

Polycythemia

Polycythemia (or *polycythaemia*) is a condition in which there is an increase in the proportion of blood volume that is occupied by red blood cells, which is measured as hematocrit level.

It can be due to an increase in the mass of red blood cells ('absolute polycythemia') or to a decrease in the volume of plasma ('relative polycythemia').

Absolute polycythemia

The overproduction of red blood cells may be due to a primary process in the bone marrow (a so-called myeloproliferative syndrome), or it may be a reaction to chronically low oxygen levels or, rarely, a malignancy.

Primary polycythemia (Polycythemia Vera)

Primary polycythemia, often called *polycythemia Vera* (PCV), polycythemia rubra Vera (PRV), or erythremia, occurs when excess red blood cells are produced as a result of an abnormality of the bone marrow. Often, excess white blood cells and platelets are also produced. Polycythemia Vera is classified as a myeloproliferative disease.

Symptoms include headaches and vertigo. Signs on physical examination include an abnormally enlarged spleen and/or liver. In some cases, affected individuals may have associated conditions including high blood pressure or the formation of blood clots.

Transformation to acute leukemia is rare. Phlebotomy is the mainstay of treatment. A hallmark of polycythemia is an elevated hematocrit, with Hct > 55% seen in 83% of cases. Mutations in *JAK2* are found in 95% of cases, though also present in other myeloproliferative disorders.

Secondary polycythemia

Secondary polycythemia is caused by either natural or artificial increases in the production of erythropoietin, hence an increased production of erythrocytes. In secondary polycythemia, there may be 6 to 8 million and occasionally 9 million erythrocytes per cubic millimeter (microliter) of blood. Secondary polycythemia resolves when the underlying cause is treated.

Secondary polycythemia in which the production of erythropoietin increases appropriately is called *physiologic polycythemia*. This physiologic (meaning normal) polycythemia is a normal adaptation to living at high altitudes (to combat altitude sickness). Many athletes train at high altitude to take advantage of this effect — a legal form of blood doping. Similarly, athletes with primary polycythemia may have a competitive advantage due to greater stamina.¹

Other causes of secondary polycythemia include smoking, renal or liver tumors, hemangioblastomas in the central nervous system, heart or lung diseases that result in hypoxia, and endocrine abnormalities including pheochromocytoma and adrenal adenoma with Cushing's syndrome. People, whose testosterone levels are high because of the use anabolic steroids, including athletes who abuse steroids and people whose doctors put them on doses that are too high, as well as people who take erythropoietin may develop secondary polycythemia.

Secondary polycythemia can be induced directly by phlebotomy to withdraw some blood, concentrate the erythrocytes, and return them to the body.

Chuvash polycythemia

Chuvash polycythemia refers to a familial form of erythrocytosis different from classical polycythemia Vera. This involved patients from Chuvashia and is associated with a C598T mutation in the von Hippel-Lindau gene (*VHL*). A cluster of patients with Chuvash

polycythemia have been found in other populations, such as on the Italian island of Ischia, located in the Bay of Naples.

Relative polycythemia

Relative polycythemia is an apparent rise of the erythrocyte level in the blood; however, the underlying cause is reduced blood plasma. Relative polycythemia is often caused by loss of body fluids, such as through burns, dehydration and stress.

There are six diseases included in the group of myeloproliferative disorders and this group includes:

- Chronic myelogenous leukemia (CML),
- Polycythemia rubra vera (PRV),
- Chronic idiopathic myelofibrosis,
- Essential thrombocythemia (ET),
- Chronic neutrophilic leukemia,
- Chronic eosinophilic leukemia.

This group is characterized by production of too many of certain types of blood cells made in the bone marrow. There is a great deal of overlap in the features of various myeloproliferative disorders and may transform from one from to another. Polycythemia rubra Vera is characterized by the production of mature red cells leading to high levels of hemoglobin.

This would lead to increase blood volume and viscosity, which can lead to various complications. Complications may vary from person to person and may include development of blood clots or bleeding.

Apart from increase in the red cells Polycythemia rubra Vera is associated with increase in platelet count and white cell counts. PRV is a relatively rare disorder, and is estimated to occur, in approximately 1 in 100,000 individuals. Polycythemia Vera is primarily affects middle-aged or elderly people. The highest incidence

of Polycythemia rubra Vera occurs in patients who are in the 51-75 age groups.

Diagnoses

Based on various symptoms and signs a diagnosis of polycythemia rubra Vera is made. There are diagnostic criteria set by Polycythemia Vera Study Group to make a diagnosis of this disease. This includes some findings in the physical examination and some findings from laboratory tests. Some conditions associated with decrease in the oxygenation of blood may be associated with increase in the red blood cells, and this is the most important challenge when making the diagnosis of polycythemia rubra Vera.

