

Erythrocytosis and Polycythemia

I. Three types to be considered

- A. Primary polycythemia
- B. Secondary polycythemia
- C. Spurious erythrocytosis

II. Primary polycythemia (polycythemia vera)

A. A chronic, proliferative, neoplastic disorder involving all hematopoietic cell lines

B. Etiology and pathogenesis

1. Cause unknown

2. Genetics

a. Not familial

b. Cytogenetic abnormalities present in 15-25% of patients early in course, and in 70-100% of patients who have developed myelofibrosis, myeloid metaplasia or leukemia

c. Trisomy 1q, 8, 9, 9p seen, as well as 20q-

d. These abnormalities do not predict the clinical course

3. Clonal proliferation (Adamson, et al)

a. Studied 2 females with polycythemia vera and heterozygosity for G6PD type

b. Unaffected cell lines, such as fibroblasts showed both G6PD types

c. Marrow elements were of one G6PD type only

4. Hematopoietic progenitor cells from these patients form erythroid colonies independently of erythropoietin when cultured in vitro.

a. Cells from patients with essential thrombocythemia can sometimes do the same. A large proportion of these ET cases may actually be masked p vera (Shih).

b. Studies using monoclonal antibodies to both EPO and EPO receptors can distinguish two populations in p vera. One set of erythroid precursors shows normal EPO-dependence in culture, while the other set proliferates independently (Fisher).

c. P vera erythroid progenitors appear to differentiate more rapidly than their normal counterparts (Spivak 2002).

5. Polycythemia vera cell lines show marked hypersensitivity to the stimulatory effects of insulin-like growth factor-1 (IGF-1), and retain this trait even after depletion of adherent cells which are thought to be the source of IGF-1. IGF-1 is an antiapoptotic cytokine. In contrast, normal progenitor cells produce no erythroid colonies when similarly treated.

6. Erythroid colonies from patients with polycythemia vera express increased levels of Bcl-X1 protein. Bcl is a known inhibitor of apoptosis.

7. Platelets from subjects with either polycythemia vera or myelofibrosis show reduced expression of the thrombopoietin receptor Mpl. The pathophysiological significance of this is unclear (Moliterno).

C. Epidemiology

1. Peak incidence in 7th decade

2. Male/female ratio \approx 1.5

3. Said to be uncommon in blacks (but certainly occurs)

D. Clinical aspects

1. Plethora, with congested mucous membranes, conjunctiva, and retinal veins
2. Central nervous system
 - a. Headache 42%
 - b. Dizziness 30%
 - c. Visual disturbances 15%
 - d. Paresthesias 13%
 - e. Strokelike symptoms 9%
 - f. Cerebral thrombosis/hemorrhage is more frequent if the hematocrit is high. Thrombotic stroke increases in incidence for several years following phlebotomy.
3. Cardiovascular
 - a. Angina
 - b. Thrombosis (thrombophlebitis in 13%)
 - i. Occur most frequently in the 2 years preceding diagnosis
 - ii. Incidence following diagnosis of p vera is 3.4%/year.
 - c. Claudication
 - d. Pulmonary embolism
4. GI system
 - a. GI discomfort 25%
 - b. Peptic ulcer disease 19%
 - c. Hepatic vein thrombosis (Budd-Chiari syndrome)
 - i. French study of 20 patients with Budd-Chiari detected spontaneous, EPO-independent growth of cultured erythroid colonies in 16. This was taken to imply presence of myeloproliferative disorder, although other clinical features were lacking.
5. Hemorrhage, both major and minor
6. Pruritis, especially after warm bath in 50%
7. Splenomegaly
 - a. Due to congestion and extramedullary hematopoiesis
 - b. Spleen palpable in 75%
8. Hepatomegaly 50%
9. Constitutional symptoms
 - a. Weakness
 - b. Weight loss

