Overview and management of polycythemia vera

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Abstract:

Polycythemia vera is a chronic myeloproliferative disorder characterized by increased red blood cell mass. In this review we discuss the diagnosis, the risk groups and management strategies. We conducted a comprehensive review through the MEDLINE database by using of PubMed to identify articles containing “polycythemia vera” and “treatment” published in English language up to November, 2017. Although PV is a chronic, incurable illness, it can be managed effectively for extended periods of time. Careful medical supervision and treatment are designed to decrease hematocrit and platelet concentrations to regular or near-normal value, in order to regulate PV-related signs, reduce the danger for arterial and venous thrombotic events and various other difficulties, and avoid leukemic transformation. Patients with PV are stratified for their risk of thrombosis based on age and history of thrombosis. Those that are older compared to age 60 years or who have a history of thrombosis go to high risk, whereas patients younger than 60 years and without history of thrombosis are typically categorized as going to low risk. Patients with low-risk PV are usually phlebotomized and receive low-dose aspirin. These patients often report an instant improvement in their PV symptoms, including headaches, tinnitus, and dizziness after phlebotomy. For many low-risk patients, phlebotomy and aspirin may be the only form of therapy required. In contrast, patients with high-risk PV need medical therapy to decrease their hematocrit level permanently, remove the need for phlebotomy, and lower their risk for clotting.

Introduction:

Polycythemia vera (PV) is a chronic myeloproliferative problem characterized by a raised red blood cell mass (RCM), or erythrocytosis, which leads to hyperviscosity and an enhanced threat of thrombosis. Patients may offer with issues of pruritus after bathing, burning pains in the distal extremities (erythromelalgia), intestinal disruptions, or nonspecific problems such as weakness, headaches, or dizziness. Various other patients are detected after an incidental searching for of an elevated hemoglobin and/or hematocrit degree on a complete blood count.

The typical age of patients detected with PV is 60 years, although it could happen personallies in all age [1].PV occurs with a minor control in males. A thorough evaluation [1] reported the incidence of PV to be 2.3 each 100,000 individuals annually. As a result, a regular family physician can expect to earn a medical diagnosis of PV once or twice during his/her job, and will frequently have at least one patient in his or her patient panel who lugs the diagnosis. The severity of PV is highlighted by the truth that the average survival in untreated symptomatic patients after diagnosis is six to 18 months [2]. With treatment, the median survival is greater than 10 years [2].

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Methodology:

We conducted a comprehensive review through the MEDLINE database by using of PubMed to identify articles containing “polycythemia vera” and “treatment” published in English language up to November, 2017. Furthermore, references list of each included article were reviewed for more identical citation concerning our review.

Discussion:

- **Diagnosis**

PV must be presumed when hemoglobin and/or hematocrit levels are elevated (i.e., hemoglobin level greater than 18 g per dL [180 g per L] in white men and 16 g per dL [160 g per L] in blacks and women; hematocrit degree higher than 52 percent (0.52) in white males and 47 percent (0.47) in blacks and females) [3].PV likewise should be thought in patients with portal venous thrombosis and splenomegaly with or without thrombocytosis and leukocytosis. Other symptoms and signs are provided in (Table 1) [1], [4].

In making the medical diagnosis of PV, the medical professional needs to initially omit a secondary erythrocytosis [5], [6].Once a secondary reason is eliminated [7], the diagnosis of PV is made using a mix of significant and small standards defined by the Polycythemia Vera Study Group (PVSG). Although brand-new diagnostic modalities have been created, these criteria continue to be the criterion approach to diagnose PV [8].

Major diagnostic requirements consist of raised RCM, normal oxygen saturation, and the presence of splenomegaly. The test for RCM is a nuclear medication research including autologous mixture of radio-labeled red cell followed by serial phlebotomy to figure out distribution. Physicians may refer patients to a specialty research laboratory for this research.

TABLE 1. Signs and Symptoms of Polycythemia Vera[1],[4].

