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Polycythemia Vera (PV)

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Alberta Health Services
CancerControl Alberta

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Background

Polycythemia vera (PV) is a clonal stem cell disorder characterized by erythrocytosis, with the majority of cases caused by constitutive activation of the *JAK-STAT* signal transduction pathway. The disease is associated with burdensome symptoms, reduced quality of life, thrombohemorrhagic complications and potential transformation to myelofibrosis (MF), myelodysplastic syndrome and/or acute myeloid leukemia (AML)[1,2]

Guideline Questions

1. What diagnostic and baseline investigations are recommended for adult patients with suspected or confirmed PV?
2. What are the recommended treatment options for PV?

Search Strategy

This guideline was generated using systematic literature searches of PubMed and MEDLINE databases, ASCO abstracts and proceedings, and ASH abstracts and proceedings. The search included practice guidelines, systematic reviews, meta-analyses, randomized controlled trials and clinical trials. The guidelines were also adapted from the Canadian MPN Group recommendations.

Target Population

The following guidelines apply to adults over the age of 18 years. Different principles may apply to pediatric patients.

Recommendations

1. Polycythemia vera (PV) should be considered when there is persistent elevation of hemoglobin (>165 g/L in men and >160 g/L in women) or hematocrit (>49% in men and >48% in women).

2. *JAK2V617F* mutation testing and erythropoietin levels should be performed when PV is suspected.

3. Bone marrow biopsy and aspiration may be necessary in some cases to confirm the diagnosis of PV and to distinguish PV from other myeloproliferative neoplasms.

4. PV is highly likely when *JAK2V617F* mutation is present and erythropoietin level is subnormal. When *JAK2V617F* mutation is seen with normal erythropoietin level, bone marrow biopsy is recommended to differentiate PV from other MPNs. When *JAK2V617F* is normal and erythropoietin is low, consider *JAK2* exon 12 mutational analysis or alternative diagnosis of congenital polycythemia. JAK2 exon 12 testing may be performed via Next Generation Sequencing (NGS) which is currently only available through bone marrow biopsy in Calgary.

5. Wildtype JAK2V617F and normal or high erythropoietin level makes PV very unlikely, and patients should be investigated for secondary causes of polycythemia.

6. Investigations for secondary polycythemia that may be indicated include:
    - **i.** Chest x-ray
    - **ii.** Pulse oximetry
    - **iii.** Arterial blood gas including carboxyhemoglobin and methemoglobin levels
    - **iv.** Kidney and liver function tests
    - **v.** Abdominal imaging studies (ultrasound or CT scan)
    - **vi.** Oxyhemoglobin dissociation curve
    - **vii.** Sleep studies

7. All patients should be treated with phlebotomy to target hematocrit less than 45%.

8. Low-dose acetylsalicyclic acid (ASA) should be used in **all patients** without a contraindication.

9. In **high-risk** PV patients (age ≥60 years and/or history of thrombosis), cytoreductive therapy should be used with or without phlebotomy in combination with low dose ASA.

10. Conventional cardiovascular risk factors (diabetes, hypertension, hyperlipidemia) should be aggressively managed, and cigarette smoking should be discouraged.

11. Thromboembolic events should be managed according to accepted management guidelines.

12. Thromboprophylaxis should be used after surgery and in other high-risk situations.

Discussion

Pathogenesis

Polycythemia vera (PV) is a *BCR-ABL1*-negative myeloproliferative neoplasm (MPN) characterized by erthryocytosis (with increased red cell mass) that is often accompanied by leukocytosis and thrombocytosis. Constitutive *JAK-STAT* signaling caused by the *JAK2V617F* mutation within exon 14 is present in ~ 95% of PV patients and by different mutations within exon 12 of the *JAK2* gene (4% of PV patients), which are responsible for the pathogenesis of PV[3,4]. The presence *of JAK2V617F* or a higher allele burden is not directly associated with PV survival or transformation rates[5,6], however, increased *JAK2V617F* allele burdens have been associated with fibrotic transformation[7].

Clinical Manifestations

The estimated incidence of PV is ~ 2.8 per 100,000 among men and ~1.3 per 100,000 in woman with a prevalence of 22 cases per 100,000. (http://www.lls.org/sites/default/files/file_assets/FS13_PolycythemiaVera_FactSheet.pdf). The median age of presentation is in the 6th decade of life with only 1/3 of patients diagnosed younger than 50 years of age[8].

The symptoms of PV can be variable with a majority of patients diagnosed incidentally by bloodwork. Splenomegaly is present in 30-40% of patients[9]. Non-specific symptoms such as headache, weakness, dizziness, and excessive sweating are present in 30% to 50% of PV patients and are often related to hyperviscosity resulting from erythrocytosis[10,11]. Fatigue is common and may be related to iron deficiency often found in PV patients at diagnosis, even before the onset of therapeutic phlebotomy.

Specific symptoms such as pruritus, especially after warm baths or showers (aquagenic pruritus) is reported in 70% of patients and suspected to be related to the degranulation of increased mast cells in the skin of PV patients, releasing histamine and other inflammatory mediators[12,13]. Erythromelalgia, described as burning pain in the feet and/or hands accompanied by erythema is seen in up to 28% of patients resulting from microvascular thrombosis and ischemia due to platelet activation and aggregation[14]. Both arterial and venous thrombotic events are a major cause of morbidity and mortality in PV. The incidence of thrombosis is approximately 18 x 1000 person years and accounts for 45% of all PV deaths[9].