c. Malaise

E. Laboratory aspects

1. Elevated red cell mass
 - a. > 39 ml/kg in 75% of cases
 - b. Measure isotopically
 - c. General correlation of hematocrit with red cell mass, but can see normal red cell mass even at Hct=59%
 - i. Hct $> 52\%$ in 80% of cases
 - ii. Hct $> 60\%$ in 50% of cases
2. Plasma volume usually normal
3. Iron metabolism
 - a. Iron stores depleted, serum iron low
 - i. May relate to phlebotomy
 - ii. Losses due to bleeding and phlebotomy
 - iii. Expansion of red cell mass
 - b. Iron turnover and incorporation rapid
4. Erythropoietin – Typically is low, but isolated measurement can be misleading, as polycythemia vera may overlap the ranges for normal or secondary erythrocytosis
5. Increased Hb F and F cells may be found
6. Granulocytes
 - a. Moderate leukocytosis, usually with shift to left
 - b. WBC $>12,000$ in 50%
 - c. Sometimes see basophilia
 - d. LAP usually elevated
 - e. There is evidence of increased neutrophil activation (Falanga) thought possibly to correlate with increased thrombotic risk.
7. Platelets
 - a. Thrombocytosis typical
 - b. Usually $< 1,000,000$
 - c. $> 500,000$ in 50% of cases
 - d. Count may increase with phlebotomy
 - e. Platelets large and bizarre
 - f. Many functional defects reported
 - i. Subnormal in vitro aggregation response
 - ii. Increased number of circulating aggregates
 - iii. Increased thromboxane production

8. Bone marrow
 - a. Cellularity
 - i. Usually hypercellular, with average of 82%
 - ii. 13% of patients have normal cellularity at presentation
 - b. Megakaryocytes plentiful
 - c. Iron decreased
 - d. Reticulin present
 - i. Correlates somewhat with cellularity
 - ii. May be seen early in the course, but is more common in the "spent" phase
9. Miscellaneous
 - a. Uric acid in serum and urine increased due to large cell turnover
 - b. B12 level elevated > 900 ng/ml in 1/3 of cases
 - c. B12 binding capacity elevated > 2200 in 75% of cases
 - i. Large increase in transcobalamin I and III; small increase in transcobalamin II
 - ii. B12 and B12 binding capacity values may be dissociated
 - d. S_{O_2} usually normal, although this is not guaranteed
 - e. Histamine levels increased due to large number of granulocytes, especially basophils

F. Diagnosis

1. Criteria of Polycythemia Vera Study Group (PVSG)
 - a. Group "A" criteria
 - i. Increased red cell mass
 - a). > 36 ml/kg for males
 - b). > 32 ml/kg for females
 - ii. Hemoglobin O_2 saturation > 92%
 - iii. Splenomegaly
 - b. Group "B" criteria
 - i. Platelets > 400,000
 - ii. WBC > 12,000
 - iii. LAP score > 100
 - iv. B12 > 900 or unbound B12 binding capacity > 2200
 - c. Diagnosis made with:
 - i. All "A" criteria
 - ii. Increased red cell mass, splenomegaly, and two "B" criteria

2. Applying this system will miss cases, but there are only rare false positives, usually heavy drinkers
3. Serum erythropoietin level is useful in diagnosis
 - a. Low level in the presence of Hgb > 18.5, or lower Hgb together with polycythemia vera-related features (leukocytosis, thrombocytosis, microcytosis, splenomegaly, pruritis after bathing, unusual thrombosis, erythromelalgia) is diagnostic.
 - b. An elevated EPO level makes PV unlikely
 - c. Normal EPO level
 - i. If PV-related features present, do bone marrow, cytogenetics, assay for growth of endogenous erythroid colony formation (if available)
 - ii. If PV-related features not present, consider causes of secondary erythrocytosis.

