REVIEW CPD

Investigation and management of erythrocytosis

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Erythrocytosis refers to an erythrocyte count above the sex-specific normal range and can be subclassified into relative erythrocytosis, caused by a reduction in plasma volume (hemoconcentration), or absolute erythrocytosis, caused by increased erythrocyte mass. Primary erythrocytosis refers to autonomous production of erythrocytes, typically from a myeloproliferative neoplasm (polycythemia vera [PV]). In contrast, secondary erythrocytosis is caused by a physiologically appropriate response to elevated serum erythropoietin levels.

Up to 4% of ambulatory men and 0.4% of ambulatory women in Canada have erythrocytosis, based on hemoglobin levels greater than 165 g/L or 160 g/L, respectively.[1] Differentiating PV from other causes of erythrocytosis is critical because early recognition and treatment of PV can prevent many of its vasomotor and thrombotic complications. Polycythemia vera is rare, with an incidence and prevalence of 0.84 and 22 per 100 000, respectively.[2,3] Although the prevalence of secondary erythrocytosis is difficult to estimate, it is higher than that of PV. Secondary erythrocytosis affects 6%–8% of patients with chronic obstructive pulmonary disease[4] and 2%–8% of patients with obstructive sleep apnea.[5,6]

In this review, we summarize a contemporary approach to differentiating PV from other causes of erythrocytosis, and review the natural history, diagnosis and management of PV (Box 1).

KEY POINTS

- Primary erythrocytosis — or autonomous production of excess erythrocytes — most commonly occurs due to polycythemia vera (PV), a myeloproliferative neoplastic process that may be asymptomatic or may present with thrombosis, constitutional or vasomotor symptoms, or splenomegaly.

- Secondary erythrocytosis, which is more common than PV, has a broad differential diagnosis that includes hypoxic lung disease, cyanotic congenital heart disease, medications (e.g., testosterone) and erythropoietin-producing malignant disorders.

- Differentiating between PV and secondary erythrocytosis requires clinical evaluation and specialized investigations including measurement of the serum erythropoietin level and Janus kinase 2 mutation testing.

- To reduce the risk of thrombosis, most patients with PV are treated with low-dose acetylsalicylic acid and phlebotomy to achieve a target hematocrit value of less than 0.45, whereas patients at high risk for thrombosis may receive cytoreductive therapy.

- Treatment of secondary erythrocytosis should be directed at the underlying cause, and phlebotomy is not routinely recommended.

Box 1: Evidence used in this review

We reviewed current guidelines on the management of polycythemia vera. For questions regarding the diagnostic investigation of erythrocytosis and the utility of specific laboratory tests such as the erythropoietin level, we searched MEDLINE to January 2020 for terms such as "polycythemia vera," "erythrocytosis" or "secondary erythrocytosis" AND "diagnosis," "erythropoietin level," "bone marrow biopsy" and "JAK2." We considered original research and review articles published between 2010 and January 2020, and searched reference lists of selected articles to identify additional studies of interest. We specifically reviewed landmark randomized trials in polycythemia vera such as the Cytoreductive Therapy in Polycythemia Vera (CYTO-PV) study,[7] the European Collaboration on Low-Dose Aspirin in Polycythemia Vera (ECLAP) study,[8] the Randomized Study of Efficacy and Safety in Polycythemia Vera with JAK Inhibitor INCB018424 versus Best Supportive Care (RESPONSE),[9] the RESPONSE-2[10] and older studies conducted by the Polycythemia Vera Study Group.

What is the differential diagnosis for erythrocytosis?

Relative erythrocytosis results from any condition that reduces plasma volume, such as gastrointestinal fluid losses or diuretic use. Absolute erythrocytosis can be driven by a clonal bone marrow disease (PV) or be secondary to another disease, including a physiologic response to increased erythropoietin secondary to hypoxia, drugs[11] or erythropoietin-producing solid tumours[12,13] (Box 2). Congenital causes of erythrocytosis include high-oxygen-affinity hemoglobins, erythropoietin receptor mutations and alterations in oxygen-sensing molecular pathways.

Polycythemia vera is a myeloproliferative neoplasm characterized by increased erythrocyte mass, thrombosis and vasomotor symptoms. A gain-of-function mutation in Janus kinase 2 (JAK2) underlies 98% of PV cases.[15]

What is the diagnostic approach to erythrocytosis?