Diagnostic Evaluation

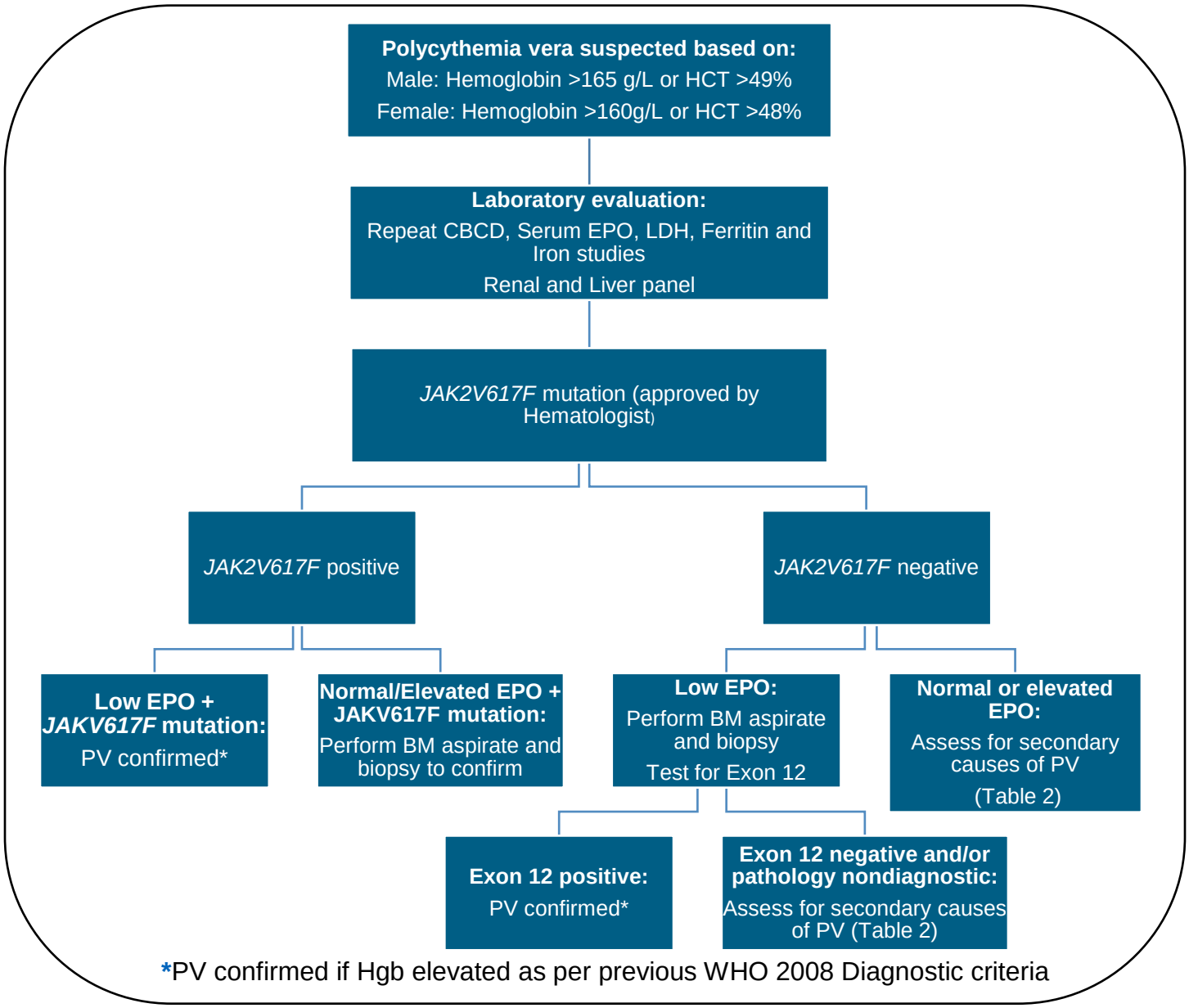
In the setting of isolated erythrocytosis, it is important to distinguish between primary and secondary polycythemia. Secondary polycythemia is caused by various factors driving erythropoiesis and may include hypoxia-driven mechanisms such as smoking, sleep apnea/hypoventilation, cardiac or pulmonary disease, high altitude or renal artery stenosis. Alternatively, oxygen-independent mechanisms include: drugs (androgens, erythropoietin, tumors- hepatic, renal, hemanigioblastomas) or post renal transplant[2]. Relative polycythemia should also be ruled out and is characterized by an isolated decrease in plasma volume with resultant elevation of hemoglobin, hematocrit and red blood cell count without an increase in red cell mass. Gaisbock's disease, stress erythrocytosis or spurious polycythemia refer to states of chronically low plasma volumes. A careful history and physical exam with select investigations can help distinguish PV from secondary causes (**Table 1**). The following basic investigations are recommended: pulse oximetry and/or arterial oxygen saturation, complete blood count with differential, liver and renal studies, chest xray.

