AN OVERVIEW OF ESSENTIAL THROMBOCYTOSIS-EPIDEMIOLOGY TO MANAGEMENT.

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ABSTRACT

Essential thrombocytosis is a myeloproliferative neoplasm, which is also known as essential thrombocythemia (ET). It was initially called as hemorrhagic thrombocythemia when it was identified in 1934. The diagnosis of ET is carried out when the level of platelets is more than 45,000, which was put forwarded by WHO. ET is distinguished by elevation in platelet levels and hyperplasia of the hematopoietic cells producing platelets in the bone marrow. In ET, the patients of more than 60 years and who has a past medical history of thrombosis with increased likely to have the risk of bleeding are regarded to have high risk of thrombosis. In this condition, transformation from one disorder to other is noted. So, the management of ET should be targeted in a way to prevent bleeding and thrombosis eliminating the chance of transformation to other disorder. The development of new models for risk stratification takes the genomic components in regards and combine them with traditional risk factors leading to the generation of precise and personalized prognosis. Also, provides greater chance to select interventions for the patients having high-risk. More studies are needed to develop systems to distinguish between the patients who are susceptible for disease transformation. So, it is possible to start the therapy according to this condition as early as possible and counteract the disease transformation.

KEYWORDS: Essential thrombocytosis, essential thrombocythemia, myelofibrosis, prognosis and transformation.

INTRODUCTION

Essential thrombocytosis (ET) is a myeloproliferative neoplasm, which is also known as essential thrombocythemia (ET). It was initially called as hemorrhagic thrombocythemia when it was identified in 1934. The diagnosis of ET is carried out when the level of platelets is more than 45,000, which was put forwarded by WHO. ET is distinguished by elevation in platelet levels and hyperplasia of the hematopoietic cells producing platelets in the bone marrow[1.] In 1951, Damesheck categorised ET as myeloproliferative neoplasm. It was kept together with polycythemia vera, primary mylofibrosis and chronic myeloid leukemia[2]. It is characterized by the mutation of JAK2 V617F in around 60% patients. In ET, the patients of more than 60 years and who has a past medical history of thrombosis with increased likely to have the risk of bleeding are regarded to have high risk of thrombosis[3]. In this condition, transformation from one disorder to other is noted. But ET is more familiar when compared to the other disorders as there is an elevated risk for vascular complications which leads to the influence in quality of patient's life than survival[4]. In 10 years, it is noted that 4-8% patients are transformed to myelofibrosis[5, 6]. So, the management of ET should be targeted in a way to prevent bleeding and thrombosis eliminating the chance of transformation to other disorder. In this article, the overview, diagnosis, pathophysiology and management of ET is discussed.

EPIDEMIOLOGY OF ET

It is a rare disease and occurring with an incidence of 1-5 person in one lakh population[7-9] and prevalence of 38-57 persons in one lakh population. ET is more common in female population than male population[10, 11]. The age of onset of ET is 50-60 years but it is also diagnosed in young population to a lower extent[12]. The survival rate of ET patients shown only mild difference when compared with normal population[8, 13]. ET patients less than 60 years old are related with myelofibrosis and reduction in leukemic transformation when compared with more than 60 years patients[6, 14].

CLINICAL FEATURES OF ET

The important feature of ET is the risk of thrombosis concomitant with the risk of arterial or venous complications. In a study conducted with ET patients diagnosed by WHO, 18% of patients were affected with thrombosis[15]. But the frequency of thrombosis in ET patients varied from one study to another studies. An international study conducted in 2012 with 891 patients who were diagnosed with ET reported that 6.17% of major thrombosis noted[16]. Even many reports shown that bleeding occurred in 37% of patients diagnosed with ET each year. Elliot and Tefferi also stated in 2005 that the bleeding events are equal to 0.33% for one person in one year[17]. The common sites in which the bleeding occurs are urogenital, gastrointestinal and CNS[18, 19]. The other common clinical feature of ET are shown in Fig. 1.