More Common	**Less Common**
o Hematocrit level > 52 percent (0.52) in white men, > 47 percent (0.47) in blacks and women o Hemoglobin level > 18 g per dL (180 g per L) in white men, > 16 g per dL (160 g per	o Bruising/epistaxis o Budd-Chiari syndrome o Erythromelalgia o Gout o Hemorrhagic events

L) in blacks and women) o Plethora o Pruritus after bathing o Splenomegaly o Weight loss o Weakness o Sweating	o Hepatomegaly o Ischemic digits o Thrombotic events o Transient neurologic complaints (headache, tinnitus, dizziness, blurred vision, paresthesias) o Atypical chest pain

Changes to these diagnostic requirements have been proposed. For example, decisions of RCM, characteristically given in milliliters per kilogram (mL per kg), can be misleading if the patient is obese, since body fat is reasonably avascular. The International Council for Standardization in Haematology (ICSH) has modified the RCM evaluation, advising the use of solutions integrating body surface area, weight, sex, and plasma quantity [8], [9], [10]. A patient with PV could have low oxygen saturation levels, due to the fact that it is feasible to have both PV and an unassociated hypoxic problem [1].Palpable splenomegaly is an important physical finding and significant requirement. However, palpation is just 58 percent delicate for medical diagnosis (i.e., if present, it will not be spotted by supervisors in 42 percent of instances). Specificity is better. This absence of level of sensitivity has resulted in some discussion about making use of imaging techniques to answer the question, although such a finding by imaging could be delegated to the status of a minor standard [10] Additionally, the minor criteria of leukocyte alkaline phosphatase (LAP) and product vitamin B12 and B12 binding ability might be decreased in the future as a result of inter-laboratory error pertaining to LAP and the unavailability of vitamin 10 B12 binding capacity. Moreover, neither of these criteria is sensitive nor certain.1 Nonetheless, the PVSG criteria stay the diagnostic requirement.

Lotion erythropoietin (EPO), bone marrow histopathology and karyotype, and the presence of endogenous erythroid nests (EEC) have been suggested as diagnostic tests for PV. Since PV is an

autonomous (i.e., EPO-independent) erythroid proliferation, lotion EPO levels in PV are reduced or typical [1], [5]. Low-serum EPO degrees for PV have a level of sensitivity of 70 percent and an uniqueness of 90 percent [1].

In PV, bone marrow shows characteristic histologic searchings for [10] and clonal cytogenetic abnormalities can be spotted [5].Use this test requires the schedule of a histologist that is particularly trained in marrow histology. Ultimately, EEC growth is based on the capacity of erythroid cells from peripheral blood and bone marrow examples in PV to expand in vitro without the enhancement of EPO. This unique finding, together with serum EPO levels, forms the basis for a brand-new diagnostic technique [5], but has the negative aspects of expense and restricted schedule [10].

Although product EPO levels and marrow biopsies could become a routine diagnostic choice, the PVSG standards stay the criterion of diagnosis. Assessment with a hematologist is appropriate to assist in medical diagnosis, and serum EPO degrees and bone marrow biopsy must be taken into consideration if offered.

- **Risk groups: what is high-risk PV?**

Treatment focused on the avoidance of thromboembolic occasions could include measures such as venesection to a target Hct of 045 (seldom, lower targets are made use of in symptomatic patients) and use low-dose aspirin.Further actions would certainly include the consideration of cytoreduction. Nonetheless, as a result of possible side- results and absence of demonstrated effectiveness at modifying condition progression occasions, cytoreduction ought to only be considered in patients who go to high danger of thrombohaemorrhagic occasions and, as a result, raised morbidity and reduced survival. This causes the question how risky PV need to be defined.

Lots of researches have been performed to recognize aspects which increase threat in PV. Older age and prior apoplexy are one of the most typical of these aspects and their value is supported by data from a huge potential study in PV, the ECLAP study, in which age > 65 years and a history of prior thrombosis were forecasters of cardiovascular events [11].Higher leucocyte counts were likewise connected with substandard end result in the ECLAP research; a white cell count (WCC) >15 9 109/ l was determined as a threat factor for thrombosis when compared with a WCC 15 9 109/ l has been found in an additional research [12] but not in various other series from the very same team [13]. Possibly confusingly, as talked about below, a reduced target WCC is utilized for response criteria [14].Various other markers have additionally been considered; for example, the JAK2 mutant allele problem has been associated with end result. This was not found to be associated with apoplexy however an allele worry over 50% was connected with danger of progression to myelofibrosis [15].Finally, bone marrow reticulin grade in PV has also been connected to thrombosis; patients with fibrosis were found to be much less most likely to have thrombotic occasions yet more likely to create myelofibrosis [16].