If erythrocytosis is accompanied by thrombocytosis and/or leukocytosis, PV should be strongly considered. Assessing an erythropoietin level (EPO) is a very reliable discriminatory test. More than

85% of patients with PV have low serum EPO concentrations. EPO levels above normal are unusual for PV and suggest secondary erythrocytosis, with a specificity of 98 %[15,16]. It should be noted, to get an accurate EPO level, testing should be performed before initiation of phlebotomies. Investigations for PV should begin with screening for serum erythropoietin levels and *JAK2V617F* mutation. A diagnostic algorithm is shown in **Figure 1**. Low serum EPO levels in the absence of *JAK2 V617F* requires additional mutational analysis for *JAK2* exon 12 mutations. If EPO levels are normal or elevated with no secondary causes found, consider high-affinity hemoglobinopathies with further investigations including oxyhemoglobin dissociation curves (P50). A low P50 suggests a high affinity hemoglobinopathy or familial 2,3-bisphosphoglycerate (2,3-BPG) deficiency in contrast normal P50 results may require VHL, PHD2/HIFα mutational testing[2,17].

Bone marrow (BM) evaluation in *JAK2 V617F*-positive patients with erythrocytosis has traditionally provided limited additional value for diagnostic purposes and is not routinely performed. However, a baseline BM biopsy might be required in cases where the diagnosis is unclear. Cytogenetic studies are not routinely performed in PV patients in Canada. Approximately 11% of PV patients have cytogenetic abnormalities which include: trisomy 8, trisomy 9, 13q-, and 20q-[18], which are not specific to PV and found in other myeloid disorders. Cytogenetic abnormalities are more common in older PV patients (>60 years of age), and increase in frequency with disease progression and transformation[19]. The prognostic value of cytogenetics in PV remains unclear and still under investigation.

Figure 1: Diagnostic algorithm for polycythemia vera



*PV confirmed if Hgb elevated as per previous WHO 2008 Diagnostic criteria

Table 1: Differential Diagnosis of Polycythemia:

Normal Red Cell Mass:
Relative polycythemia Gaisbock's syndrome
Elevated Red Cell Mass:
Primary Polycythemia (JAK2 V617F or exon 12 mutation) ***Secondary Polycythemia*** ***Appropriately elevated EPO level (hypoxia driven):*** Chronic pulmonary disease Right –to –left cardiac shunts Sleep apnea Massive obesity (Pickwickian syndrome) High altitude Chronic carbon monoxide poisoning/chronic smoking Red cell defects: methemoglobinemia Renal artery stenosis ***Inappropriately elevated EPO (non-hypoxia driven):*** Renal cell carcinoma Hepatocellular carcinoma Cerebellar Hemangioblastoma Uterine fibroids Pheochromocytoma ***Congenital/Familial Polycythemia*:** Activating mutations of erythropoietin receptor (EPOR gene) Chuvash polycythemia (VHL gene mutation) Other rare gene mutations (PHD2, HIF2-alpha) ***Miscellaneous:*** Drugs: Androgens/Anabolic steroids/Erythropoetin Renal transplant

Table 2: Evaluation of Secondary Causes of Polycythemia

Differential Diagnosis of Secondary Polycythemia	Investigations to Consider:
Hypoxia Driven: Cardiac or Pulmonary Disease Sleep Apnea High oxygen affinity hemoglobin	 Pulse oximetry Arterial Blood Gas Chest X-ray Pulmonary Function tests Echocardiogram Overnight oximetry +/- Polysomnography Oxyhemoglobin dissociation curve
Non-hypoxia driven: Hepatic or Renal tumors Uterine Fibroids	 Liver and Renal studies US abdomen/pelvis or CT abdomen/pelvis

Diagnosis

The diagnosis of PV is based on World Health Organization (WHO) criteria utilizing a composite assessment of clinical and laboratory features as shown in **Table 3.** Recently, 2016 revisions of the WHO classification have been made that have modified diagnostic hemoglobin levels as well as the utility of BM morphology. A bone marrow biopsy is not uniformly required in all cases, in particular, if patients meet previously defined WHO 2008 hemoglobin requirements and there is low likelihood of masked PV. **Figure 1** demonstrates an approach to diagnosis with indications for additional molecular testing and bone marrow biopsy. The rationale for the changes is based on recent observations that some *JAK2 V617F*-positive PV patients present with hemoglobin levels lower than the 2008 WHO threshold with characteristic bone marrow findings of PV. This would be classified as "masked PV" (mPV) and such patients may have increased risk of thrombosis, secondary to late diagnosis and resulting inadequate disease control[20-22]. In PV, the classical BM features are increased cellularity with trilineage proliferation (panmyelosis). Megakaryocytes are pleomorphic with varying sizes without significant abnormalities in maturation and minimal reticulin fibrosis (grade1-2) is present[23].

