POLYCYTHEMIA VERA

Introduction
Polycythemia (erythrocytosis) is a general term referring to an increase in the number of circulating red blood cells per volume of blood, as reflected by an elevated hematocrit or hemoglobin level. Polycythemia vera (P. vera) is a neoplastic stem cell disorder characterized by autonomous overproduction of red blood cells and frequently, leukocytosis and thrombocytosis. The three major categories of erythrocytosis (polycythemia) are (1) primary polycythemia, or polycythemia vera (2) secondary polycythemia, (3) relative polycythemia and (4) inapparent polycythemia.

Secondary Polycythemia
Secondary polycythemia occurs when erythropoietin production is increased because of chronic tissue hypoxia. Causes of tissue hypoxia include life at high altitude, high-affinity hemoglobin, cardiopulmonary disease, obesity-hypoventilation syndrome, obstructive sleep apnea, and high serum levels of carboxyhemoglobin. Secondary polycythemia also occurs in some renal and hepatic disorders, in rare genetic disorders, and from treatment with androgens or erythropoietin.

Relative polycythemia
Patients with relative polycythemia (Gaisböck syndrome) are often obese, hypertensive men who may also be heavy smokers, are usually 45 to 55 years of age. They are typically a decade younger than the average age for P. vera patients. It has been estimated that 0.5% to 0.7% of the healthy male population in the United States have relative polycythemia. Diuretic use for treatment of hypertension may exacerbate the deficit in plasma volume, and smoking-induced high carboxyhemoglobin levels or hypoxemia may also play a role. Relative polycythemia is usually associated with a mild increase in hematocrit that almost always less than 60% and frequently less than 55%. The hematocrit returns to normal over time in approximately one third of patients.

Inapparent Polycythemia
Inapparent polycythemia is a true increase in red cells accompanied by a proportional increase in plasma volume. This is "inapparent" P. vera because the hematocrit and hemoglobin levels are within the normal range even though the red cell mass is increased. Chronic GI bleeding (so-called auto-phlebotomy) with a compensatory increase in plasma volume can mask P. vera. The red cell mass is normal in this setting. Duodenal bleeding is a frequent problem in P. vera and may cause the disease to be unrecognized.

Diagnosis
The National Polycythemia Study Group developed criteria in 1970's for the diagnosis of P. vera. The criteria are divided into major and minor, listed in Table 1 below.[2]

**Table 1 - Classic Criteria for Diagnosis of P. vera**

> ***Major criteria***
> Increased Red Cell Mass
> Splenomegaly
> Normal oxygen saturation
>
> ***Minor criteria***
> Increased platelet or neutrophil count
> Increased leukocyte alkaline phosphate activity
> Increased vitamin B12 binding protein

Strict adherence to the original cr[...] should no longer be considered a prerequisite to the diagnosis. A[...] [pro]posed by A. Tefferi at the

Mayo Clinic utilizes new laboratory tests to define the disease. [1,3] The algorithm is a paradigm shift from the classic criteria and not accepted by all. After confirmation of the hemoglobin and hematocrit, the algorithm begins with the evaluation of specific clinical findings. He utilizes serum erythropoietin (EPO), bone marrow examination and the endogenous erythroid colony (EEC) assay (growth of erythroid colonies without stimulation) instead of the classic major and minor criteria listed above. An increase in erythrocytes results in a compensatory suppression of the EPO level. Therefore, low EPO levels in conjunction with abnormally high hemoglobin is highly suggestive of P. vera. Among the causes of erythrocytosis, only P. vera has below-normal serum EPO levels. A positive EEC assay in the presence of below-normal serum EPO levels is specific for P. vera. However, the EEC assay is not widely available and requires a high level of expertise to perform. If the EPO level is increased, the cause for the erythrocytosis is secondary polycythemia (tissue hypoxia). If the EPO level is normal and the hemoglobin and hematocrit values are >18.5g/dl and >60% in males and >16.5 and >53% in females, the work-up proceeds to evaluate for P. vera. Noticeably absent in the algorithm is the red cell mass study.