Clinical evaluation

The history-taking and physical examination should be directed toward ruling out relative erythrocytosis and then distinguishing between primary and secondary erythrocytosis. For secondary erythrocytosis, this includes a review of cardiac, respiratory and abdominal signs and symptoms. Patients should be asked about tobacco smoking, medications (especially androgenic steroids, including testosterone[11]), exposure to carbon monoxide and symptoms of obstructive sleep apnea. A full cardiopulmonary examination should be completed, and the abdomen should be examined for organomegaly or erythropoietin-producing intra-abdominal tumours (e.g., hepatocellular or renal cell carcinoma).

Oxygen saturation less than 92% on room air by pulse oximetry suggests that erythrocytosis is secondary to hypoxic cardiopulmonary disease.[14] Some causes of hypoxia may present with a normal or falsely elevated oxygen saturation value (e.g., obstructive sleep apnea, high-oxygen-affinity hemoglobins, or carboxyhemoglobinemia from tobacco smoking or carbon monoxide poisoning).

The World Health Organization diagnostic criteria for PV were updated in 2016 (Box 3).[16] Patients with PV may have symptoms of splenomegaly, constitutional symptoms or vasomotor symptoms such as headache, visual disturbances or light-headedness. Two specific symptoms for myeloproliferative neoplasms are pruritus and erythromelalgia.[15] Pruritus is often aquagenic and may be debilitating. Erythromelalgia is a recurrent burning sensation accompanied by erythema and warmth, most commonly affecting the hands.

Investigations to differentiate primary from secondary erythrocytosis

Initial tests to differentiate primary from secondary erythrocytosis include a complete blood count, peripheral blood film, renal and liver function tests, and determination of the ferritin level.[14] Erythrocyte mass can be measured directly to confirm absolute erythrocytosis by nuclear isotope dilution, but this test is not widely available in Canada.[1] As PV is associated with panmyelosis (expansion of all myeloid elements of the bone marrow), patients often have mild to moderate leukocytosis and thrombocytosis rather than isolated erythrocytosis.[15] Many patients with PV are iron deficient at diagnosis owing to erythroid expansion and altered iron metabolism.[17] A low mean erythrocyte volume and low ferritin level (< 35–45 ng/mL) support a diagnosis of iron deficiency.[18] Baseline abdominal–pelvic imaging is indicated when the clinical examination for splenomegaly gives equivocal findings or when endogenous erythropoietin production is suspected.[19]

The serum erythropoietin level can differentiate between primary and secondary erythrocytosis. In a cohort study of 125 patients, a low erythropoietin level (< 2.9 mU/mL) was specific (92%) and moderately sensitive (64%) for the diagnosis of PV.[20] A high erythropoietin level (> 15.1 mU/mL) was specific (98%) but had poor sensitivity (47%) for the diagnosis of secondary erythrocytosis.[20]

Ninety-five percent of patients with PV have a V617F point mutation in exon 14 of JAK2.[21] JAK2 V617F-negative PV is rare, and mutations in exon 12 of JAK2 account for most of these cases.[22] The JAK2 V617F mutation is not specific to PV; it can also

be seen in other myeloproliferative neoplasms including essential thrombocythemia and primary myelofibrosis.[21] Some cases of PV with iron deficiency may resemble essential thrombocythemia.[17] In these cases, erythrocytes are microcytic, the hemoglobin level is low or within normal limits, and there is marked thrombocytosis.

Our approach to sequencing investigations is adapted from Canadian consensus recommendations[1] and a British guideline for the diagnosis and management of PV[14] (Figure 1). Front-line tests are selected based on the pretest probability of PV and the availability of JAK2 mutation testing.

In the primary care setting, where the probability of PV is low, clinical evaluation for secondary causes of erythrocytosis paired with a high erythropoietin level can rule out PV in most patients.

In hematology clinics, where the probability of PV is higher, erythropoietin level and JAK2 V617F mutation testing are done concurrently. Patients with a low or normal erythropoietin level and no JAK2 V617F mutation are further evaluated with JAK2 exon 12 mutation testing (on peripheral blood or marrow aspirate, based on local practice) and a bone marrow biopsy.[14] Findings on bone marrow biopsy in a patient with PV are shown in Figure 2.