Table 3: World Health Organization Diagnostic Criteria for Polycythemia Vera

	2008 WHO diagnostic criteria[a]	2016 WHO Diagnostic criteria[b]
Major Criteria	1) Hgb >185 g/L (men); >165 g/L (women)Ŧ 2) Presence of *JAK2V617F* or *JAK2* exon 12 mutation	1) Hgb >165 g/L (men); >160g/L (women) OR HCT>49% (men) and HCT >48% (women) OR increased red cell mass(RCM)* 2) BM hypercellular for age with trilineage myeloproliferation 3) Presence of *JAK2V617F* or *JAK2* exon 12 mutation
Minor Criteria	1) BM hypercellular for age and trilineage myeloproliferation 2) Subnormal serum EPO Level 3) Endogenous erythroid colony formation in vitro	1) Subnormal serum erythropoietin level

a PV diagnosis requires meeting BOTH major criteria and 1 minor criterion OR first major criterion and 2 minor criteria.
b PV diagnosis requires meeting ALL 3 major criteria, OR first 2 major criteria and the minor criteria
*More than 25% above mean predicted value.
Ŧ OR Hgb or Hct >99th %ile of ref range for age, sex or altitude OR increased red cell mass* OR Hgb >170 g/L (men) or >150 g/L (women) if associated with sustained increase of ≥ 20g/L from baseline not attributed to correction of iron deficiency

Prognosis

Patients with PV have a shortened life expectancy compared with the age and sex-matched general population, with an estimated 10-year survival being 28% lower in PV patients[24]. The median survival of PV patients is approximately 14 years; or 24 years if younger than age 60 at diagnosis[25]. Based on

large cohort studies, risk factors for survival include: advanced age, leukocytosis, venous thrombosis and abnormal karyotype. A prognostic model was developed to predict survival with adverse points for ≥67 years (5 points), age 57–66 years (2 points), leukocyte count ≥15 × 10^9/L (1 point) and venous thrombosis (1 point), resulting in low-risk (0 points), intermediate-risk (1 or 2 points) and high-risk (≥3 points) groups with median survivals of 27.8 years, 18.9 years and 10.9 years, respectively[17]. This was validated in a population-based PV study of 327 patients whereby age >70, leukocyte count >13 x 10^9/L and thrombosis at time of diagnosis resulted in poorer survival with 10-year survival rates of 84%, 59% or 26% with the presence of none, one or ≥ 2risk factors[26]. Overall, 45% of PV-related deaths are associated with cardiovascular disease[27].

Approximately 10% of PV patients transform into post-polycythemia vera myelofibrosis (PPV-MF), with progressive splenomegaly, MF-related symptoms, and anemia[28]. The IWG criteria for PPV-MF is shown in **Table 4**. Disease duration (>10 years) and *JAK2V617F* allele burden (>50%) are associated with a higher risk of evolution to PPV-MF[27,29]. The risk of leukemic transformation has been reported at 2.3% at 10 years and 5.5% at 15 years and remains <10% at 20 years. Older age, abnormal karyotype, and leukocytes ≥15 X 10^9/L are independent risk factors for leukemic transformation[30,31]. Post PV AML is an aggressive disease with very poor outcomes. Intensive chemotherapy followed by consolidated by allogeneic transplant is recommended in young fit patients. Hypomethylating agents and/or experimental therapies can be considered[32,33].

Table 4: International Working Group (IWG) definition of Post Polycythemia Myelofibrosis[34].

Required Criteria:
1. Previous WHO diagnosis of PV 2. BM fibrosis (grade 2 or 3 of 3-point scale)
Additional Criteria (2 required):
1. Anemia (Hgb < 135 g/L men, <120 g/L women) 2. Leukoerythroblastic peripheral blood 3. Increased splenomegaly 4. ≥ 1 constitutional symptoms (≥ 10% weight loss/6 months, drenching night sweats, unexplained fevers > 37.5° C)