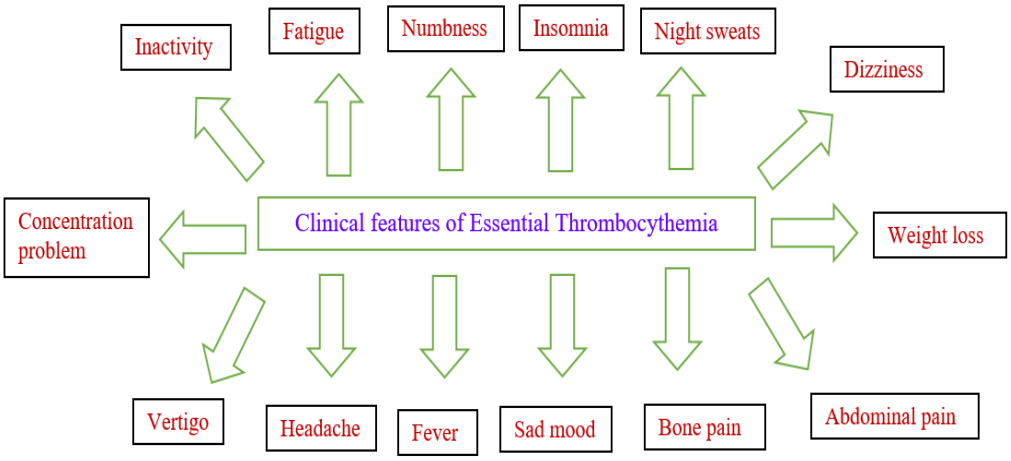

Figure 1. Other common clinical features of ET

DIAGNOSIS OF ET

In the diagnosis of ET, it is important to eliminate many hereditary and neoplastic sources. The other conditions which may be similar to ET are CML, CIMF, PV and myelodysplastic syndromes. The cause of reactive thrombocytosis is due to hemolytic anemia, iron deficiency anemia, rebound alcohol withdrawal, infections, inflammatory diseases and drug reactions[20, 21]. Factors favoring ET are shown in Fig. 2:

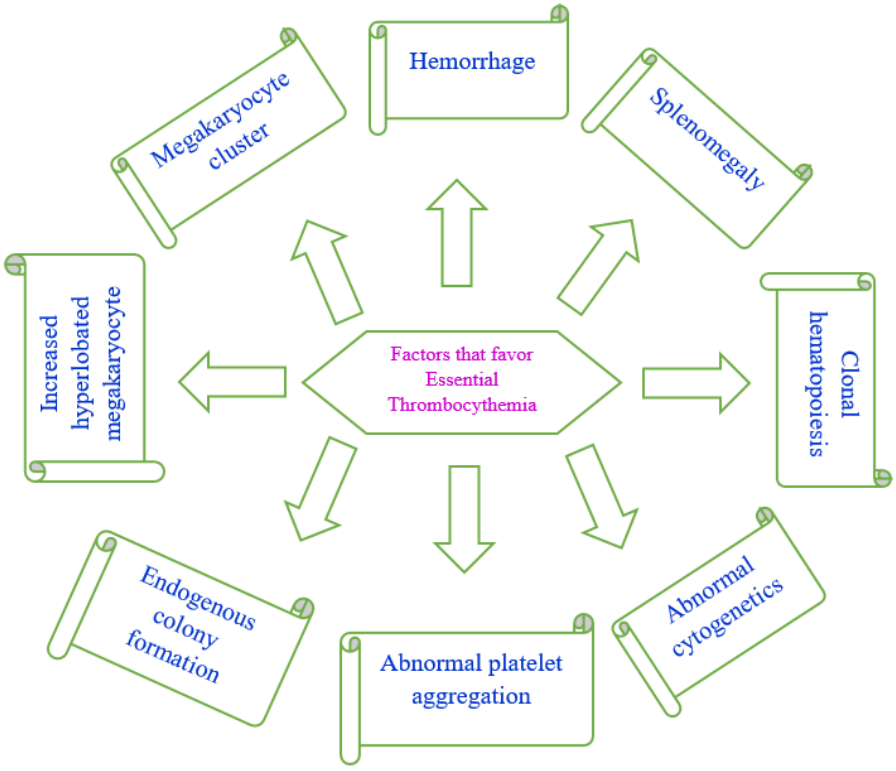

Figure 2. Factors favoring ET.

The WHO recommended diagnostic criteria for ET is shown in Figure. 3.

