ERYTHROCYTOSIS

TERM DEFINITION

Erythrocytosis and polycythemia are terms that are used interchangeably to describe a patient with an elevated hemoglobin (Hb) and hematocrit (Hct).

CAUSES

RELATIVE ERYTHROCYTOSIS

Erythrocytosis that is associated with decreased plasma volume.

Causes include: Vomiting, diarrhea, diuretics, burns, and fever.

ABSOLUTE ERYTHROCYTOSIS

Associated with elevated red cell mass.

PRIMARY	SECONDARY	
Congenital: • Congenital mutations in erythropoietin receptor gene (EPOR) **Acquired:** • Polycythemia vera	**Congenital:** • Changes in hemoglobin oxygen affinity • Mutations in oxygen sensing / hypoxia-inducible factor (HIF) signaling pathway	**Acquired:** • "Appropriate" response to hypoxia: ◦ Pulmonary disease ◦ Heart disease ◦ Sleep apnea ◦ High altitude • Inappropriate response: ◦ Androgens ◦ Steroids ◦ EPO-producing tumors ◦ Renal disorders ◦ Post-renal transplantation

Epo, erythropoietin

CLINICAL PEARLS

A low oxygen saturation points to secondary erythrocytosis / polycythemia.

Pruritus points to polycythemia vera.

Elevated basophils points to polycythemia vera.

Clinical presentation varies according to the cause of the erythrocytosis.

General symptoms and signs:

Patients may be asymptomatic or may complain of symptoms of hyperviscosity, including:
- Fatigue
- Dizziness
- Blurred vision
- Parasthesias
- Headache

Physical findings include:
- Hypertension
- Plethora

CLINICAL PRESENTATION

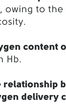
Why increased blood pressure?

Mean arterial pressure = cardiac output x **total peripheral resistance**

Total peripheral resistance correlates with **blood viscosity**

Blood viscosity correlates with **Hct**

DIAGNOSIS



GOALS OF TESTING

- Confirm diagnosis of erythrocytosis / polycythemia
- Rule out polycythemia vera
- Identify cause of secondary erythrocytosis / polycythemia

CONFIRM DIAGNOSIS

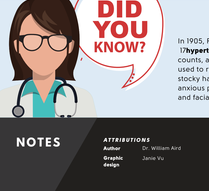
- **Strictly speaking, defined by >25% increase in red cell mass; however, red cell mass no longer measured:**
  - Must rely on Hb and Hct as surrogates.
- **Hct > 60% in men or > 56% in women always reflect increased RCM that is > 25% above normal predicted RCM:**
  - Elevated hematocrit (> 52% in men and > 48% in women) persisting longer than 2 months should prompt further investigation to determine cause of erythrocytosis.

DIAGNOSIS OF CAUSE

- **Complete blood count:**
  - Leukocytosis & thrombocytosis more common in PV
- **Renal and liver function**
- **Arterial oxygen saturation**
- **Serum erythropoietin level:**
  - Low in PV
- **Sleep study**
- **Jak2 mutation**
  - Almost 100% sensitive for diagnosing PV
- **Other**
  - P50 measurement
  - Abdominal ultrasound

PV, polycythemia vera

COMPARATIVE CONSIDERATIONS



The optimal Hb/Hct is remarkable conserved among mammalian species. There are some exceptions, including deep diving marine mammals such as the bottlenose dolphin and the killer whale who have a Hct around 60%. This may reflect an adaptation for increased oxygen stores via increased hemoglobin for deep, long-duration dives, at the expense of a more limited oxygen transport capacity from increased hematocrit (blood viscosity).

PROXIMATE MECHANISMS

Since erythrocytosis / polycythemia is operationally defined by an elevated Hb and Hct, the two possible mechanisms are **decreased plasma volume** or **increased red cell mass**.

Decreased plasma volume occurs in the setting of diarrhea, vomiting, acute pancreatitis and burns.

Increased red cell mass, in turn, is almost always mediated by elevated erythropoietin (the mechanism for testosterone-induced polycythemia is not so clear).

Oxygen delivery =
Cardiac output x Oxygen content of blood

Cardiac output is inversely proportional to Hct, owing to the effect of Hct on blood viscosity.

Oxygen content of blood correlates directly with Hb.

The relationship between Hb/Hct and oxygen delivery can be illustrated as follows:

OPTIMAL HEMOGLOBIN / HEMATOCRIT

There is an **evolutionary trade-off** when it comes to the Hb and Hct: increasing the Hb will increase the Hct (that is the price paid for packaging Hb inside cells).

So, while oxygen carrying capacity of the blood increases, so does blood viscosity. There comes a point where the negative influence of Hct on blood viscosity begins to outweigh the beneficial effect of increased Hb on oxygen content of blood.

Patients on the left side of this curve have anemia and Hb is limiting for oxygen delivery. Patients on the right have polycythemia, and the Hct is limiting. The apex of the curve defines the optimal Hb/Hct.

TREATMENT

POLYCYTHEMIA VERA

Current therapy is based on the risk of developing thrombotic complications:

- **Low risk** = < 60 years old and no prior thrombosis
- **High risk** = ≥ 60 years old and/or prior thrombosis

	Low risk	High risk
Target Hct	+	+
Therapeutic phlebotomy	+	+
Low dose aspirin	+	+
Cytoreductive therapy	— *	+
Correction of cardiovascular risk factors	+	+

*Low risk patients may be eligible for cytoreductive therapy if they have extensive disease-related symptoms, progressive / symptomatic splenomegaly, extreme / progressive thrombocytosis, and/or persistent leukocytosis.

SECONDARY POLYCYTHEMIA

Management of underlying cause may reduce or resolve erythrocytosis

HISTORY OF MEDICINE

In 1905, Felix Gaisbock, an Austrian physician, first described a group of "**hypertensive** male patients who had **high hematocrit levels**, normal leukocyte counts, and no splenomegaly. Over time, the term ***Gaisbock's syndrome*** was used to refer to patients with relative polycythemia who had an overweight, stocky habitus, a plethoric appearance with suffusion of the eyes, tense and anxious personalities, a cigarette smoking habit, vascular disease, headaches, and facial rubor.

Arch Intern Med. 1964;114(6):734-740

NOTES

ATTRIBUTIONS
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