Table 5: Prognostic Models in PV

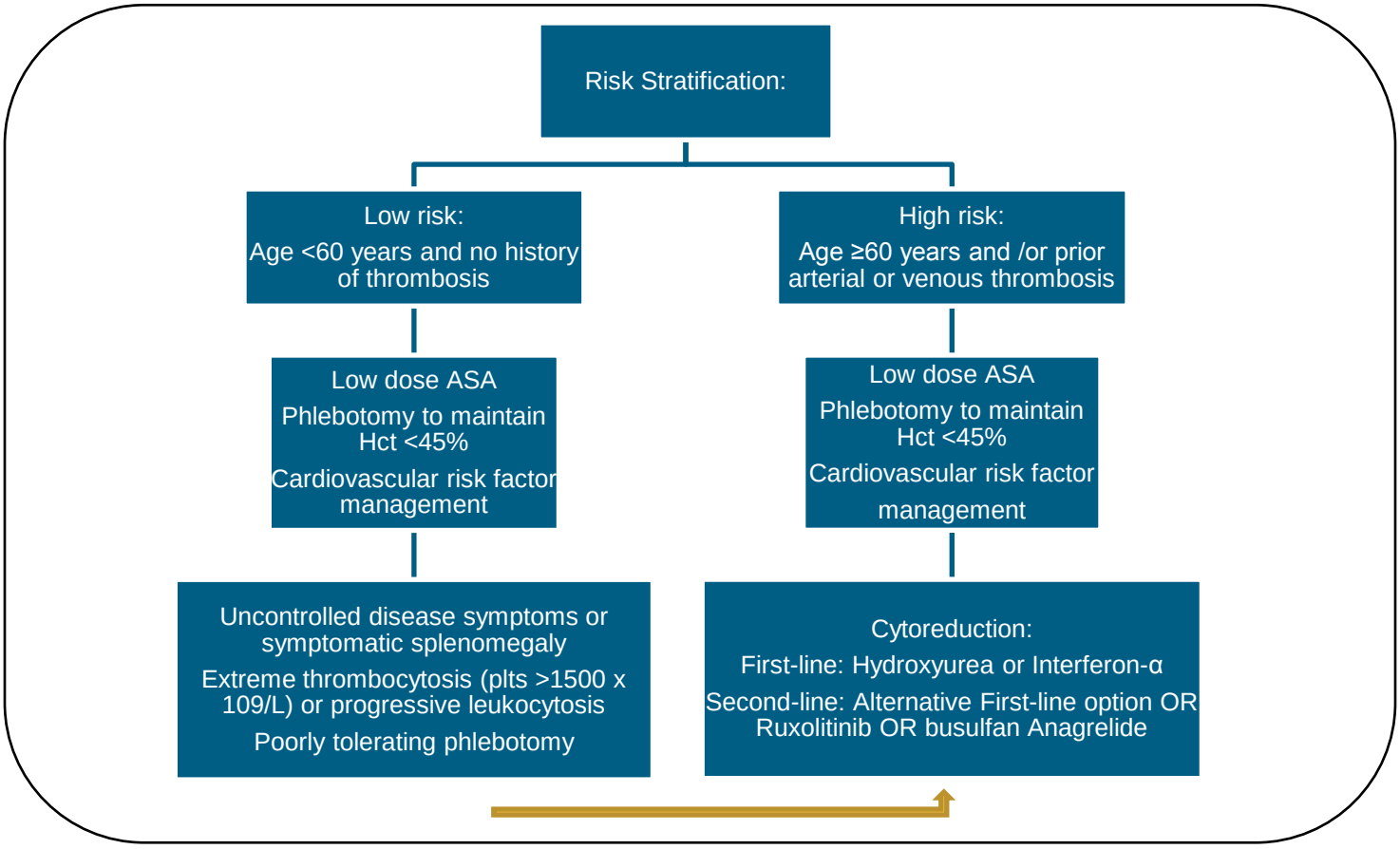
Prognostic Model:	Risk Categories:
Thrombosis score (European Leukemia NET)[35] Risk factors: Age ≥ 60 years Previous arterial or venous thrombosis	Low risk: 0 RFS High Risk: ≥ 1 RFs
IPSS Overall Survival[30] Risk factors: Age ≥ 67 yr (5 points) Age 55-66 yr (2 points) WBC ≥ 15 x 10^9/L (1 point) Previous VENOUS thrombosis (1 point)	Low risk: 0 points (Median survival 28 years) Intermediate Risk: 1-2 points (Median survival 19 yrs) High risk: ≥ 3 points (Median survival 11 years)

Treatment

The main goal of therapy in PV is to prevent thrombohemorrhagic complications and control symptoms. The currently available treatments are non-curative. All patients should be counselled regarding their disease course and associated complications with management of their vascular risk factors. Currently, there are no specific lipid or blood pressure target ranges for individuals with PV. However, with the increased risk of arterial thrombosis, it is important that patients control atherosclerotic risk factors such as hypertension, dyslipidemia, diabetes and obesity as well as smoking cessation. The Framingham Heart Study and the risk assessment tools incorporated in current Canadian Cardiovascular Society guidelines should be applied for general prevention of cardiovascular disease[36].

The European Leukemia Net (ELN) guidelines for Philadelphia-Negative Classical Myeloproliferative neoplasms (MPNs) recommends that **all patients** with PV be managed with phlebotomy to maintain a hematocrit (HCT) below 45%, and low-dose Aspirin[35]. Current risk stratification in PV is based on an estimate of thrombosis risk (**Table 5**) and patients are treated according to their risk group (**Figure 2**). The ELN has also defined criteria for response which are mainly intended for standardization in clinical trials and are not typically applied as rigorously in clinical practice[37].

Figure 2: Treatment algorithm for PV



Low-risk patients:

Treatment options for low risk patients include phlebotomy and low-dose Aspirin (81 -100 mg/day)[35] (Figure 2)

Phlebotomy.

Phlebotomy is well tolerated and can be performed as an emergency therapy if patients are experiencing symptoms of hyperviscosity as well as an important treatment for long-term maintenance in PV[35,38]. Typically, initial phlebotomy involves removal of 500 mL of blood every other day until a hematocrit of <45% is achieved. Lower quantity (i.e 250 mL) and frequency of phlebotomy should be considered in the elderly or patients with multiple comorbidities such as cardiovascular disease. Once an optimal hematocrit has been obtained a CBC can be assessed every 4-8 weeks and phlebotomy maintenance can be arranged accordingly (i.e every 2-3 months) to maintain Hct levels. Frequent phlebotomies will lead to iron deficiency and eventually result in reactive thrombocytosis and microcytosis. As a result, phlebotomy-induced iron deficiency can lead to complications such as increasing fatigue and restless leg syndrome. Iron supplementation is generally avoided in the setting of PV[9].

Based on several studies, the recommended HCT target in PV is < 45%[39,40]. The 2013 Italian Cytoreductive Therapy in Polycythemia Vera (CYTO-PV) was a multicenter, randomized controlled trial (n=365) that compared maintaining a HCT of ≤ 45% “low hematocrit” to a HCT between 45-50% (“high hematocrit”) using phlebotomy and/or hydroxyurea. The primary composite end point was the time until death from cardiovascular causes or major thrombotic events. At a median follow-up of 31 months, the primary end point was 2.7% among those with a HCT of <45% compared to 9.8% in the “high hematocrit” group (HR 3.91; 95% CI, 1.45 to 10.53; P = 0.007). There was no significant between-group difference in the rate of adverse events[40].