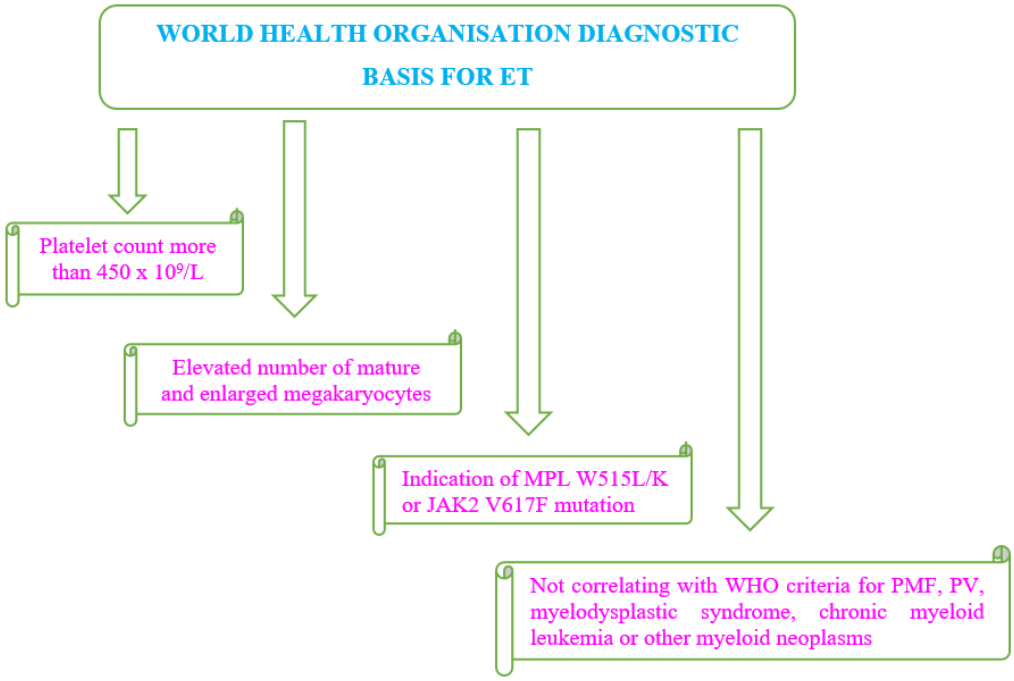

Figure 3. WHO diagnostic basis for ET

PROGNOSIS OF ET

The information on long term survival of ET is still lacking. It is found in many retrospective studies that death rates of patients diagnosed with ET is close to the control population for the first 10 years but it is increasing after 10 years. This increase in death rate is due to the complications caused by ET including thrombosis and myelofibrosis transformation[22].

The risk factors for ET are more than 60 years of age, past history of thrombosis, diabetes mellitus, hypertension, tobacco use and hyperlipidemia. The leukocyte count during diagnosis is considered as the independent factor for the prediction of thrombosis in ET diagnosed patients[23]. It is found that the MPL mutation has greater ability to cause arterial thrombosis than negatively diagnosed JAK2 or MPL patients[24].

PT-1 trials identified that elevated levels of reticulin fibrosis in the bone marrow during the diagnosis is considered as an independent factor for the hemorrhagic or thrombotic complications[25]. In the multivariate analysis, it is found that the increase level of platelets, WBCs and reticulin in bone marrow during the diagnosis is an important factors for the prediction of hemorrhage and thrombosis.

TREATMENT OF ET

Aspirin is used in the management of ET. The recommended dosage is 75mg to 100 mg, once a day for the reduction of thrombosis in myeloproliferative neoplasms (MPNs). It also benefits for the symptomatic relief from erythromelalgia[26]. In a retrospective observational study, it is reported that the use of aspirin in low-risk ET showed reduced thrombosis in mutated ET with JAK2 V617F whereas the patients who has not taken aspirin had no effects on bleeding[27]. But in the patients diagnosed with ET of CALR mutation, it was shown that there was no variation in thrombotic rate when it was compared with aspirin administered and not administered group but the bleeding events were greater in aspirin administered group[28].

In MPL- mutated ET and low risk JAK2 ET, it is recommended to administer aspirin. It is advised to monitor bruising and bleeding the patients if their platelet level is 1000-1500 x 109/L. Moreover, aspirin is recommended in the patients with cardiovascular diseases and in elderly patients but it should be abstain from patient with the platelet count of 1000 x 109/L. There is also a possibility of developing resistance to aspirin therapy due to the elevated platelet turnover and renewal of cyclooxygenase-1 enzyme[29, 30]. This type of aspirin resistance can be overcome by administration of aspirin with the increase in dosage of 75-100 mg, twice a day.