Figure 1. Diagnostic approach to suspected erythrocytosis[1]
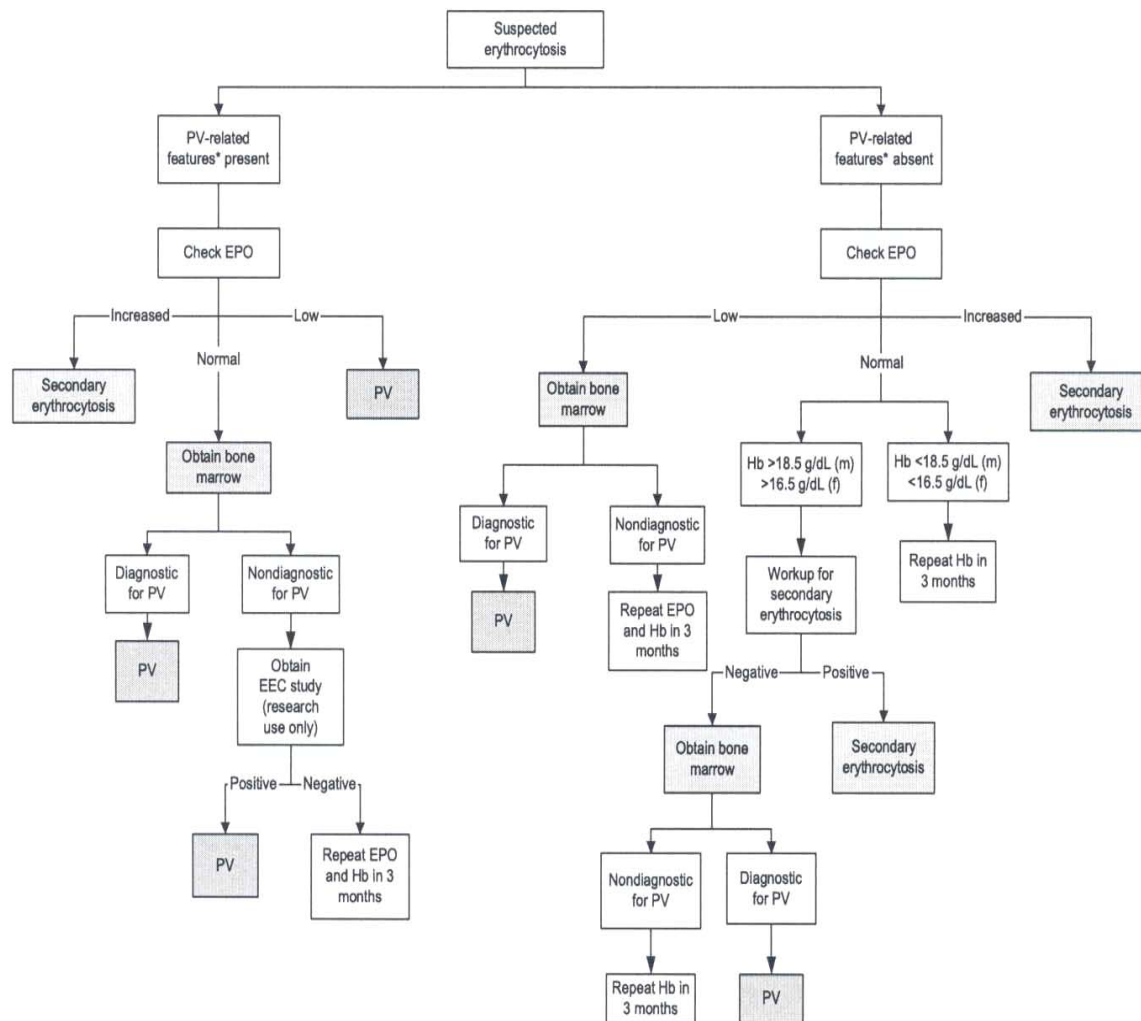
*P.vera related features include portal vein thrombosis, Budd-Chiari syndrome, splenomegaly, erythromelalgia, persistent leukocytosis, thrombocytosis, or microcytosis, post-bath pruritus and digital ischemia.

Clinical Features of P. vera

Clinical findings are of greatest importance in making the diagnosis of P. vera. The usual P. vera patient is over 60 years of age, with slightly more men than women developing the disease. They may exhibit a flushed or ruddy

appearance. While some patients with P. vera may experience no symptoms, clinical features that are commonly seen in P. vera are listed in Table 2 below.

Table 2 - Polycythemia vera (Clinical Features)

Hyperviscosity symptoms (dizziness, headaches, visual changes, paresthesias, fatigue)
Splenomegaly, night sweats
Post bath pruritus (itching)
Digital ischemia
Budd-Chiari syndrome
Erythromelalgia (pain, throbbing burning in one or more extremities)
Unusual thrombotic history
Retinal vein distention

Laboratory Features of P. vera
Polycythemia vera patients are often asymptomatic, presenting with an incidental elevated hemoglobin or hematocrit. Leukocytosis, thrombocytosis, occasional circulating immature white blood cells, or increased basophils suggest a myeloproliferative disorder such as polycythemia vera. Numerous tests may be utilized to reach a diagnosis and are listed in Table 3 below.

