF	Splenomegaly Bone marrow fibrosis		4%	< 5 years

The Future for MPDs? Cytogenetics?

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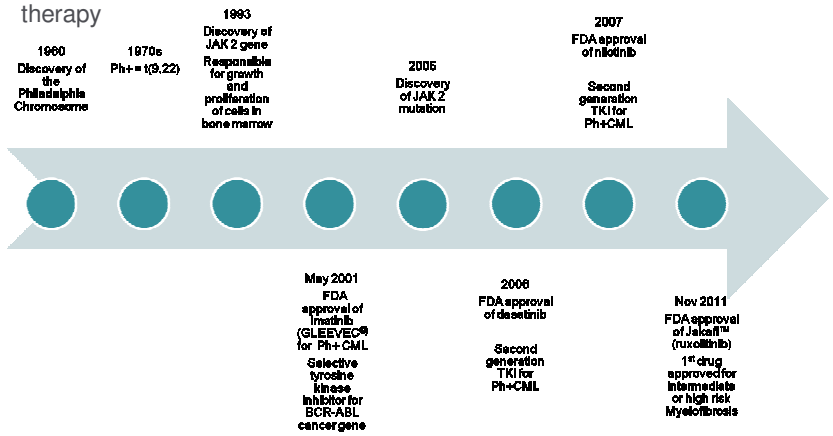
Current research focuses on JAK2 inhibitors/TKIs, potential for targeted therapy



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THANK YOU VERY MUCH
FOR YOUR ATTENTION

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