In a randomized trial conducted with 243 patients diagnosed with ET with the treatment with aspirin showed that the level of thromboxane B2 specified that the patients administered with aspirin, once a day had insignificant inhibition of platelets. The patients administered aspirin for twice a day had suggestive improvement in the inhibition of platelets with well-tolerance. The patients administered aspirin for thrice a day had no other benefits in inhibition of platelets whereas it caused gastrointestinal discomfort at higher rates[30, 31].

Another therapy used to reduce thrombosis in ET diagnosed patients and high-risk patients is cytoreduction therapy[29]. But the regular use of cytoreduction is not recommended in the patients without high-risk for thrombosis. Even though cytoreduction is considered in some conditions such as increasing platelet counts, elevated risk for hemorrhage and major thrombocytosis. The conditions in which cytoreduction should be commenced are when the platelet level is greater than 1500 x 109/L and in case of severe headaches in low vascular risk patients[34].

In low risk ET patients who were in need for cytoreduction, the choices are anagrelide, hydroxycarbamide and interferon-alfa. An anti-metabolite, hydroxycarbamide is an orally administered well tolerated medication having common side-effects such as GI upset, mouth ulcers, myelosuppression, leg sores, and allergic reactions. The safety and efficacy of this medication in high risk ET patients is distinguished well[33, 35]. As this drug is teratogenic, the administration of this drug should be avoided in pregnant patients and those who are planning for pregnancy[36]. There is also a chance of developing elevated risk for the occurrence of non-melanoma skin cancer[37].

The replacement for hydrocycarbamide is anagrelide[35]. This is a second line drug in ET diagnosed patients[34]. It has more withdrawal incidences caused by the side-effects of this drug. At low doses, this drug is well tolerated and it is also used concomitantly with hydroxycarbamide. But is elevates the side-effects when the doses are increased which includes palpitations and headaches. This drug is contraindicated in pregnancy patients[37]. But coming to herbal point of view, many traditional plants are also known to treat wide range of cancers which includes Artabotrys hexapetalus. We also seek many research regarding this for further proceedings against essential thrombocytosis.

Another drug used in the treatment of MPN for many years is interferon-alpha. This drug is used as subcutaneous injection with side-effects of mood disturbance and flu-like symptom[38]. The efficacy of tis drug has no shown in randomized studies but it is licensed for the management for ET patients. The pegylated interferon-alfa has good efficacy and is tolerated in ET patients. This therapy has an advantage over cytoreducion therapy in younger ET patients.

Radioactive phosphorus and busulfan are other agents used in cytoreduction therapy but they have elevated risk of transforming to leukemia. So they should be avoided in low risk ET patients[39-41].