Measurement of red cell volume, level of increase in the platelet count and white cell count, level of erythropoietin and presence of enlargement of spleen, all may help to make a differential diagnosis in this situation. These physical and laboratory findings are critical in the diagnosis of polycythemia rubra Vera. Increased leukocyte alkaline phosphate activity, or increased vitamin B12 levels are often helpful in making the diagnosis.

Polycythemia rubra Vera is a slowly progressive disease which may progress over a period of one to three years before it is brought to medical attention. Many times polycythemia rubra Vera is diagnosed by routine blood counts done during a routine physical examination. Polycythemia rubra Vera is associated with increase in the red blood cells. Increase in red blood cells may be associated with increase in platelets and white cells. This may be associated with increased risk of blood clots and bleeding. Blood clot results from increased blood volume and associated increase in viscosity.

There are several symptoms that may be associated with symptoms like plethora (red coloration), visual disturbances, headache, dizziness, inability to concentrate and numbness and tingling.

Patients may develop high blood pressure because of increased blood volume. Blood clots may occur in one third to one half of all untreated patients.

Phlebotomy is the term used to describe the removal of blood. Phlebotomy is a good and speedy way of reducing the increased red blood cells down to normal levels. Phlebotomy is the most common therapeutic strategy in polycythemia rubra Vera. Physicians have been using phlebotomy for this disease for a long time. Stroke and many other forms of blood clots may occur in polycythemia rubra Vera. Phlebotomy reduces the blood volume and viscosity there by decreasing the risk of complications like stroke. The quantity of blood removed at one phlebotomy may be around 400-450cc of which approximately 60 percent are red blood cells. The rate at which polycythemia rubra Vera patients may need phlebotomy may vary depending up on the rate of production of red blood cells. Once the blood volume is replete and the viscosity of the blood is normal, the red blood cells can fulfill their function of oxygen delivery to the tissues with better efficiency.

Some patients may also need treatment with drugs to reduce the red blood cell count, platelet count and white cell count. The medications that are commonly used include hydroxyurea, anagrelide (agrylin), and interferon. Hydroxyurea is a bone marrow suppressant and would suppress production of red cells, white cells and platelets; however the effect on platelet suppression is more pronounce than on red cells and many patients would need a combination of phlebotomy and hydroxyurea. Anagrelide is more specific in decreasing the platelet counts.

Men seem to get it more often than women, it almost never hits under the age of 20, rarely under 40 and the average age it hits is at 60.

The recently released Pennsylvania study points to chemical exposure as a causation factor. The author, Dr Hoffman said, “This

study may prove that diagnosis of this cancer based solely on clinical criteria may be inaccurate. The frequency of this form of bone marrow cancer could be specifically related to the environment.” The study also pointed to a connection of environmental pollutants having a role in causing bone marrow cancers.

A study of Jak2 found that treatment of the Jak2 with the antioxidant N-acetylcysteine decreased cell growth or expression of cyclin D2 (prostaglandin D2 does several things including involvement in cell growth) and increased expression of the cell cycle inhibitor called p27. JAK2 V617F is a mutation and is the most common genetic defect observed in blood malignancies. It can be found in essential thrombocythemia (ET), polycythemia Vera (PV) and primitive myelofibrosis (PMF).

Although scientist are still arguing whether it is the initial cause of these diseases or not in these 3 myeloproliferative disorders (MPD). They do agree that the malignancies are considered to arise from a defect in a hematopoietic stem cell (HSC).

Studies show that oxidative stress is associated with gene mutation. Thus, glutathione is more than just an antioxidant. Of the 27 main functions of glutathione, it protects cells from mutation and helps the body destroy mutant cells and dispose of the bodies, so to speak.

This mutagenic effect was largely caused by oxidative stress since blocking the production of hydryl radicals significantly reduced the mutation rate as well as delayed the cell death. Glutathione works to eliminate free radical insurgents in our body. At the same time, they undo the damage the free radicals do. Then they dispose of the evidence of the work they have done. Jack Bower can not hold a candle to these internal counter terrorist units in each and every cell of our body. They need the help that can only come from your dietary intake. Science knows that glutathione detoxifies the body. It rids it of the many toxins we are exposed to. So it could possibly prevent the disease when we get older.

Symptoms

In its earliest form before there are any symptoms, a person may have an enlarged spleen or just have a high hematocrit. These progresses over years to a symptomatic form, in which the spleen is enlarged and all blood elements are elevated. During this phase, people are more susceptible to clots in their blood vessels. This may cause heart attacks or strokes. These people may also have an increased likelihood of bleeding with surgery or injury. They may develop other nonspecific symptoms such as generalized itching, increased sweating, weight loss, intolerance to heat and, sometimes, disturbance of their vision. They may have an enlarged liver and spleen and often have an elevated blood pressure.