When no diagnosis is made, selected patients with onset of erythrocytosis at a young age or compatible family history should undergo testing for high-oxygen-affinity hemoglobins, and gene sequencing for mutations involving the erythropoietin receptor or oxygen-sensing pathways.[14,23] Idiopathic erythrocytosis is a diagnosis of exclusion.
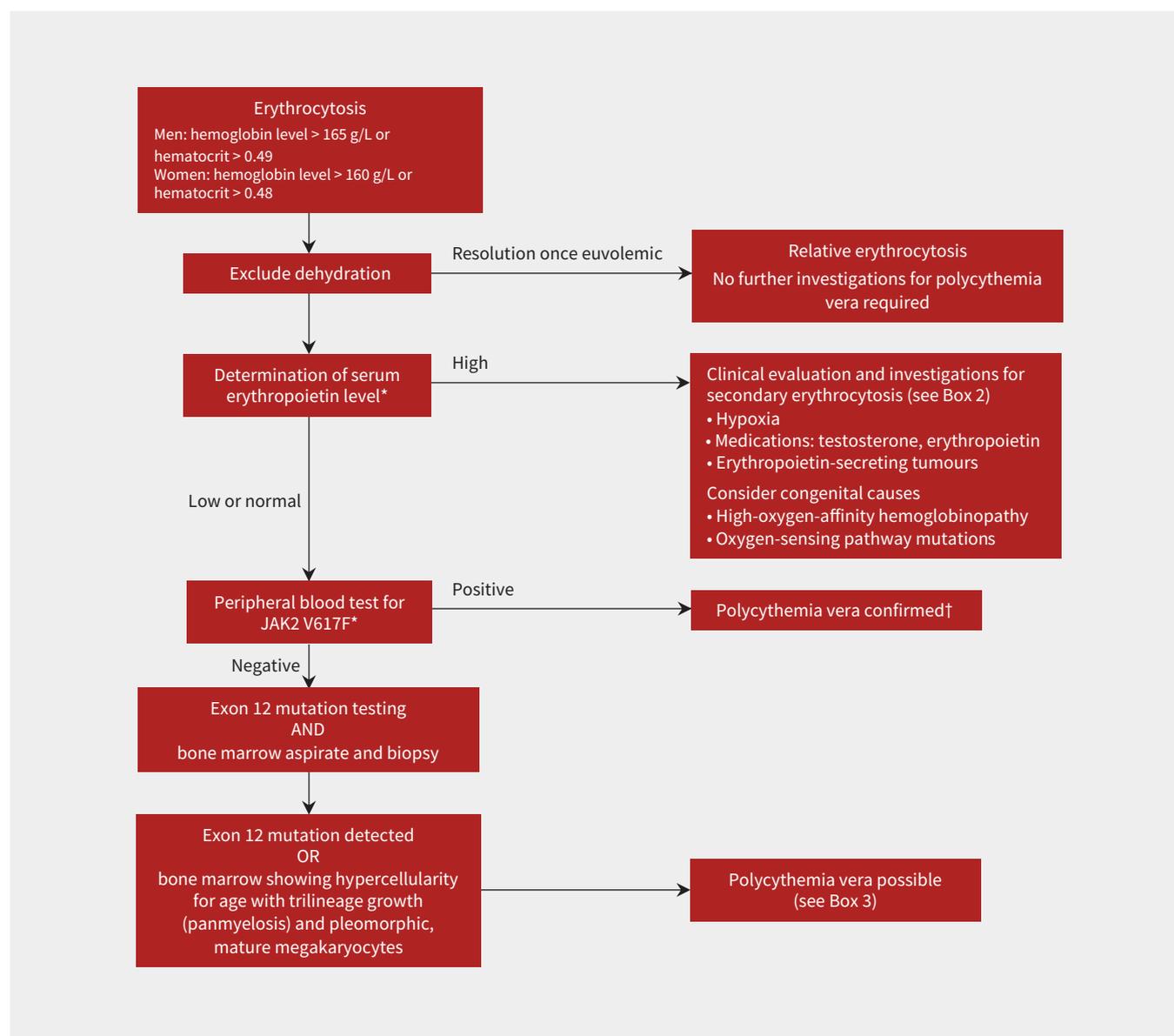
Figure 1: Practical diagnostic approach to erythrocytosis. *Some clinicians order determination of the erythropoietin level and JAK2 V617F mutation testing concurrently in settings when there is a high probability of diagnosing polycythemia vera. †Bone marrow biopsy is required to meet the World Health Organization 2016 diagnostic criteria[16] if the hemoglobin level is less than 185 g/L (hematocrit 0.55) in men or less than 165 g/L (hematocrit 0.50) in women.
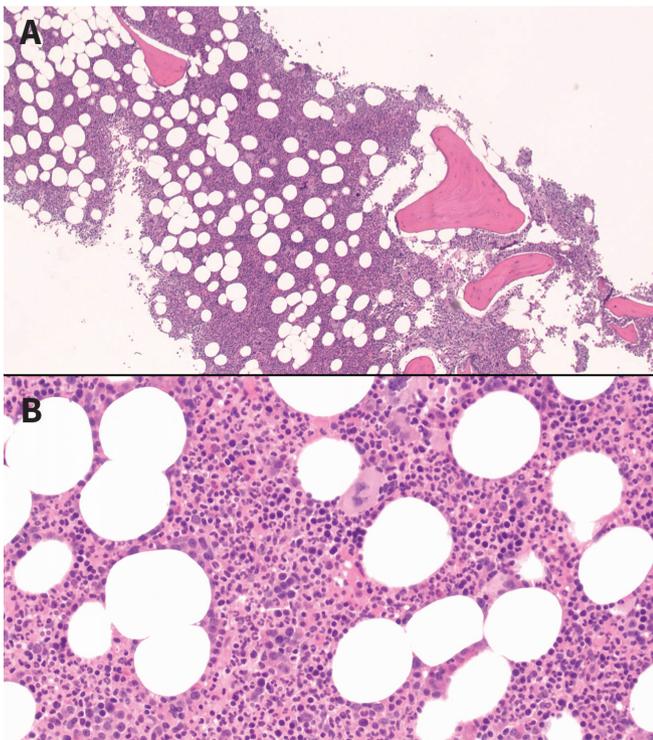
Figure 2: Bone marrow biopsy specimen of a patient with polycythemia vera. (A) Hypercellularity for age and panmyelosis (expansion of all myeloid elements of the bone marrow) (hematoxylin–eosin, ×40 magnification). (B) Panmyelosis and pleomorphic megakaryocytes (hematoxylin–eosin, ×200 magnification). Images courtesy of Dr. Catherine Ross, Pathology and Molecular Medicine, Juravinski Hospital, Hamilton, Ontario.

