



Summer 2010

# Polycythemia Vera

## Information for Healthcare Providers Serving Carbon, Luzerne and Schuylkill Counties

### *About ATSDR*

ATSDR serves the public by using the best science, taking responsive public health actions, and providing trusted health information to prevent harmful exposures and diseases related to toxic substances.

ATSDR is a sister agency to the Centers for Disease Control and Prevention (CDC) and has partnered with PADOH since 1989.

### *Summary*

Polycythemia vera (PV) is a rare, chronic myeloproliferative neoplasm (MPN) in which uncontrolled production of erythrocytes leads to hyperviscosity of the blood, resulting in signs and symptoms related to poor circulation and thrombosis. Most people develop PV later in life; the median age at diagnosis is 60 years old. The etiology of PV is unknown.

In 2008, the Pennsylvania Department of Health (PADOH) and the Agency for Toxic Substances and Disease Registry (ATSDR) identified a PV cluster in parts of Schuylkill, Carbon and Luzerne counties in northeast Pennsylvania. PADOH and ATSDR are investigating the cause of this cluster, which is currently unknown.

PV patients can be asymptomatic. As the disease progresses, patients might present with mild or vague symptoms, such as fatigue, dyspnea and headache. Eventually, patients might develop more serious complications, such as stroke and myocardial infarction.

Diagnosis is based on blood tests and sometimes bone marrow biopsy. At this time, there is no cure for PV, but treatment can control symptoms and minimize complications.

This fact sheet provides information about PV epidemiology, pathophysiology, clinical assessment, diagnosis and treatment.

### *Epidemiology*

#### *National Incidence and Prevalence*

Reported values for national incidence of PV vary from about 1 in 100,000 to as high as 2.3 in 100,000.

National prevalence of PV is not well understood because no nationwide studies have been conducted. Based on a study of PV patients in Connecticut that reported a total prevalence of 22 per 100,000 in that state, researchers have estimated that the total number of patients living with PV in the United States in 2003 was 65,243.

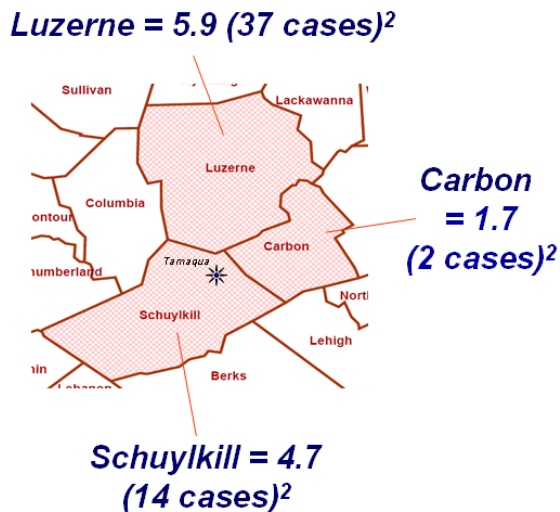
#### *Regional Incidence*

State cancer data from 2001 to 2002 show that the incidence of PV in Pennsylvania is 1.6 in 100,000. These same data identified three Pennsylvania counties with higher PV incidence:

- Carbon County, 1.7 per 100,000
- Luzerne County, 5.9 per 100,000
- Schuylkill County, 4.7 per 100,000

In a subsequent survey (December 2006 to July 2007), ATSDR found that three parts of the tri-county area had more confirmed cases of PV than expected: one area near Pottsville, another area near Tamaqua, and a third area in eastern Carbon County.

**Polycythemia Vera Rates (2001–2002) for Tri-County Area (Adjusted for Age)**



<sup>1</sup>U.S. Cancer Statistics Working Group. United States Cancer Statistics: 1999–2004 Incidence and Mortality Web-based Report

<sup>2</sup>Pennsylvania Cancer Registry, Final 2001-2005 Report, Feb.2008

**Risk Factors**

The table below summarizes risk factors for PV.

Risk Factors	
Age	Median age at diagnosis is 60 years, although anyone at any age can develop PV.
Gender	PV is slightly more common in men than in women (1.2:1).
History of thrombosis	History of thrombosis may increase risk of developing PV if other risk factors are also present.
Thrombocyte count	High thrombocyte count may increase risk of developing PV if other risk factors are also present.
Cardiovascular health	History of cardiovascular problems may increase risk of developing PV if other risk factors are also present.
Family history	PV is not considered hereditary, but there have been reported cases of family clustering.
Environment	No link has been established between environmental factors and the risk of developing PV.

**Environmental Risk Factors**

A few studies published more than 20 years ago reported that PV might be caused by coming in contact with certain chemicals (benzene, embalming fluid, petroleum products) or radiation. But these studies were limited by small sample size, and other studies have not confirmed these findings.