Diagnosis

The specific cause is not known. There is a clone of abnormal cells that is not regulated like normal bone marrow cells. Most commonly, people are diagnosed in their 50's and 60's. In some cases, a red cell volume and total blood volume test may be ordered to prove the diagnosis. Other tests may be necessary to tell the difference between this disease and others that cause elevated counts.

A bone marrow biopsy may be helpful but is not, in itself, diagnostic of this condition.

Treatment of Polycythemia Vera

Polycythemia Vera (PV) is one of three chronic myeloproliferative disorders, along with essential thrombocythemia and myelofibrosis with myeloid metaplasia. The incidence of PV is 2.3 per 100,000 patients, and the median age at diagnosis is 60 years.

Polycythemia describes an increase in red blood cell mass. The increase in red blood cell mass may be caused by an actual increase in red blood cell mass (true polycythemia) or a spurious laboratory value (apparent polycythemia). True polycythemia is classified as either primary or secondary. Primary polycythemia is caused by a myeloproliferation and is not mediated by excess erythropoietin. In contrast, secondary polycythemia can be caused by an external source, such as "smoker's polycythemia," or an internal disorder, such as renal cancer. Erythropoietin levels in secondary polycythemias vary depending on the etiology.

PV can have life-threatening complications, including stroke and evolution into either myelofibrosis with myeloid metaplasia or acute

leukemia. Treatment is directed according to patient risk stratification. Frequent phlebotomy and chemotherapy are the cornerstones of treatment. Hematocrit levels should be maintained below 45 percent in men and 42 percent in women. Chemotherapy using hydroxyurea, busulfan, or pipobroman is indicated for high-risk patients. (Pipobroman is not available in the United States.) Interferon-alfa is another chemotherapeutic option for reducing red blood cell burden and treating PV-associated pruritus.

Non-life threatening sequelae include microvascular complications and aquagenic pruritus. Microvascular complications may appear clinically as headache, light-headedness, transient neurologic abnormality, transient ocular disturbance, tinnitus, atypical chest pain, paresthesias, and erythromelalgia (a rare but painful burning sensation of the hands or feet). Low-dose aspirin (81 mg or less per day) can be used to treat these disorders. Aquagenic pruritus is a generalized body itching often brought on by a hot bath. Treatment options include either selective serotonin reuptake inhibitors or interferon-alfa.

People with PRV are at an increased risk of having blood clots. This can lead to a heart attack, a stroke, or a clot in some of the larger veins in the body. Obviously, it is important to try to prevent this; the best way is to bring down the blood count. This may be done in several ways.

The most utilized and safest way is by bleeding the patient (phlebotomy). A pint of blood is taken once or twice a week until the hematocrit is below a chosen level (for example, 45%) and then at whatever interval it takes to keep it there. This will not lower the white blood cell count or the platelet count. Sometimes it is hard to keep the red count down or the platelets may be quite elevated and phlebotomy is not enough. If that happens, either medications or injected radioactive material (radioisotopes) are used to keep the counts down.

Phlebotomy is not dangerous. Radioisotopes or chemotherapy (Hydroxyurea or Myleran) will slightly increase the risk of leukemia in people with polycythemia. However, not keeping the blood volume down is sometimes even more dangerous because of the potential for clots to occur. Many large studies have been done, showing that the safest treatment is bloodletting (phlebotomy). However, if that is not controlling the disease, then it is better to give medicine or radioactive phosphorus even though there is a slight increase in the risk of developing leukemia.

Most commonly used is a drug called Hydroxyurea, which is least likely to cause leukemia. Other effective drugs exist. If the patients are managed in this way, they may live comfortably for many years. If patients are protected from having a blood clot, after many years they may go through a phase where their blood counts stay down, or they even become anemic. Sometimes they have to be given iron, but other times their bone marrow will be ineffective and scar tissue (fibrosis) develops. This is called myeloid metaplasia. During this time, the spleen may enlarge and become very uncomfortable. This stage is variable but usually lasts about three years or longer. Some of these people go on to develop leukemia.

The outlook for cure is not good at this stage; however, with proper management, the patient may live ten or more years of enjoyable life. There are several other possible problems. Individuals may have higher uric acids and develop gout. Therefore, medicine needs to be given if this is a problem.

Sometimes, itching can be a real problem. A number of different drugs can be tried in controlling this; many times, however, they do not work very well. Probably the most serious thing is that people may hemorrhage with surgery or from an accident. It is not always possible to tell who will bleed excessively, so the blood count should be well controlled and surgery only done when needed. Five percent or less people with this disease develop Leukemia.

It is important to remember that patients can live normal lives for many years while under treatment. Treatment is very important to try and prevent strokes and other vascular problems.