G. Therapy

1. For erythrocytosis, to reduce the dangers of hyperviscosity and high blood volume
 - a. Phlebotomy
 - i. Can remove up to 500 ml/day, though usually phlebotomize weekly
 - ii. Achieve normal hematocrit, then stop and observe
 - iii. Complications
 - a). Iron deficiency
 - 1). Weakness
 - 2). Glossitis, cheilosis
 - 3). Relative increase in viscosity of microcytes
 - b). Reactive thrombocytosis
 - c). PVSG reported increase in thrombotic events and death with phlebotomy. Thrombosis did not correlate with hematocrit or platelet count. Spivak, in a critique of this study, pointed out that plasma volume is increased along with red cell mass in P vera. As a consequence, phlebotomy to a "normal" hematocrit of 45% to 50% in fact represents under treatment, and may explain the results obtained by PVSG.
 - iv. May need to treat with iron at the same time
 - b. Cytotoxic therapy (See below)
2. For thrombocytosis and refractory erythrocytosis
 - a. ³²P – was popular years ago, but increased incidence of acute leukemia
 - b. Alkylating agents - chlorambucil, busulfan, cytoxan, melphalan

- i. Maintenance therapy generally necessary, although maybe less so with busulfan
- ii. Oncogenesis is an issue
 - a). 15% incidence of acute leukemia in chlorambucil treated patients (PVSG), which was a 13-fold increase in risk
 - b). PVSG also reported an increase in skin and GI malignancies in patients receiving chlorambucil. GISP study also found a 3-fold increase in cancer-related deaths in those treated with radiophosphorus or alkylating agents.
 - c). European Cooperative Study Group did not show such bad statistics for busulfan
- c. Agent of choice currently is hydroxyurea (HU)
 - i. S-phase specific; inhibits ribonucleoside phosphate reductase
 - ii. Short acting drug requiring fairly intensive monitoring
 - iii. HU plus phlebotomy did not produce the high incidence of thrombosis seen with phlebotomy alone.
 - iv. A French study (Najean, 1997) indicated a 10% risk of acute leukemia at 13 years of follow up. Many subjects required dosage reduction because of skin and mucosal ulceration. The experimental drug pipobroman appeared to be superior. Tatarsky, et al reported only a 5.6% incidence of acute leukemia at a median treatment duration of 7.3 years.
 - v. Used to maintain remission after ^{32}P , HU shortened survival except in those with the most active disease (Najean, 1997).
- d. Anagrelide slows maturation of megakaryocytes and is effective at reducing platelet count in P vera in about 75% of cases.
- e. Aspirin use remained controversial for many years. While platelets in P vera are inherently hyperactive, they become "spent" due to spontaneous aggregation in the circulation. Patients thus have increased bleeding as well as increased thrombotic risk. Landolfi, et al studied 518 patients with P vera, but did little to lift the fog.
 - i. Treatment with aspirin 100 mg daily
 - ii. MI, stroke, and cardiovascular death combined were reduced by 60% each, although this was not statistically significant.
 - iii. MI, stroke, pulmonary embolism, venous thrombosis,

- and cardiovascular death combined were also reduced 60%, and this was statistically significant ($p=0.03$)
- iv. Bleeding risk was increased 60%, and was not statistically significant.
 - v. Overall mortality and cardiovascular mortality were not affected
3. Interferon alpha at $3-5 \times 10^6$ units 3 to 5 times weekly appears to be quite effective at decreasing platelet count and need for phlebotomy, especially if continued for prolonged periods (Silver).
4. PVSG 1986 recommendations
- a. Patients over age 70 should receive ^{32}P with supplementary phlebotomy, as they have a high risk of thrombosis.
 - i. Dose is $2.7 \text{ mC}/\text{M}^2$, with a maximum of 5 mC iv Q12 weeks.
 - ii. Phlebotomize for hematocrit $>45\%$
 - b. Patients below age 50 should be phlebotomized only, unless thrombotic risk factors are present, in which case use hydroxyurea
 - c. Between ages 50 and 70, try phlebotomy alone if thrombotic risk is low (no prior thrombosis), else add hydroxyurea
 - d. Hypermetabolic patients or those with splenic symptoms require myelosuppression
5. Spivak advocates phlebotomy for all patients to an Hct $<45\%$ for men or 42% for women. Cytotoxic agents should be employed only when phlebotomy has failed, and even then exposure to them should be limited. Inhibitors of platelet function and/or number are indicated if microvascular thrombosis is present, but normalization of red cell mass is essential to decrease thrombotic risk.
6. Imatinib, a kinase inhibitor used to treat CML, has been shown to produce marked inhibition of spontaneous erythroid proliferation in vitro of red cell precursors obtained from patients with polycythemia vera (Oehler).
7. Pruritis associated with polycythemia vera responds to selective serotonin reuptake inhibitor antidepressants (Tefferi 2002)