Investigations for secondary erythrocytosis

Investigations for secondary erythrocytosis should be symptom-directed and may include chest radiography, overnight oximetry for suspected sleep apnea, pulmonary function tests for hypoxic lung disease, venous blood gas sampling (carboxyhemoglobin level) and echocardiography to rule out right to left cardiac shunting. Abdominal–pelvic imaging can help exclude an erythropoietin-producing tumour or conditions associated with local renal hypoxia (Box 2). Neuroimaging to rule out meningioma or cerebellar hemangioblastoma should be ordered for patients with unexplained neurologic symptoms as these tumours have been associated with autonomous erythropoietin production.[14]

When should patients be referred to a hematologist?

There are no established criteria for referral to a hematologist. Patients with a low or normal erythropoietin level and negative findings on investigation for secondary erythrocytosis are typically referred to a general internist or hematologist to arrange additional investigations starting with JAK2 V617F testing (Figure 1). Internists or hematologists often manage patients who require phlebotomy. Referral to a hematologist is warranted for women with PV who desire pregnancy, patients who are refractory or intolerant to treatment with hydroxyurea, and patients with no diagnosis despite extensive appropriate investigations.

What are the principles of treating polycythemia vera?

The goals of treatment of PV are to reduce the risk of arterial and venous thromboembolism, and minimize symptoms.[14] Unfortunately, existing treatments do not successfully reduce the risk of transformation to myelofibrosis or acute leukemia.