To clear up and boost risk stratification in PV, a retrospective evaluation of a large worldwide mate of more than 1500 PV patients was executed [18].This recognized threat variables for survival and leukaemic transformation. A prognostic model for survival was established that included age (67 years), leucocytosis (>15 9 109/ l) and venous thrombosis. Low-risk (0 factors) intermediate-risk and risky groups were identified. Points were designated for age >67 years, age 57-66 years (2 points), WCC >15 9 109/ l and venous thrombosis [18].This prognostic rating recognizes risky PV however the scoring is really greatly weighted by age and the data are accordinged to retrospective cohorts of patients dealt with in different centres. In parallel, experts developing trials and wanting to determine a risky team of patients who need to have

cytoreductive treatment have taken a more pragmatic approach. They have included those with any of the following features: age >60 years, prior thrombosis, considerable splenomegaly, platelet matter >1000 9 109/ l and existence of diabetes or hypertension calling for drug therapy study.Concluding that these patients must be taken into consideration risky and treated with cytoreductive treatment, this set of criteria is similar to that used for the BCSH definition, although the latter additionally consisted of those with bad resistance of venesection, symptomatic or modern splenomegaly, or various other proof of disease progression (e.g., fat burning, night sweats or thrombocytosis) [17]. The BCSH guidelines were the first time that symptoms or splenomegaly have been integrated right into specifying criteria for a high-risk PV group. These guidelines highlight thrombocytosis (without suggesting a numerical value), which is additionally not stated specifically by other groups. A much more exact interpretation of high danger continues to be extremely desirable however is currently evasive, and represents a top priority subject for attention.

- **Management recommendations**

Cornerstones of management, along with assessment, optimization of vascular danger, signs and symptom measurement and signs and symptom management, is venesection to preserve the Hct at less than 0,45 and use of low-dose pain killers. The limit for venesection has been sustained with proof from the randomized Cytoreductive Therapy in PV (CYTOPV) research study, where the patient team with a target Hct of <0,45 had lower rates of cardiovascular fatality and major thrombosis compared to the group with a greater target Hct [19].Low-dose pain killers has been advised for all patients without a details contra-indication, on the basis of evidence from the ECLAP research. Because, the combined threat of non-fatal cardio events and death was lower in those patients taking pain killers [20].Iron deficiency can be troublesome in patients took care of

with venesection just; iron supplements is unusually used and, when it is, an extremely cautious strategy with really reduced doses and close tracking is needed. If iron shortage stays problematic for a low-risk patient this could be thought about an indicator for cytoreductive therapy .There have formerly been concerns that iron-defi- cient erythrocytes are less deformable and could contribute to raised blood viscosity: nevertheless this has not been documented in an experiemntal setting [17].Finally, preferably patients must not be above the target Hct for a long term period of time therefore there must be understanding of this in organizing testimonials for these patients.

Concerning risky PV, as reviewed above, the BCSH treatment referrals based on readily available trial proof are:

1.For those less than 40 years of age: first line treatment interferon alpha (IFN-a), second line hydroxycarbamide (HC) or anagrelide.

2.For those between the ages of 40 and 75 years: first line HC and second line IFN-a or anagrelide.

3.For those over the age of 75 years: first line HC and second line 32P or intermittent low dose busulphan.

The age ranges selected were those that the BCSH team really felt served to the professional neighborhood when the support was generated [17].The European LeukaemiaNet(ELN) referrals are broadly similar but supply IFN-a to a broader variety of patients as first-line treatment [16].A number of current trials, reviewed below,could need to be taken into consideration in future when making treatment recommendations, particularly concerning the relative benefits of HC and IFNa.

Therapy targets for WCC and platelets have additionally been formulated by specialist agreement [21], however lack proven effectiveness. Attainment of a so-called full haematological reaction, using previous definitions [22] has not always translated right into clinical benefit (Hernandez-Boluda et alia, 2011). Additionally, these reaction standards were developed for clinical tests

rather than routine medical method and, particularly, the target WCC stays controversial. As talked about above, there is proof that a WCC >15 9 109/ l is associated with 'high-risk condition' and it is vague why a treatment target of 10 9 109/ l is established without clear sustaining data. Of note, whilst the CYTO-PV research study provided evidence of advantage for a rigorous Hct target; leucocyte counts for both CYTO-PV cohorts varied. The restrictive Hct group had a median WCC of 7,5-8,6 9 109/ l throughout the research study and the higher Hct team had a mean WCC of 8,6-9,5 9 109/ l [23].These data could indicate a role for reducing the target WCC. Further problems with existing feedback requirements is that they just specify dynamic illness as improvement. Significant surge in WCC or spleen dimension, without transformation, is not specified as development, nor is development of thrombosis. Additionally, for functional purposes, if a patient has partial reaction and then needs a venesection they are defined as revealing no feedback. These reaction targets likewise could not conveniently be made use of for patients who offer with regular blood counts and significant thrombosis, especially splanchnic vein thrombosis; more information are required. Evidence for the very best management of these patients is lacking; our existing technique is to lower the blood counts much more aggressively and utilize anticoagulation as appropriate.