## Pathophysiology

PV is one of the myeloproliferative neoplasms (MPNs), a group of blood diseases characterized by disruptions in the regulation of hematopoiesis. Major MPNs include PV, essential thrombocytopenia and primary myelofibrosis.

Before 2005, the pathophysiology of PV was not well understood. Significant progress has been made since the discovery of a mutation in the gene for janus kinase 2 (JAK2), a tyrosine kinase that plays a regulatory role in hematopoiesis.

### ***JAK2 Mutation***

JAK2 is an inhibitory regulatory domain involved in Type I cytokine receptor signaling, which includes the ligands erythropoietin (EPO), thrombopoietin (TPO) and granulocyte macrophage colony stimulating factor (GM-CSF). An acquired mutation in the gene for JAK2 results in a nonfunctional inhibitory domain, resulting in overproduction of all cell lines, including thrombocytes, leukocytes and, in particular, erythrocytes. It can also lead to extramedullary erythropoiesis, increased cell turnover and eventually a spent phase, as well as sequelae related to chronic erythrocytosis.

More than 90 percent of PV patients have the JAK2 mutation. Those who do not are believed to have less common mutations that have a similar effect on the JAK2 domain. Why some people acquire the JAK2 gene mutation is unknown.

### ***Increased Myeloid Hematopoiesis***

In PV, increased myeloid hematopoiesis increases packed cell volume leading to hyperviscosity. Hyperviscosity hinders normal blood flow, potentially resulting in:

- Signs and symptoms related to poor circulation (see Clinical Assessment).
- Thrombosis and related complications (transient ischemic attacks, stroke, myocardial infarction, Budd-Chiari syndrome).

While PV is associated with a risk of thrombosis, it is also associated with a risk of hemorrhage. Vascular engorgement can lead to bleeding even in the absence of significant insult. In addition, hyperviscosity can slow the movement of platelets to injured blood vessels and hinder coagulation, which can lead to hemorrhage during injury or surgery.

### ***Extramedullary Erythropoiesis***

As hyperviscosity impedes circulation, oxygenation of tissues may become insufficient, triggering extramedullary erythropoiesis. This occurs most often in the spleen and liver, sometimes causing splenomegaly and hepatomegaly. Although less common, extramedullary hematopoiesis can also occur in the nervous system. This can lead to compression of the spinal cord, nerve root, cranial nerve, cortical brain tissue and meningeal layer.

### ***Pathophysiology of MPNs***

*Myeloproliferative neoplasms involve dysregulation at the multipotent hematopoietic stem cell (CD34), with one or more of the following shared features:*

- *Overproduction of one or several blood elements with dominance of a transformed clone.*
- *Hypercellular marrow or marrow fibrosis.*
- *Cytogenetic abnormalities.*
- *Thrombotic and/or hemorrhagic diatheses.*
- *Extramedullary hematopoiesis (liver/spleen).*
- *Transformation to acute leukemia.*
- *Overlapping clinical features.*

**In most cases, PV begins with the JAK2 V617F mutation or one of several other rarer JAK2 mutations.**

### ***Thrombosis in PV***

*Although previously most experts believed that hyperviscosity was the main contributing factor to thrombosis, some newer studies show a stronger connection between thrombosis and the leukocytosis that occurs with PV.*

### ***Increased Cell Turnover***

The persistent red cell hypervolemia caused by hematopoietic hyperfunction can also result in an increased rate of cell turnover. As the spleen removes larger and larger numbers of erythrocytes, the increased workload can lead to splenomegaly.

Increased cell turnover can also lead to hyperuricemia, increasing the risk of gout and urate kidney stones.

### ***Spent Phase***

Eventually, in some patients, persistent myeloid hyperfunction and hyperplasia can result in bone marrow failure, leading to myelofibrosis and anemia.

### ***Sequelae***

PV might eventually evolve into a syndrome simulating another MPN, idiopathic myelofibrosis, myelodysplastic syndrome or acute leukemia. In addition, some PV patients develop complications from chronic erythrocytosis; some of these, such as stomach ulcers or gout, may present as signs of PV (see Clinical Assessment).

## ***Diagnosis***

The World Health Organization (WHO) provides standard criteria for diagnosis of PV.