III. Secondary erythrocytosis

- A. Definition: Increased red cell mass due to stimulation of erythrocytosis
 - 1. Physiologically appropriate (as compensation for tissue hypoxia)
 - 2. Physiologically inappropriate
- B. Physiologically "appropriate" secondary erythrocytosis
 - 1. High altitude

a. Andean natives at 4500 m altitude have mean Hgb = 21 gm, Hct = 63%, red cell mass \approx 60 ml/kg, and $P_{50} = 30$ mmHg

b. Adaptations to altitude

i. Hyperventilation causes decreased $P_{A\text{CO}_2}$, thus increased $P_{A\text{O}_2}$

a). Alveolar air equation

$$P_{A\text{O}_2} = P_{I\text{O}_2} - P_{A\text{CO}_2} \times (F_{I\text{O}_2} + (1-F_{I\text{O}_2})/R)$$

b). The benefit of this is limited by increased work of breathing

ii. Hyperinflation of lungs causes increased alveocapillary diffusing area, and decreased A-a gradient (in contrast to COPD)

iii. P_{50} is shifted to right in individuals living at altitude

a). Enhances transfer of O_2 from hemoglobin to tissues, but hinders oxygenation of hemoglobin in the lung

b). Net shift is result of increased red cell 2,3-DPG

c). May be maladaptive - llamas have left-shifted curve

iv. Erythrocytosis

a). Increased oxygen carrying capacity, proportional to total hemoglobin

b). Increased blood volume might lead to opening of new capillaries and shorter diffusion path for O_2 to tissues

c. Capacity for work is greatest when these people are phlebotomized to normal hemoglobin levels

2. Chronic obstructive pulmonary disease

a. Decreased oxygen saturation is common

b. Increase in hemoglobin nowhere near the levels seen in altitude exposure

i. Plasma volume is increased (red cell mass correlates better with saturation than does hematocrit)

ii. Anemia of chronic disease? - usually, Fe/TIBC are normal

iii. Mildly decreased RBC survival

iv. Other mechanisms?