Conclusion:

Although PV is a chronic, incurable illness, it can be managed effectively for extended periods of time. Careful medical supervision and treatment are designed to decrease hematocrit and platelet concentrations to regular or near-normal value, in order to regulate PV-related signs, reduce the danger for arterial and venous thrombotic events and various other difficulties, and avoid leukemic transformation.Patients with PV are stratified for their risk of thrombosis based on age and history of thrombosis. Those that are older compared to age 60 years or who have a history of

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Reference:

1. Tefferi A. Polycythemia vera: a comprehensive review and clinical recommendations. Mayo Clin Proc. 2003;78:174–94.
2. Berk PD, Goldberg JD, Donovan PB, Fruchtman SM, Berlin NI, Wasserman LR. Therapeutic recommendations in polycythemia vera based on Polycythemia Vera Study Group protocols. Semin Hematol. 1986;23:132–43.
3. Lamy T, Devillers A, Bernard M, Moisan A, Grulois I, Drenou B, et al. Inapparent polycythemia vera: an unrecognized diagnosis. Am J Med. 1997;102:14–20.
4. Hoffman R. Hematology: basic principles and practice. 3d ed. New York: Churchill Livingstone, 2000:1130–55.
5. Tefferi A. Diagnosing polycythemia vera: a paradigm shift. Mayo Clin Proc. 1999;74:159–62.
6. Murphy S. Diagnostic criteria and prognosis in polycythemia vera and essential thrombocythemia. Semin Hematol. 1999;36(1 Suppl 2):9–13.
7. Polycythemia: primary and secondary. In: Kjeldsberg CR. Practical diagnosis of hematologic disorders. 3d ed. Chicago: ASCP Press, 2000:121.
8. Berlin NI. Polycythemia vera: diagnosis and treatment 2002. Expert Rev Anti-cancer Ther. 2002;2:330–6.
9. Pearson TC, Guthrie DL, Simpson J, Chinn S, Barosi G, Ferrant A, et al. Interpretation of measured red cell mass and plasma volume in adults: Expert Panel on Radionuclides of the International Council for Standardization in Haematology. Br J Haematol. 1995;89:748–56.

10. Pearson TC. Evaluation of diagnostic criteria in polycythemia vera. Semin Hematol. 2001;38(1 Suppl 2):21–4.
11. Marchioli, R., Finazzi, G., Landolfi, R., Kutti, J., Gisslinger, H., Patrono, C., Marilus, R., Villegas, A., Tognoni, G. & Barbui, T. (2005) Vascular and neoplastic risk in a large cohort of patients with polycythemia vera. Journal of Clinical Oncology, 23, 2224–2232.
12. Gangat, N., Strand, J., Li, C.Y., Wu, W., Pardanani, A. & Tefferi, A. (2007) Leucocytosis in polycythaemia vera predicts both inferior survival and leukaemic transformation. British Journal of Haematology, 138, 354–358.
13. Gangat, N., Wolanskyj, A.P., Schwager, S.M., Hanson, C.A. & Tefferi, A. (2009) Leukocytosis at diagnosis and the risk of subsequent thrombosis in patients with low-risk essential thrombocythemia and polycythemia vera. Cancer, 115, 5740–5745.
14. Barosi, G., Mesa, R.A., Thiele, J., Cervantes, F., Campbell, P.J., Verstovsek, S., Dupriez, B., Levine, R.L., Passamonti, F., Gotlib, J., Reilly, J.T., Vannucchi, A.M., Hanson, C.A., Solberg, L.A., Orazi, A., Tefferi, A. & International Working Group for Myelofibrosis Research and Treatment (IWG-MRT). (2008a) Proposed criteria for the diagnosis of post-polycythemia vera and post-essential thrombocythemia myelofibrosis: a consensus statement from the International Working Group for Myelofibrosis Research and Treatment. Leukemia, 22, 437–438.
15. Passamonti, F., Rumi, E., Pietra, D., Elena, C., Boveri, E., Arcaini, L., Roncoroni, E., Astori, C., Merli, M., Boggi, S., Pascutto, C., Lazzarino, M. & Cazzola, M. (2010) A prospective study of 338 patients with polycythemia vera: the impact of JAK2 (V617F) allele burden and leukocytosis on fibrotic or leukemic disease transformation and vascular complications. Leukemia, 24, 1574– 1579.
16. Barbui, T., Thiele, J., Passamonti, F., Rumi, E., Boveri, E., Randi, M.L., Bertozzi, I., Marino, F., Vannucchi, A.M., Pieri, L., Rotunno, G., Gisslinger, H., Gisslinger, B., Mullauer, L., Finazzi, G., Carobbio, A., Gianatti, A., Ruggeri, M., Nichele, I., D'Amore, E., Rambaldi, A. & Tefferi, A. (2012) Initial bone marrow reticulin fibrosis in polycythemia vera exerts an impact on clinical outcome. Blood, 119, 2239–2241.
17. McMullin, M.F., Bareford, D., Campbell, P., Green, A.R., Harrison, C., Hunt, B., Oscier, D., Polkey, M.I., Reilly, J.T., Rosenthal, E., Ryan, K., Pearson, T.C. & Wilkins, B. (2005) Guidelines for the diagnosis, investigation and management of polycythaemia/erythrocytosis. British Journal of Haematology, 130, 174–195.
18. Tefferi, A., Rumi, E., Finazzi, G., Gisslinger, H., Vannucchi, A.M., Rodeghiero, F., Randi, M.L., Vaidya, R., Cazzola, M., Rambaldi, A., Gisslinger, B., Pieri, L., Ruggeri, M., Bertozzi, I., Sulai, N.H., Casetti, I., Carobbio, A., Jeryczynski, G., Larson, D.R., Mullauer, L., Pardanani, A., Thiele, J., Passamonti, F. & Barbui, T. (2013) Survival and prognosis among 1545 patients with contemporary polycythemia vera: an international study. Leukemia, 27, 1874– 1881.
19. Marchioli, R., Finazzi, G., Specchia, G., Cacciola, R., Cavazzina, R., Cilloni, D., De Stefano, V., Elli, E., Iurlo, A., Latagliata, R., Lunghi, F., Lunghi, M., Marfisi, R.M., Musto, P., Masciulli, A., Musolino, C., Cascavilla, N., Quarta, G., Randi, M.L., Rapezzi,