<b>WHO Criteria for Diagnosis of Polycythemia Vera*</b>	
<b>Level</b>	<b>Specifics</b>
Major criteria	<ol style="list-style-type: none"> <li>Evidence of increased RBC volume, including <math>\geq 1</math> of the following: <ul style="list-style-type: none"> <li>Hb &gt; 18.5 g/dL in men or &gt; 16.5 g/dL in women</li> <li>Hb or Hct &gt; 99th percentile of method-specific reference range for age, sex, and altitude of residence</li> <li>Hb &gt; 17 g/dL in men or 15 g/dL in women if associated with a documented and sustained increase of at least 2 g/dL from the patient's baseline value not accounted for by correction of iron deficiency</li> <li>Elevated RBC mass &gt; 25% above mean normal predicted value</li> </ul> </li> <li>Presence of JAK2 617VF or other functionally similar mutation (eg, JAK2 exon 12 mutation)</li> </ol>
Minor criteria	<ol style="list-style-type: none"> <li>Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) and prominent erythroid, granulocytic, and megakaryocytic proliferation</li> <li>Serum erythropoietin level below the reference range for normal</li> <li>Endogenous erythroid colony formation in vitro</li> </ol>

\*Diagnosis requires presence of the 2 major criteria and one minor criterion or the presence of the first major criterion plus 2 minor criteria.

<sup>†</sup>This research was originally published in *Blood*. Adapted from Tefferi A, Thiele J, Orazi A, et al: Proposals and rationale for revision of the World Health Organization diagnostic criteria for polycythemia vera, essential thrombocythemia, and primary myelofibrosis: Recommendations from an ad hoc international expert panel. *Blood* 110:1092, 2007 © the American Society of Hematology.

### ***Clinical Assessment***

PV patients often present as asymptomatic, especially early in the disease. As the disease progresses, PV patients might experience signs or symptoms related to increased blood cell mass and hyperviscosity. The most common symptoms are headache, fatigue, dyspnea, weakness, pruritis, vertigo and diaphoresis. Nevertheless, any of the following can be signs or symptoms of PV:

- **General:** Weakness, fatigue, diaphoresis. In more advanced cases, low-grade fever and unexplained weight loss could be caused by hypermetabolism associated with the spent phase of PV.
- **Skin:** Skin discoloration (reddish or purplish palms, ear lobes, cheeks), ischemic digits, pruritis (especially after bath or shower).
- **Cardiovascular:** Bleeding gums, bruising, epistaxis, hemorrhage, thrombotic events (e.g., arterial and venous thrombosis, cerebrovascular accident, deep venous thrombosis, myocardial infarction, peripheral arterial occlusion, pulmonary infarct).
- **Neurologic:** Headache, dizziness, paresthesias, tinnitus, erythromelalgia, vertigo, visual disturbances (e.g., diplopia, blind spots, flashes of light).
- **Abdominal:** Splenomegaly, Budd-Chiari syndrome, stomach ulcers, urate kidney stones, hepatomegaly.
- **Musculoskeletal:** Gout, bone pain (rare).

### ***Blood Tests***

A complete blood count (CBC) is essential to identify evidence of increased red blood cell mass (see WHO criteria above). The CBC must be repeated to verify persistence. Blood tests might also reveal elevated leukocyte and thrombocyte counts, microcytosis, or sideropenia (sometimes with normal hemoglobin levels).

A JAK2 test can identify the presence of the JAK2 V617F mutation (or one of several other rarer JAK2 mutations), which is present in more than 90 percent of patients with PV.

Other signs of PV include:

- Low serum EPO level.
- Presence of endogenous erythroid colony formation.

### ***Bone Marrow Biopsy***

Bone marrow histology can identify the following signs of PV:

- Hypercellularity for age, with panmyelosis.
- Increased number of megakaryocytes, including cluster formation.
- Giant megakaryocytes.
- Pleomorphism in megakaryocyte morphology.
- Mild reticulin fibrosis.
- Decreased bone marrow iron stores.

**At this time, it is unknown whether all people with the JAK2 mutation will eventually develop PV or another MPN.**

## ***Differential Diagnosis***

Once tests reveal polycythemia, the diagnostic question becomes whether the disease is polycythemia vera or secondary polycythemia. Differential diagnosis is accomplished via:

- Use of WHO diagnostic criteria (see above).
- Medical history (to identify other possible causes of polycythemia; see table).
- Serum EPO test (usually very low with polycythemia vera; often normal or high with secondary polycythemia).
- Bone marrow biopsy (see above).

<b>Causes of Secondary Polycythemia</b>	
<b>More Common</b>	<b>Less Common</b>
<ul style="list-style-type: none"> <li>• <b>Smoking</b></li> <li>• <b>Chronic arterial hypoxemia</b></li> <li>• <b>Tumors (tumor-associated erythrocytosis)</b></li> </ul>	<ul style="list-style-type: none"> <li>• <b>High O<sub>2</sub>-affinity hemoglobinopathies</b></li> <li>• <b>Erythropoietin receptor mutations</b></li> <li>• <b>Chuvash polycythemia (in which a mutation in the <i>VHL</i> gene affects the hypoxia-sensing pathway)</b></li> <li>• <b>Proline hydroxylase 2 and HIF-2 <math>\alpha</math> mutations</b></li> </ul>

## ***Management***

PV is not curable at this time, but can be managed through a combination of interventions aimed at slowing hematopoiesis, reducing the risk of thrombotic events, and controlling symptoms.