Low-dose Aspirin.

The randomized, placebo-controlled, European Collaboration on Low-Dose Aspirin in Polycythemia Vera (ECLAP) study (n=518) demonstrated a significant risk reduction (RR 0.40) in a combined endpoint of cardiovascular events and venous thrombotic events (nonfatal MI, nonfatal stroke, PE, major venous thrombosis or death from CV causes) with the use of low-dose Aspirin (100 mg daily) over placebo, with no significant increased risk of bleeding[39]. Based on this data, daily low-dose Aspirin is recommended for all PV patients in the absence of contraindications[35]. Low dose Aspirin is effective in alleviating vasomotor microvascular symptoms particularly erythromelagia, which are resulting from platelet-rich arteriolar microthrombi[41].

High-risk patients:

High risk patients as shown in **Table 5** (≥ 60 years of age and/or prior history of thrombosis) should be on cytoreductive therapy[35]. Cytoreductive therapy can be considered on an individual case basis (irrespective of risk) in patients with any of the following features[9]: (Figure 2)

- **i.** Extreme thrombocytosis (platelet count ≥1500×10^9/L) or if thrombocytosis is associated to bleeding or avWD
- **ii.** Progressive leukocytosis ≥20 - 25×10^9/L
- **iii.** Symptomatic splenomegaly
- **iv.** Severe disease-related symptoms
- **v.** Intolerance to phlebotomy

Cytoreductive therapies.

The European Leukemia Net (ELN) guidelines recommend either hydroxyurea or interferon-α as first-line cytoreductive therapy[35].

Hydroxyurea.

Hydroxyurea (HU) is an oral antimetabolite that prevents DNA synthesis by inhibiting the enzyme ribonucleoside reductase. Hydroxyurea is typically started at a dose of 15-20mg/kg/day (~1000mg/day). After a response is attained, a maintenance dose is continued to ensure a CBC remains within a normal range with CBC initially performed monthly and every 3 months thereafter once in a steady state[9]. Hydroxyurea is well tolerated with side effects including skin and nail changes, gastrointestinal toxicities, oral and leg ulcers myelosuppression and development of macrocytosis[9].

In the Polycythemia Vera Study Group (PVSG) trial, patients treated with HU had a lower incidence of thrombosis compared with historical controls treated with phlebotomy (9.8% vs. 32.8%)[42]. Long-term outcomes comparing hydroxyurea to pipobroman were reported in the French Polycythemia Study Group (FPSG) study, which randomly assigned HU versus pipobroman as first-line therapy in 285 patients < 65 years old. Median survivals were 20.3 and 15.4 years for the HU and pipobroman, respectively (P = .008). At 10, 15, and 20 years, cumulative incidence of acute myeloid leukemia/ myelodysplastic syndrome (AML/MDS) was 6.6%, 16.5%, and 24% in the HU arm and 13%, 34%, and 52% in the pipobroman arm (P = .004). Cumulative myelofibrosis incidence at 10, 15, and 20 years was 15%, 24%, and 32% with HU versus 5%, 10%, and 21% with pipobroman (P = .02). This illustrated the higher leukemogenic potential for pipobroman and its lack of suitability as first-line therapy in PV[43]. Hydroxyurea became a preferred first-line agent and although the incidence of evolution to AML with HU has been reported, it has been considered significantly lower than historical controls treated with chlorambucil or radiophosphorus (5.9% vs. 10.6% vs 8.3%, respectively)[42]. Studies have confirmed a low incidence of AML in PV patients treated with hydroxyurea and that exposure to P32, busulphan, and pipobroman (HR, 5.46; 95% CI, 1.84-16.25; P = .0023), but not to

hydroxyurea (HU) alone (HR, 0.86; 95% CI, 0.26-2.88; P = .8021), increases the risk for progression to AML/MDS compared with treatment with phlebotomy or interferon[31]. The data for HU use in PV is also extrapolated from essential thrombocythemia (ET) studies. Cortelazzo et al. randomized 114 high-risk ET patients to HU versus no therapy. At a median follow-up of 27 months, 3.6% of patients on HU experienced a thrombotic event compared to 24% of those in the control group[44]. Likewise, in 809 high-risk ET patients, HU plus low dose Aspirin (100mg/day) was compared to Anagrelide plus low dose Aspirin. Hydroxyurea resulted in better reduction of arterial thrombosis, major bleeding and fibrotic progression. Anagrelide resulted in lower venous thrombosis rates however patients on this treatment were more likely to withdraw from their assigned treatment (P<0.001)[45]. The ANAHYDRET study, was a prospective randomized noninferiority phase 3 study of 259 high-risk ET patients. During the total observation time of 730 patient-years, there was no significant difference between the anagrelide and hydroxyurea group regarding incidences of arterial and venous thrombosis, bleeding events, or rates of discontinuation. Disease transformation into myelofibrosis or secondary leukemia was not reported in this study. Anagrelide was considered not inferior compared with hydroxyurea in the prevention of thrombotic complications in patients with ET however, is not considered a first line treatment option in PV[46].