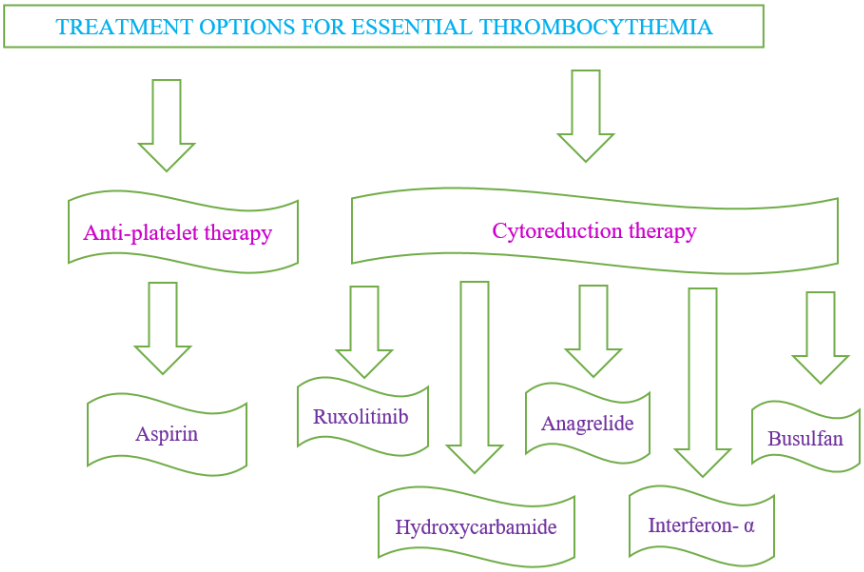

Figure 3. Treatment options for ET

CONCLUSION

The management of ET is still lacking at this time and it involves treatment by classifying ET into low-risk and high-risk based on the vascular events. Conventional therapy is the one which is targeted in case of low-risk ET. This involves the use of an anti-platelet agent aspirin. For the patients who lacks factors predicting high-risk for thrombosis, the cytoreduction therapy will not provide excess defense against the vascular events. However, for the patients with low-risk ET who are requiring cytoreduction therapy, there are several agents that are accessible with greater efficacy proved in clinical trials. The risk-stratification and standard diagnostic approaches were designed in the pregenomic period. It is known that the description of the disease is more detail in the genomic categorization when compared to the standard systems used for diagnosis. Moreover, development of new models for risk stratification takes the genomic components in regards and combine them with traditional risk factors leading to the generation of precise and personalized prognosis. Also, provides greater chance to select interventions for the patients having high-risk. More studies are needed to develop systems to distinguish between the patients who are susceptible for disease transformation. So, it is possible to start the therapy according to this condition as early as possible and counteract the disease transformation.

CONFLICT OF INTEREST:

The authors have no conflicts of interest regarding this investigation**.**

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REFERENCES

1. Ashorobi D, Gohari P. Essential Thrombocytosis. 2022 Jun 21. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan–. PMID: 30969531.
2. DAMESHEK W. Some speculations on the myeloproliferative syndromes. Blood. 1951 Apr;6(4):372-5. PMID: 14820991.
3. Cervantes F. Management of essential thrombocythemia. Hematology Am Soc Hematol Educ Program. 2011;2011:215-21. doi: 10.1182/asheducation-2011.1.215. PMID: 22160037.
4. Cervantes F, Passamonti F, Barosi G. Life expectancy and prognostic factors in the classic BCR/ABL-negative myeloproliferative disorders. Leukemia. 2008 May;22(5):905-14. doi: 10.1038/leu.2008.72. Epub 2008 Apr 3. PMID: 18385755.
5. Cervantes F et al. Myelofibrosis with myeloid metaplasia following essential thrombocythaemia: actuarial probability, presenting characteristics and evolution in a series of 195 patients. Br J Haematol. 2002 Sep;118(3):786-90. doi: 10.1046/j.1365-2141.2002.03688.x. PMID: 12181046.
6. Passamonti F et al. Prognostic factors for thrombosis, myelofibrosis, and leukemia in essential thrombocythemia: a study of 605 patients. Haematologica. 2008 Nov;93(11):1645-51. doi: 10.3324/haematol.13346. Epub 2008 Sep 11. PMID: 18790799.
7. Abdulkarim K et al. Risk factors for vascular complications and treatment patterns at diagnosis of 2389 PV and ET patients: Real-world data from the Swedish MPN Registry. Eur J Haematol. 2017 Jun;98(6):577-583. doi: 10.1111/ejh.12873. Epub 2017 Apr 3. PMID: 28251679.
8. Roman E et al. Myeloid malignancies in the real-world: Occurrence, progression and survival in the UK's population-based Haematological Malignancy Research Network 2004-15. Cancer Epidemiol. 2016 Jun;42:186-98. doi: 10.1016/j.canep.2016.03.011. Epub 2016 Apr 16. PMID: 27090942; PMCID: PMC4911595.
9. Hultcrantz M et al. Incidence of myeloproliferative neoplasms - trends by subgroup and age in a population-based study in Sweden. J Intern Med. 2020 Apr;287(4):448-454. doi: 10.1111/joim.13019. Epub 2020 Jan 11. PMID: 31927786; PMCID: PMC7598815.
10. Mehta J, Wang H, Iqbal SU, Mesa R. Epidemiology of myeloproliferative neoplasms in the United States. Leuk Lymphoma. 2014 Mar;55(3):595-600. doi: 10.3109/10428194.2013.813500. Epub 2013 Jul 29. PMID: 23768070.
11. Frederiksen H, Szépligeti S, Bak M, Ghanima W, Hasselbalch HC, Christiansen CF. Vascular Diseases In Patients With Chronic Myeloproliferative Neoplasms - Impact Of Comorbidity. Clin Epidemiol. 2019 Nov 1;11:955-967. doi: 10.2147/CLEP.S216787. PMID: 31807079; PMCID: PMC6830370.
12. Campo E et al. WHO classification of tumours of haematopoietic and lymphoid tissues. Swerdlow SH, editor. Lyon, France: International agency for research on cancer; 2008 Sep 20.
13. Barbui T et al. Survival and disease progression in essential thrombocythemia are significantly influenced by accurate morphologic diagnosis: an international study. J Clin Oncol. 2011 Aug 10;29(23):3179-84. doi: 10.1200/JCO.2010.34.5298. Epub 2011 Jul 11. PMID: 21747083.
14. Boddu P et al. Patient characteristics and outcomes in adolescents and young adults with classical Philadelphia chromosome-negative myeloproliferative neoplasms. Ann