PV patients who have symptoms and do not receive medical intervention have a life expectancy of less than 5 years after diagnosis. PV patients who have symptoms and *do* receive medical intervention have a life expectancy of more than 20 years after diagnosis.

Factors to consider when choosing the appropriate management strategy(ies) include:

- Disease expression
- Rate of disease progression
- Patient's age
- Concurrent chronic diseases

### ***Phlebotomy***

For decades, periodic phlebotomy has been a primary tool to reduce hematocrit (and the risk of thrombotic events) in PV patients. Repeated phlebotomy sometimes results in iron deficiency, but otherwise presents little risk to the patient. In some cases, phlebotomy is the only intervention a patient will need.

### ***Hematocrit and Thrombosis***

*Some recent studies suggest that hematocrit might not be the primary determinant of risk of thrombosis, leading some experts to question the utility of phlebotomy in reducing thrombotic episodes. Nevertheless, phlebotomy is still a widely accepted form of PV treatment.*

Initially, 300 to 500 milliliters of blood are removed every other day. Less blood is removed from patients who are elderly or have cardiac or cerebrovascular disorders. Once hematocrit falls below the threshold level, it is checked monthly and phlebotomy is repeated as needed to maintain hematocrit below threshold. Common thresholds are:

- Hematocrit > 45 percent in men
- Hematocrit > 42 percent in women

### ***Myelosuppression***

Myelosuppressive agents can be used to reduce erythrocyte and thrombocyte counts. This intervention can complement phlebotomy (which can result in increased thrombocyte counts) or can be administered alone. Chronic or repeated use of some myelosuppressive agents has been associated with acute transformation of PV to leukemia.

Hydroxyurea, which inhibits the enzyme ribonucleoside diphosphate reductase, is the most commonly used myelosuppressive agent for PV. Hydroxyurea has not been shown to induce leukemic changes, but the possibility of acute leukemic transformation exists.

Patients with extremely high thrombocyte counts might benefit from other myelosuppressive agents that reduce thrombocyte counts; for example, anagrelide can be used to slow the rate of myeloid thrombopoiesis. Interferon-alpha and other chemotherapy agents may also be used in special cases to lower thrombocyte counts, but they are difficult to administer and may have serious side effects.

### ***Aspirin***

Unless contraindicated, patients undergoing phlebotomy and/or myelosuppressive therapy should take aspirin (81 to 100 milligrams po once daily) to reduce the risk of thrombotic complications.

### ***Symptom Control***

Interventions aimed at controlling symptoms include antihistamines to relieve itching and aspirin to relieve bone pain and paresthesias.

### ***Treatment Trends***

There is evidence of a trend toward increased use of phlebotomy as first-line therapy for erythrocytosis. Hydroxyurea is used more frequently than other myelosuppressive agents.

Since the discovery of the JAK2 mutation, researchers have begun developing and testing JAK2 inhibitors to treat PV and other MPNs. Drugs with the ability to inhibit JAK2 function could drastically change management of MPNs in the future.

### **Acute Leukemic Transformation**

In PV, transformation to acute leukemia has been observed for decades. Some have questioned whether this is a natural occurrence or a result of use of myelosuppressive agents for pharmacologic cytoreduction. Research suggests that both factors contribute to the risk, with some pharmacologic agents associated with higher risk than others. The apparent lower risk of acute leukemic transformation is one reason why many physicians prefer hydroxyurea over some other agents.

### ***Reporting PV***

*Pennsylvania laws and PADOH regulations require reporting of new cancer cases, including new cases of PV, to the Pennsylvania Cancer Registry (PCR).*

*The PCR collects information about occurrence of cancer, types of cancers diagnosed and their locations within the body, extent of cancer at the time of diagnosis, and treatment patients receive.*

*All malignant polycythemias and other myeloproliferative neoplasms are reportable to the PCR, including:*

- PV
- Proliferative polycythemia
- Polycythemia rubra vera
- Essential thrombocytosis
- Primary myelofibrosis
- Chronic myelomonocytic leukemia

## More Information

Organization	Website	Phone Number
The Myeloproliferative Diseases Foundation	<a href="http://www.mpdfoundation.org">www.mpdfoundation.org</a>	312-683-7243
The National Institutes of Health National Heart Lung and Blood Institute	<a href="http://www.nhlbi.nih.gov/health/dci/Diseases/poly/poly_what.html">www.nhlbi.nih.gov/health/dci/Diseases/poly/poly_what.html</a>	301-592-8573
Leukemia & Lymphoma Society	<a href="http://www.lls.org">www.lls.org</a>	914-949-5213 800-955-4572
Northeast Regional Cancer Institute	<a href="http://www.cancernepa.org">www.cancernepa.org</a>	800-424-6724

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