Although not a common problem in PV, the development of HU resistance or intolerance occurs and has been estimated as 11.5% in a median of 5.8 years from time of diagnosis. Hydroxyurea intolerance/resistance is associated with a 5.6 fold increase risk of death[47]. The ELN panel of experts has developed a standardized definition of resistance and intolerance to HU in PV[34] (**Table 6**). Younger patients with intolerance/resistance are alternatively treated with Interferon- α therapy (IFN) or Ruxolitinib. Older patients can be treated with alternatives such as Ruxolitinib or select elderly patients may be considered for busulphan[35].

Table 6: Definition of Hydroxyurea Intolerance/Resistance In PV[34]

Any of the following criteria:
1. Need for phlebotomy to keep HCT <45% after 3 months of at least 2 g/day of HU 2. Uncontrolled myeloproliferation: plt >400 x 10^9/L AND WBC >10 x 10^9/L after 3 months of at least 2 g/day of HU 3. Failure to reduce massive splenomegaly* by more than 50% as measured clinically, OR failure to completely relieve symptoms related to splenomegaly, after 3 months of at least 2 g/day of HU 4. Persistent cytopenias: ANC <1 x 10^9/L OR plt <100 x 10^9/L OR Hgb <100 g/l at the lowest dose of HU required to achieve a complete or partial response§ 5. Presence of leg ulcers or other unacceptable HU-related toxicities, such as mucocutaneous manifestations, GI symptoms, pneumonitis or fever

*Spleen more than 10 cm from the costal margin.
§Complete response defined as: Hct <45% without phlebotomy, platelet count ≤400 x 10^9/L, WBC ≤ 10 x 10^9/Land no disease related symptoms. Partial response defined as: Hct <45% without phlebotomy, or response in three or more of the other criteria[37].

Interferon.

Both short-acting Interferon (IFN) and pegylated interferon (IFN)-α are effective in controlling blood counts as well as spleen size and symptoms (aquagenic pruritus) in PV, and is considered first-line therapy, particularly in younger patients (< 40 years)[35,48]. Unfortunately, side effects can limit therapy

and include autoimmune disorders, flu-like manifestations, depression, heart and ocular disease which have led to permanent discontinuation in 20% to 40% of patients on conventional IFN and 20% to 25% on pegylated IFN[48]. It is contraindicated in patients with mental disorders. IFN is commonly administered subcutaneously at a starting dose of 3 million units daily until a response is achieved. Pegylated IFN is given at a starting dose of 45 µg weekly and if there is lack of response after 12 weeks, a dose increase is indicated (90 ug to 135 ug/weekly) The dose should be titrated individually based on efficacy and toxicity with CBC monitoring on a monthly basis.

Apart from the absence of leukemogenic risk, the other benefit of IFN may be its ability to attain molecular responses[48,49]. A phase II study of pegylated interferon alfa-2a (PEG-IFN-alpha-2a) in patients with ET (n=39) and PV (n=40) demonstrated that PEG-IFN-alpha-2a reduces the size of the malignant clones measured by *JAK2* allele burden. Overall hematologic response rate was 80% in PV and 81% in ET (complete in 70% and 76% of patients, respectively). Molecular response rates were 38% in ET and 54% in PV, with complete (undetectable JAK2(V617F)) in 6% and 14%, respectively[49]. Two phase III studies comparing HU to pegylated forms of IFN-α are ongoing in the United States and Europe; PROUD-PV (NCT01949805) and MPD-RC 112 (NCT01259856), with aims of determining the efficacy of these two therapies as first line cytoreductive agents in high-risk PV and ET.

Second line therapies:

Ruxolitinib.

Ruxolitinib is a JAK1/JAK2 inhibitor that has demonstrated clinical benefit and has been approved in patients with myelofibrosis[50,51]. A phase II study of PV patients (n=34) who were intolerant or refractory to HU received ruxolitinib for a median of 35 months. Achievement of a HCT <45% without phlebotomy occurred in 97% of patients by week 24. Patients with palpable splenomegaly at baseline, resulted in 44% and 63%, respectively, having a nonpalpable spleen at weeks 24 and 144. The RESPONSE study was a phase III open-label study evaluating the efficacy and safety of ruxolitinib versus investigator determined best available therapy (BAT) in patients with polycythemia vera who were intolerant or refractory to HU. The primary end point was both hematocrit control and ≥ 35% reduction in spleen volume at week 32, based on imaging. The primary end point was achieved in 21% of the patients in the ruxolitinib group versus 1% of those in the BAT group (OR 28.64; 95% CI 4.50-1206; P <0.0001). Hematocrit control was achieved in 60% of patients receiving ruxolitinib and 20% of those receiving BAT. Spleen volume reduction occurred in 38% and 1% of ruxolitinib versus BAT patients, respectively. Ruxolitinib achieved ≥ 50% reduction in the total symptom score at week 32 in 49% versus 5% of those with BAT. Thromboembolic events occurred in one patient receiving ruxolitinib and in six patients receiving standard therapy however, further investigations are needed to determine its role in reducing thrombotic risk among PV patients[23]. The most common hematologic adverse events (AEs) were anemia and thrombocytopenia; however, no patient in the RESPONSE trial discontinued treatment due to these cytopenias. Common non-hematologic AEs are headache,

dizziness, diarrhea, and fatigue and there were herpes zoster infections noted in ~6% of patients. Ruxolitinib is now approved by Health Canada for treatment of PV patients resistant to or intolerant of a cytoreductive agent.