Hematol. 2018 Jan;97(1):109-121. doi: 10.1007/s00277-017-3165-9. Epub 2017 Nov 15. PMID: 29143068.
15. Scherber R et al. The Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF): international prospective validation and reliability trial in 402 patients. Blood. 2011 Jul 14;118(2):401-8. doi: 10.1182/blood-2011-01-328955. Epub 2011 May 2. PMID: 21536863.
16. Accurso V et al. Cardiovascular Risk in Essential Thrombocythemia and Polycythemia Vera: Thrombotic Risk and Survival. Mediterr J Hematol Infect Dis. 2020 Jan 1;12(1):e2020008. doi: 10.4084/MJHID.2020.008. PMID: 31934318; PMCID: PMC6951352.
17. Finazzi G et al. Incidence and risk factors for bleeding in 1104 patients with essential thrombocythemia or prefibrotic myelofibrosis diagnosed according to the 2008 WHO criteria. Leukemia. 2012 Apr;26(4):716-9. doi: 10.1038/leu.2011.258. Epub 2011 Sep 16. PMID: 21926959.
18. Elliott MA, Tefferi A. Thrombosis and haemorrhage in polycythaemia vera and essential thrombocythaemia. Br J Haematol. 2005 Feb;128(3):275-90. doi: 10.1111/j.1365-2141.2004.05277.x. PMID: 15667529.
19. Budde U, van Genderen PJ. Acquired von Willebrand disease in patients with high platelet counts. Semin Thromb Hemost. 1997;23(5):425-31. doi: 10.1055/s-2007-996119. PMID: 9387201.
20. Jaffe, E. S et al. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues.Lyon, France: IARC Press; 2001. World Health Organization Classification of Tumours; vol 3.
21. Thiele J, Kvasnicka HM, Orazi A. Bone marrow histopathology in myeloproliferative disorders--current diagnostic approach. Semin Hematol. 2005 Oct;42(4):184-95. doi: 10.1053/j.seminhematol.2005.05.020. PMID: 16210032.
22. Wolanskyj AP et al. Essential thrombocythemia beyond the first decade: life expectancy, long-term complication rates, and prognostic factors. Mayo Clin Proc. 2006;81:159–166.
23. Barbui T, Carobbio A, Rambaldi A, Finazzi G. Perspectives on thrombosis in essential thrombocythemia and polycythemia vera: is leukocytosis a causative factor? Blood. 2009:114:759–763.
24. Vannucchi AM et al. Characteristics and clinical correlates of MPL 515W>L/K mutation in essential thrombocythemia. Blood. 2008;112:844–847.
25. Campbell PJ et al. Reticulin accumulation in essential thrombocythemia: prognostic significance and relationship to therapy. J Clin Oncol. 2009;27:2991–2999.
26. Michiels JJ et al. Platelet-mediated erythromelalgic, cerebral, ocular and coronary microvascular ischemic and thrombotic manifestations in patients with essential thrombocythemia and polycythemia vera: a distinct aspirin-responsive and coumadin-resistant arterial thrombophilia. Platelets. 2006 Dec;17(8):528-44. doi: 10.1080/09537100600758677. PMID: 17127481.
27. Alvarez-Larrán A et al. Antiplatelet therapy versus observation in low-risk essential thrombocythemia with a CALR mutation. Haematologica. 2016 Aug;101(8):926-31. doi: 10.3324/haematol.2016.146654. Epub 2016 May 12. PMID: 27175028; PMCID: PMC4967571.
28. Harrison CN et al. British Committee for Standards in Haematology. Guideline for investigation and management of adults and children presenting with a thrombocytosis. Br J Haematol. 2010 May;149(3):352-75. doi: 10.1111/j.1365-2141.2010.08122.x. Epub 2010 Mar 15. PMID: 20331456.