D., Ruggeri, M., Rumi, E., Scortechini, A.R., Santini, S., Scarano, M., Siragusa, S., Spadea, A., Tieghi, A., Angelucci, E., Visani, G., Vannucchi, A.M. & Barbui, T. (2013) Cardiovascular events and intensity of treatment in polycythemia vera. The New England Journal of Medicine, 368, 22–33.

20. Landolfi, R., Marchioli, R., Kutti, J., Gisslinger, H., Tognoni, G., Patrono, C. & Barbui, T. (2004) Efficacy and safety of low-dose aspirin in polycythemia vera. The New England Journal of Medicine, 350, 114–124.
21. Barosi, G., Mesa, R., Finazzi, G., Harrison, C., Kiladjian, J.J., Lengfelder, E., McMullin, M.F., Passamonti, F., Vannucchi, A.M., Besses, C., Gisslinger, H., Samuelsson, J., Verstovsek, S., Hoffman, R., Pardanani, A., Cervantes, F., Tefferi, A. & Barbui, T. (2013) Revised response criteria for polycythemia vera and essential thrombocythemia: an ELN and IWG-MRT consensus project. Blood, 121, 4778–4781.
22. Barosi, G., Birgegard, G., Finazzi, G., Griesshammer, M., Harrison, C., Hasselbalch, H.C., Kiladjian, J.J., Lengfelder, E., McMullin, M.F., Passamonti, F., Reilly, J.T., Vannucchi, A.M. & Barbui, T. (2009) Response criteria for essential thrombocythemia and polycythemia vera: result of a European LeukemiaNet consensus conference. Blood, 113, 4829–4833.
23. Marchioli, R., Finazzi, G., Specchia, G., Cacciola, R., Cavazzina, R., Cilloni, D., De Stefano, V., Elli, E., Iurlo, A., Latagliata, R., Lunghi, F., Lunghi, M., Marfisi, R.M., Musto, P., Masciulli, A., Musolino, C., Cascavilla, N., Quarta, G., Randi, M.L., Rapezzi, D., Ruggeri, M., Rumi, E., Scortechini, A.R., Santini, S., Scarano, M., Siragusa, S., Spadea, A., Tieghi, A., Angelucci, E., Visani, G., Vannucchi, A.M. & Barbui, T. (2013) Cardiovascular events and intensity of treatment in polycythemia vera. The New England Journal of Medicine, 368, 22–33.