3. Postural hypoxemia

a. P_{O_2} may drop into 50's with supine posture

b. Mechanism is V-Q mismatch

4. Right-to-left cardiac shunt

a. May cause red cell mass > 100 ml/kg, hematocrit $> 75\%$

- b. Debatable whether or not this is beneficial to the patient
 - i. O₂ carrying capacity increases with increasing hemoglobin level
 - ii. Higher viscosity at high hematocrits eventually leads to decreased flow and diminishes O₂ transport
 - iii. Thrombosis and bleeding may occur, and respond to phlebotomy
 - c. Perloff, et al reviewed their experience with 124 patients, and issued recommendations
 - i. Phlebotomize only for symptoms of hyperviscosity, which are unlikely to occur if the HCT is < 65
 - ii. Patients may develop symptoms of iron deficiency, in which case they should have iron replacement
 - iii. Anticoagulants are not recommended
 - d. Right-to-left shunting may occur in the liver in cirrhosis
5. Hypoventilation
- a. Occurs with (Pickwick syndrome) or without obesity
 - b. May be due to chest wall deformity or to nerve or muscle failure
 - c. May be due to obstruction of the upper airway with sleep
 - d. Net result is hypercarbia, somnolence, and hypoxia
6. High oxygen affinity hemoglobins
- a. More than 20 types described
 - b. P₅₀ dependent on pH, temperature, 2,3-DPG, interaction of hemoglobin subunits
 - c. Hemoglobin dissociation curve described by empirical Hill equation
 - i. High affinity hemoglobins show decreased P₅₀
 - ii. Departure from sigmoid shape (decreases n in Hill equation)
 - d. Altered heme-heme interaction
 - i. Two states of the molecule - oxy or R state, and deoxy or T state
 - ii. Transition involves sliding of globin chains along $\alpha_1 - \beta_2$ interface, as well as shift of heme group.
 - iii. Structural mutations causing high affinity
 - a). $\alpha_1 - \beta_2$ interface: Hbs Ranier, Bethesda, Osler, Creteil
 - b). $\beta - \beta$ interface: Hbs Andrew-Minneapolis, Hiroshima
 - c). Heme pocket - most are unstable
 - 1). Hb Heathrow has increased affinity
 - 2). Hb Bucuresti has decreased affinity
 - d). 2,3-DPG binding site

- 1). 2,3-DPG reacts with deoxyhemoglobin to stabilize it
 - 2). Alterations in structure lead to decreased 2,3-DPG affinity and increased O₂ affinity
 - 3). Hbs Little Rock, Rahere, Syracuse, Helsinki
 - e. Inheritance of high affinity hemoglobin is autosomal dominant
 - f. About 50% have abnormal starch gel electrophoresis at pH 8.6, and many are abnormal at pH 6.2
 - g. It has been demonstrated that the high hematocrit found is necessary for adequate O₂ transport, and that phlebotomy to normal levels is counter-productive.
 - h. Course is generally benign, although there is fetal wastage due to inability of fetus to obtain oxygen at low P_{O₂}.
7. Congenital decreased red cell 2,3-DPG as cause of high O₂ affinity
8. Smoker's polycythemia (Smith and Landaw)
- a. Analyzed 22 smokers without polycythemia vera, but with high hematocrit
 - b. Most were symptomatic, complaining of fatigue, headache, syncope
 - c. Red cell mass increased to mean of 37 ml/kg vs. 27 ml/kg in controls
 - d. Red cell mass normal in 4/18 patients
 - e. Plasma volume elevated in 2/18, normal in 2/18, and decreased in 14/18
 - f. Four patients had low plasma volume with normal red cell mass as cause of elevated hematocrit
 - g. Carboxyhemoglobin was 16.6% in cigar smokers, 9.3% in cigarette smokers, and 0.6% in controls
 - h. Carboxyhemoglobin not only ties up O₂ binding sites irreversibly, it increases the O₂ affinity of the remaining hemoglobin
 - i. P₅₀ was 21.6 in patients and 26.7 in controls
 - ii. The amount of shift correlated with carboxyhemoglobin value
 - i. In 5 patients who quit or reduced smoking, the red cell mass, plasma volume, and hematocrit returned to normal
9. Cobalt was once given to stimulate erythropoiesis. It does so by inhibiting oxidative metabolism causing tissue hypoxia.
- C. Physiologically inappropriate secondary polycythemia
1. Tumors
 - a. Debate as to whether tumors secrete erythropoietin, an erythropoietin stimulating substance, or cause renal ischemia via compression of the organ.
 - b. Hypernephroma