Symptom assessment

PV-related symptoms are troublesome to patients, and alleviation of this burden is an important treatment objective. It is important to carefully assess patients' symptoms and to have an objective means to monitor disease progression or response to treatment. The Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS) is a validated objective tool for evaluating patient symptoms[11]. The MPN-SAF TSS, also known as MPN10, is a shorter questionnaire that includes 10 items: fatigue, concentration, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss, and fever. This score has been validated in a prospective study of 1433 patients and results correlated with other measures of disease burden and remains consistent between serial administrations[11].

Special Topics

Pregnancy

Typically, only 10% of PV patients are diagnosed at <40 years of age[52]. PV increases risks for both fetus and mother with less than 60% of pregnancies occurring in PV patients being successful. Patients are at risk of miscarriages with first trimester losses being most common. Maternal complications include preeclampsia, postpartum hemorrhage and thrombosis[45,53]. Phlebotomy should be used to keep the hematocrit at less than 45% but of note, the physiological changes of pregnancy often can reduce hematocrit levels. Female patients should be advised that HU is contraindicated in pregnancy and, therefore, appropriate contraceptive precautions should be taken while on this therapy and HU should be discontinued in setting of pregnancy. Interferon alfa-2b is recommended for those requiring cytoreductive therapy during pregnancy since all other cytoreductive agents are contraindicated due to possible teratogenic effects. Indications for cytoreduction in pregnancy include if platelet count >1500 x 10^9/L or related complications of bleeding. There is some evidence that the use of low-dose aspirin throughout pregnancy improves live birth rate. The ELN has published treatment recommendations for PV patients during pregnancy (**Table 7**). It is recommended that prophylactic low-molecular-weight heparin (LMWH) be used for 6 weeks postpartum in all patients with consideration for its use during pregnancy in high risk pregnancy[9,35].

Table 7: Suggested management of PV patients during pregnancy based on ELN guidelines[35].

Pregnancy Risk	Management
LOW Risk	Target HCT < 45% Low dose ASA + Prophylactic dose LMWH postpartum x 6 weeks
HIGH Risk: Includes patients with prior thrombosis history, major bleeding due to MPN or severe pregnancy complication*	Target HCT <45% Low dose ASA + LMWH throughout pregnancy and postpartum

*Recurrent (≥3) first-trimester pregnancy loss, intrauterine growth restriction (IUGR), unexplained intrauterine death or if secondary to placental dysfunction, severe preeclampsia necessitation preterm delivery before 34 weeks, significant ante-postpartum hemorrhage, placental abruption, or marked sustained increase of platelets >1500 x 109/L (Adapted from: Gerds A. Oncology 2017;92:179-189[54]).

Perioperative Management:

Surgery in patients with PV has a high risk of both peri-operative bleeding and postoperative thromboembolism. In a multicenter retrospective study of 255 PV and ET patients, a high proportion of patients experienced vascular occlusions (7.7%) and major hemorrhage (7.3%)[55]. Elective surgeries should be delayed until cytoreductive measures and/or phlebotomy can be used to achieve blood count control since risks may be lower with hematologic control prior to surgery[56]. It is recommended that hematocrit maintenance <45% and normalization of blood counts be achieved ≥ 3 months prior to surgery[57]. Aspirin should be held for 5-7 days before surgery to reduce the risk of hemorrhage. LMWH should be given after surgery to prevent deep venous thrombosis[57]. Mechanical compression stockings are an option for patients with bleeding that prevents the use of anticoagulation. Ruxolitinib has potential rebound effects with discontinuation therefore it is recommended it be continued through surgery. If discontinuations are needed, a taper is required whereby it is discontinued 1-2 weeks prior to surgery[54]. When thromboembolic events do occur, treatment should be according to current management guidelines. Indefinite anticoagulation should be considered because of the high risk of recurrent events.

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Development and Revision History

This guideline was reviewed and endorsed by the Alberta Hematology Tumour Team. Members include [surgical oncologists, radiation oncologists, medical oncologists, dermatologists, nurses, pathologists, and pharmacists]. Evidence was selected and reviewed by a working group comprised of members from the Alberta Tumour Teams, external participants identified by the Working Group Lead, and a knowledge management specialist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in 2020.

Maintenance

A formal review of the guideline will be conducted in 2022. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

2,3-BPG, 2,3-bisphosphoglycerate; AEs, adverse events; AML, acute myeloid leukemia; ASA, acetylsalicylic acid; BAT, best available therapy; BM, bone marrow; CBCD, complete blood count with differential; ELN, European Leukemia Net; EPO, erythropoietin; ET, essential thrombocythemia HCT, hematocrit; Hgb, hemoglobin; HU, hydroxyurea; IFN, interferon; IWG, international working group; LDS, lactate dehydrogenase; LMWH, low-molecular-weight-heparin; P50, oxyhemoglobin dissociation curve; PPV-MF, post-polycythemia vera myelofibrosis; PV, Polycythemia vera; MDS, myelodysplastic syndrome; MF, myelofibrosis; MPN, myeloproliferative neoplasm; mPV, masked PV; NGS, Next Generation Sequencing; RCM, red cell mass; WHO, whole health organization.

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial Hematology Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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Conflict of Interest Statements

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