Table 3 - Polycythemia vera (Laboratory Values)

Elevated Hematocrit (>60% in men and > 53% in females)
Persistent leukocytosis
Persistent thrombocytosis
Red cell microcytosis due to iron deficiency (low MCV)
Low Erythropoietin level
Red cell mass study
Elevated vitamin B12 and LAP score
Bone marrow pan-hyperplasia with atypical megakaryocytes
Clonal cytogenic abnormalities
In vitro endogenous erythroid colonies (EEC)
Oxygen dissociation P_{50} of erythrocytes

Red Cell Mass (RCM) measurement
During the past several years, it has become evident that the RCM measurement may not be reliable or necessary to make the diagnosis of P. vera. RCM is not able to separate P. vera from secondary erythrocytosis. Also, patients with early P. vera or who have either concurrent iron deficiency may not fulfill the classic criterion of an increased RCM proposed by the National Polycythemia Study Group. The RCM is redundant when the hemoglobin is increased higher than 18.5 g/dl in men and 16.5 g/dl in women. This degree of increase is almost always associated with in increased RCM. At Rex Lab the normal range of the RCM study is adjusted for sex, height and weight. The adjusted normal range may result in labeling a small number of the normal population as having P. vera because of the "statistically narrow" limits. On the other hand, a wide normal range would miss cases of increased red cell mass. The red cell mass is expensive to maintain and run for the low volume of studies ordered by physicians (less than one a month) and may be discontinued in the future.

Treatment
The mainstay in therapy is phlebotomy. Removal of 500 cc. (one unit) of blood is performed on a daily or weekly schedule until target hematocrit levels are reached: <45% in men and <42% in women. Patients older than 60 and those with a history of thrombosis usually need some chemotherapy. Treatment with regular strength aspirin should be avoided. Although it has an antiplatelet effect , aspirin increases the risk of gastric bleeding. Low-dose aspirin (81mg/day) has a decreased risk of gastric bleeding and can be used to treat vasomotor symptoms. In contrast to hemochromatosis patients, the phlebotomized blood from P. vera patients cannot be used in the general donor pool since it is considered a neoplastic hematologic disorder.

Summary

The algorithm and discussion are provided as suggestions for an alternative approach to the evaluation of erythrocytosis. A diagnosis of P. vera should be based primarily on the clinical presentation and patient history. Laboratory findings alone cannot diagnose P. vera and must be correlated with patient information. Strict adherence to the classic criteria of the National Polycythemia Vera Study Group should not longer be considered a prerequisite to the diagnosis of P. vera. Once diagnosed, patients with P. vera can undergo treatment to minimize their risk for the serious, life-threatening complications that accompany P. vera.

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References:
1. Ayalew Tefferi, MD, "Diagnosing Polycythemia Vera: A Paradigm Shift" Mayo Clinic Proceedings, February 1999, Volume 74, pages 159 – 162.
2. Virginia C. Broudy, MD, WebMD Scientific American Medicine, Hematology Chapter V, The Polycythemias, p 1-10.
3. Polycythemia Vera, Mayo Reference Communique′, April 2003, Volume 28, Number 4, p. 1 – 4.

Questions about the diagnosis of polycythemia vera

1. Which <u>one </u>of the following statements about erythrocytosis in polycythemia vera is <u>true</u>?
    a. It is erythropoietin independent.
    b. It is erythropoietin dependent.
    c. It is reactive
    d. It is always detected by measurement of the red cell mass.
    e. It is always detected by measurement of plasma volume

2. Which <u>one</u> of the following is <u>correct</u> regarding relative polycythemia?
    a. An increased red cell mass (RCM)
    b. A decreased RCM
    c. An increased plasma volume
    d. A decreased plasma volume
    e. An increased RCM and decreased plasma volume

3. Which <u>one</u> of the following combinations refers to inapparent polycythemia?
    a. Normal red cells mass (RCM) and decreased plasma volume
    b. Normal RCM and increased plasma volume
    c. Increased RCM and decreased plasma volume
    d. Increased RCM and normal plasma volume
    e. An increased RCM and increased plasma volume

4. Which <u>one</u> of the following <u>best</u> describes the serum erythropoietin level in polycythemia vera?
    a. Always low
    b. Usually low but can be normal
    c. Usually normal but can be low
    d. Can be low, normal or increased
    e. Always normal

5. During the assessment of a patient with a hemoglobin value of 20 g/dl, which <u>one</u> of the following steps is <u>necessary</u>?
    a. Measure red blood cell mass
    b. Measure plasma volume
    c. Measure serum erythropoietin
    d. consider the possibility of relative polycythemia
    e. consider the possibility of inapparent polycythemia

Correct answers:
1. a, 2. d, 3. e, 4. b, 5. c