Risk stratification for thrombosis

Thrombosis in PV is common and highly morbid. Up to 15% of patients with newly diagnosed PV have a history of arterial or venous thromboembolism.[15,24] Patients with PV have venous thrombosis at unusual sites, such as the splanchnic or cerebral veins.[25] A meta-analysis of observational studies showed that more than 15% of patients with splanchnic vein thrombosis or Budd–Chiari syndrome are later diagnosed with a myeloproliferative neoplasm.[26]

In a cohort of 1638 patients with PV, cardiovascular mortality accounted for 45% of all deaths over more than 4000 person-years of follow-up.[27] The 2 most important predictors of cardiovascular events were age greater than 65 years and prior thromboembolism. Patients with neither, 1 or both risk factors experienced 2.5, 5.0 and 10.9 cardiovascular events per 100 person-years, respectively. Treatment guidelines classify patients as being at high risk for thromboembolism if they are more than 60 or 65 years old or have a history of thrombosis, or both.[14,28] Patients who meet neither of these criteria are considered to be at low risk.

Management of low-risk polycythemia vera

Patients with PV are treated with daily low-dose acetylsalicylic acid (ASA) and phlebotomy to achieve a target hematocrit value of less than 0.45 based on the results of 2 randomized trials.[14,28] Patients are monitored regularly (every 3–6 mo) for symptoms, treatment complications, cardiovascular events and disease progression.

In the European Collaboration on Low-Dose Aspirin in Polycythemia Vera (ECLAP) study,[8] 518 patients with PV were randomly allocated to receive low-dose ASA (100 mg/d) or placebo. Acetylsalicylic acid reduced the composite outcome of nonfatal myocardial infarction, nonfatal stroke, venous thrombosis or death from cardiovascular causes by 60% (relative risk [RR] 0.40, 95% confidence interval [CI] 0.18–0.91), with no statistically significant increase in major bleeding.

In the Cytoreductive Therapy in Polycythemia Vera (CYTO-PV) study, 365 adults with PV were randomly allocated to a low hematocrit target (< 0.45) or a less-intensive hematocrit target (0.45–0.50).[7] The primary outcome of death from cardiovascular causes or major thrombotic events was observed in 5 of 182 patients (2.7%) in the low-hematocrit group compared to 18 of 183 patients (9.8%) in the higher-hematocrit group (RR 3.91, 95% CI 1.19–6.12), with no significant difference in adverse events between the groups.

Most patients with an indication for anticoagulation therapy should receive an anticoagulant in place of ASA. A multicentre observational study of 2510 patients with PV showed that patients who received both an anticoagulant and ASA had a four-fold increased risk of bleeding (95% CI 2.57–6.94) compared to

those who received either treatment alone or no treatment.[29] We could not identify any high-quality data comparing warfarin to direct anticoagulants for oral use in PV.[30] The British guideline recommends that cardiovascular risk factors, including blood pressure, lipid control, and counselling around smoking cessation and weight loss, be addressed in all patients.[14]

Management of high-risk polycythemia vera

Observational studies suggest that patients with high-risk PV benefit from cytoreductive therapy in addition to low-dose ASA therapy and phlebotomy.[14,28] In North America, hydroxyurea (hydroxycarbamide), an orally administered antimetabolite chemotherapy drug that causes myelosuppression, is used owing to its known efficacy, low cost, oral formulation and acceptable toxicity profile (discussed below). A study showed that 51 patients with PV treated with hydroxyurea had a lower incidence of thrombosis at 2 years than historical controls treated with phlebotomy alone (7% v. 14%).[31] Some clinicians titrate the dosage of hydroxyurea to achieve peripheral blood count remission (hematocrit < 45% without phlebotomy, platelet count ≤ 400 × 10^9/L and leukocyte count < 10 × 10^9/L).[32] Response definitions for PV have been created for use in clinical trials, but their routine application to clinical practice is not evidence-based.[32] Other clinicians titrate the dosage of hydroxyurea to minimize the need for phlebotomy. An observational study showed that patients receiving hydroxyurea who needed 3 or more phlebotomy procedures per year had a significantly higher rate of thrombosis than those who required fewer phlebotomy procedures (21% v. 5% at 3 yr, $p < 0.001$).[33]