29. Robinson AJ, Godfrey AL. Low-Risk Essential Thrombocythemia: A Comprehensive Review. Hemasphere. 2021 Jan 27;5(2):e521. doi: 10.1097/HS9.0000000000000521. Erratum in: Hemasphere. 2022 Jan 31;6(2):e689. PMID: 33880431; PMCID: PMC8051994.
30. Dragani A et al. The contribution of cyclooxygenase-1 and -2 to persistent thromboxane biosynthesis in aspirin-treated essential thrombocythemia: implications for antiplatelet therapy. Blood. 2010 Feb 4;115(5):1054-61. doi: 10.1182/blood-2009-08-236679. Epub 2009 Nov 3. PMID: 19887674.
31. Dillinger JG et al. Twice daily aspirin to improve biological aspirin efficacy in patients with essential thrombocythemia. Thromb Res. 2012 Jan;129(1):91-4. doi: 10.1016/j.thromres.2011.09.017. Epub 2011 Oct 19. PMID: 22014557.
32. Pascale S et al. Aspirin-insensitive thromboxane biosynthesis in essential thrombocythemia is explained by accelerated renewal of the drug target. Blood. 2012 Apr 12;119(15):3595-603. doi: 10.1182/blood-2011-06-359224. Epub 2012 Jan 10. PMID: 22234683.
33. Cortelazzo S et al. Hydroxyurea for patients with essential thrombocythemia and a high risk of thrombosis. N Engl J Med. 1995 Apr 27;332(17):1132-6. doi: 10.1056/NEJM199504273321704. PMID: 7700286.
34. Barbui T et al. Philadelphia chromosome-negative classical myeloproliferative neoplasms: revised management recommendations from European LeukemiaNet. Leukemia. 2018 May;32(5):1057-1069. doi: 10.1038/s41375-018-0077-1. Epub 2018 Feb 27. PMID: 29515238; PMCID: PMC5986069.
35. Harrison CN et al. United Kingdom Medical Research Council Primary Thrombocythemia 1 Study. Hydroxyurea compared with anagrelide in high-risk essential thrombocythemia. N Engl J Med. 2005 Jul 7;353(1):33-45. doi: 10.1056/NEJMoa043800. PMID: 16000354.
36. Robinson SE, Harrison CN. How we manage Philadelphia-negative myeloproliferative neoplasms in pregnancy. Br J Haematol. 2020 May;189(4):625-634. doi: 10.1111/bjh.16453. Epub 2020 Mar 9. PMID: 32150650.
37. Barbui T et al. negative myeloproliferative neoplasms (MPN-K). A nested case-control study. Leukemia. 2019 Aug;33(8):1996-2005. doi: 10.1038/s41375-019-0487-8. Epub 2019 May 29. PMID: 31142846.
38. Quintás-Cardama A et al. Pegylated interferon alfa-2a yields high rates of hematologic and molecular response in patients with advanced essential thrombocythemia and polycythemia vera. J Clin Oncol. 2009 Nov 10;27(32):5418-24. doi: 10.1200/JCO.2009.23.6075. Epub 2009 Oct 13. PMID: 19826111; PMCID: PMC4881362.
39. Björkholm M et al.Treatment-related risk factors for transformation to acute myeloid leukemia and myelodysplastic syndromes in myeloproliferative neoplasms. J Clin Oncol. 2011 Jun 10;29(17):2410-5. doi: 10.1200/JCO.2011.34.7542. Epub 2011 May 2. PMID: 21537037; PMCID: PMC3107755.
40. Stott H et al. Acute leukaemia after busulphan. Br Med J. 1977 Dec 10;2(6101):1513-7. doi: 10.1136/bmj.2.6101.1513. PMID: 589308; PMCID: PMC1632782.
41. Campbell PJ, Green AR. Management of polycythemia vera and essential thrombocythemia. Hematology Am Soc Hematol Educ Program. 2005:201-8. doi: 10.1182/asheducation-2005.1.201. PMID: 16304381.