- i. EPO production has been localized to the tumor
 - ii. Usually associated with severe anemia
 - iii. This tumor may have other endocrine activity, such as PTH
 - c. CNS tumors
 - i. Cerebellar hemangioblastomas have been shown to contain erythropoietin
 - ii. Three reported cases of meningioma with erythrocytosis. Tumor production of EPO demonstrated in 1/1 case studied.
 - d. Hepatoma
 - i. Erythrocytosis unusual in hepatomas in USA
 - ii. Probable ectopic production of erythropoietin
 - e. Uterine fibroids
 - i. Almost always, the tumor is very large
 - ii. Possible renal ischemia
 - iii. Possible ectopic erythropoietin production. Renin has been demonstrated in these tumors.
 - f. Adrenal tumors
 - i. Cortical adenoma or hyperplasia (Cushing's disease) - probably due to mild myelostimulatory effect of glucocorticoids
 - ii. Pheochromocytoma - due to production of erythropoietin
 - g. Ovarian carcinoma - due to androgen secretion
- 2. Renal causes
 - a. Renovascular disease
 - i. No striking increase in red cell mass (renal parenchymal damage?)
 - ii. The hematocrit in renovascular hypertension patients is significantly higher than in those with hypertension of other cause
 - b. Cysts of the kidney cause erythropoietin secretion by pressure on the renal parenchyma.
 - c. Hydronephrosis, via the same mechanism
 - d. Bartter's syndrome (1 case)
 - i. Syndrome is hypokalemic alkalosis, normotension, resistance to effects of renin-angiotensin, very high plasma renin, and hyperplasia of the juxtaglomerular apparatus
 - ii. Pathophysiology?
 - e. Kidney transplantation
 - i. High red cell mass sometimes seen as a sign of impending transplant

rejection

- ii. Seen in 4 to 17% of allograft recipients with good renal function, possibly as a result of excessive EPO production by the native kidneys
- iii. Theophylline lowers the EPO level and red cell mass in transplant recipients (and less so in normals) by antagonizing adenosine activity.
- iv. Enalapril is effective at lowering the hematocrit into the normal range (and can cause anemia when given to non-polycythemic transplant recipients). Mechanism of action unknown.

3. Recessive familial polycythemia - 2 families in which overproduction of erythropoietin is found

- 4. Autosomal dominant erythrocytosis due to increased sensitivity to erythropoietin
 - a. One family described, in which the erythropoietin receptor was mutated and had lost an inhibitory region.
 - b. Erythroid colonies in culture respond to minute concentrations of EPO
 - c. The index case has won world championships and Olympic gold medals in cross-country skiing (!)

D. Treatment

- 1. May or may not be necessary and appropriate, depending on the cause of the polycythemia.
- 2. Phlebotomy is standard treatment
- 3. Cytotoxic agents are to be avoided
- 4. Angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB) have been shown to be effective in decreasing the hematocrit in erythrocytosis due to lung disease, residence at high altitude, renal transplantation, and polycystic kidney disease (Fakhouri).

IV. Relative (spurious) polycythemia, Gaisböck's syndrome

A. Defined by presence of elevated venous hematocrit in absence of elevated red cell mass

B. In practice, refers to a specific set of patients with well-described findings

C. Etiology not known

- 1. Red cell mass is normal to high-normal
- 2. Plasma volume is low-normal to frankly low

D. Clinical and laboratory aspects

- 1. Classic patient is middle-aged, stressed, overweight, white male smoker with hypertension
- 2. Nonspecific complaints are common - fatigue, dizziness
- 3. High incidence of hyperlipidemia and cardiovascular disease

4. Hypertension more common in the low plasma volume-types

E. Treatment

1. Stop smoking

2. Control cardiac risk factors such as hypertension

F. Virtually all of these patients smoke, and this is probably the most important etiologic factor.

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A classic!
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Table - Differential Diagnosis of Polycythemia

	<u>P vera</u>	<u>Secondary</u>	<u>Spurious</u>
Red cell mass	↑	↑	nl
Splenomegaly	+	-	-
O ₂ saturation	nl	nl or ↓	nl
Thrombocytosis	+	-	-
Histamine	↑	-	-
B12, B12BC	↑	nl	nl
Leukocyte alkaline phosphatase	↑	nl	nl
WBC	↑	nl	nl
Basophilia	+	-	-
Erythropoietin	↓	nl or ↑	nl
Serum iron	↓	nl	nl
Marrow	Panmyelosis	Erythroid hyperplasia	nl