Alternatives to hydroxyurea include pegylated interferon α or busulfan. The former can be used safely during pregnancy and induces molecular remission in some patients; for these reasons, it is often used as front-line therapy for young patients or women desiring pregnancy.[34]

Ruxolitinib, an orally administered JAK1 and JAK2 inhibitor, is a second-line agent for patients who are refractory or intolerant to hydroxyurea.[9,10] The Randomized Study of Efficacy and Safety in Polycythemia Vera with JAK Inhibitor INCB018424 versus Best Supportive Care (RESPONSE) investigators randomly allocated 222 such patients with splenomegaly to ruxolitinib versus best available therapy.[9] The composite primary outcome of hematocrit control and at least a 35% reduction in spleen volume was achieved in 20.9% of the patients in the ruxolitinib arm, compared to 0.9% of those in the best-available-therapy arm ($p < 0.001$). The RESPONSE-2 investigators enrolled similar patients without splenomegaly and found that a higher proportion of ruxolitinib-treated patients than patients who received best available therapy achieved hematocrit control (62% v. 19%, $p < 0.001$).[10]

Monitoring patients with polycythemia vera receiving hydroxyurea

Hydroxyurea is well tolerated, but common adverse effects include complications from cytopenia, oral and leg ulcers, gastrointestinal upset, drug fever, and skin and nail changes. An international retrospective cohort study of 1545 patients with PV showed that hydroxyurea does not increase the incidence of leukemia.[15]

Management of pruritus

Ruxolitinib is the most effective treatment for pruritus in PV. A phase III randomized trial showed that patients treated with ruxolitinib were more likely to experience alleviation of pruritus than those who received hydroxyurea (54% v. 32%, $p = 0.03$).[35] Other treatments for pruritus are supported by lower-quality evidence, mostly from case series. These include selective serotonin reuptake inhibitors, interferon α, psoralen and ultraviolet A, and antihistamines.[36]

Management of polycythemia vera in pregnancy

The prevalence of PV among females of reproductive age is less than 0.3 per 100 000,[37] so management recommendations are based on case series or extrapolated from essential thrombocythemia.[5,34] The hematocrit is maintained in the normal range for gestation.[5] Women without a contraindication receive low-dose ASA throughout pregnancy, and interferon α is used for women who require cytoreductive therapy. Thromboprophylaxis with low-molecular-weight heparin, in addition to ASA, may be beneficial for selected patients at high risk.[5,28]

What are the principles of treating secondary erythrocytosis?

Treatment should be directed at the underlying cause. There is no definitive evidence that the risk of thromboembolism is increased in patients with secondary erythrocytosis, and, therefore, phlebotomy is not recommended routinely.[38] We direct the reader to a recently published guideline on the management of secondary erythrocytosis,[5] which recommends the following approach:

- Long-term oxygen therapy should be considered in patients with hypoxic lung disease.
- Testosterone should be discontinued in patients with moderate to severe testosterone-induced erythrocytosis and can be resumed at lower dosages once the hematocrit normalizes[11,39]
- Erythrocytosis after renal transplantation should be treated with an angiotensin-converting-enzyme inhibitor or angiotensin receptor blocker.
- Patients with cyanotic congenital heart disease or high-oxygen-affinity hemoglobins have physiologic erythrocytosis and should be under specialist care. These patients are at risk for thrombosis, although optimal target hematocrit values are unknown.
- Idiopathic erythrocytosis is a diagnosis of exclusion that carries a low risk of thrombosis and bleeding.[40] However, some experts recommend an arbitrary target hematocrit value of 0.45–0.55 for patients with symptomatic hyperviscosity or a history of thrombosis.[5]

Conclusion

Secondary erythrocytosis can be distinguished from PV in most patients with a focused clinical evaluation and, where available, determination of the erythropoietin level and JAK2 V617F mutation testing. Goals of treatment in PV are to alleviate symptoms,

reduce the risk of thromboembolism, and monitor patients for transformation to myelofibrosis or acute leukemia. The majority of patients with PV should be treated with low-dose ASA and phlebotomy to achieve a target hematocrit value of less than 0.45. Cytoreduction, most commonly with hydroxyurea, should be considered in patients at high risk for thrombosis. Treatment of secondary erythrocytosis should be directed at the underlying cause.

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