MINISTRY OF HEALTH OF THE REPUBLIC OF MOLDOVA

„NICOLAE TESTEMITANU" STATE UNIVERSITY OF MEDICINE AND PHARMACY

Musteata Vasile, Robu Maria, Musteata Larisa

BIOLOGY, DIAGNOSIS AND TREATMENT OF POLYCYTHEMIA VERA

(Methodical guidelines for students)

CHISINAU, 2021

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Authors:

Musteață Vasile, Ph.D. in Medical Sciences, associate professor;
Robu Maria, Ph.D. in Medical Sciences, associate professor;
Musteata Larisa, Ph.D. in Medical Sciences, associate professor.

Reviewers:

Nicolae Ghidirim, Ph.D. in Medical Sciences, associate professor;
Buruiană Sanda, Ph.D. in Medical Sciences, associate professor.

Copy editors:

Cazac Viorica, university assistant, Ph.D. student;
Maxian Liuba, university assistant.

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CONTENTS

LIST OF ABBREVIATIONS

PV – polycythemia vera,
CD – cluster of differentiation,
BM – bone marrow,
JAK – Janus kinases,
FISH–fluorescence in situ hybridization,
EPO – erythropoietin,
CT – computed tomography,
ECOG – The Eastern Cooperative Oncology Group,
WHO – Word Health Organisation,
BCR-ABL1 – breakpoint cluster region-Abelson 1,
JAK2 – Janus kinase 2,
MPNs – myeloproliferative neoplasms,
PMF – primary myelofibrosis,
ET – essential thrombocythemia,
CML – chronic myeloid leukemia,
CBC – complete blood count,
LDH – lactate dehydrogenase,
RT-QPCR – reverse transcriptase quantitative polymerasechain reaction,
HSCT – hematopoietic stem cell transplantation,
OS – overall survival,
RFS – relapse free survival,
SAChT – single-agent chemotherapy,
IFN-α – Interferon-α

Definition

Polycythemia vera (PV) is a chronic myeloproliferative neoplasm, which emerges due stem cell disorder characterized by hyperplasia of all three major myeloid cell lineages. The central pathological feature of PV is an expansion in the total red cell mass, although elevations in the platelet and/or neutrophil counts are relatively common [1]. The clinical evolution of PV (plethora, engorged veins) was appreciated long before the disease was formally described by Vaquez in 1892 [2] and subsequently by Osler in 1903 [3]. By 1910, it was evident that erythrocytosis in PV was commonly associated with leukocytosis, thrombocytosis, and panmyeloid hyperplasia of the BM [4, 5, 6]. The development of myelofibrosis and acute leukemia as part of the natural history of PV was first reported in 1935 and 1938, respectively [7, 8]. In 1951, Dameshek classified PV as a chronic myeloproliferative disorder along with other related myeloid disorders, including CML and PMF due to their similarities in both clinical and laboratory features [9]. During 1967 and 1981, Fialkow et al showed that chronic myeloproliferative disorders are biologically interrelated on the basis of being clonal stem cell disorders with involvement of both myeloid and lymphoid lineage [10, 11]. Over the last two decades, a significant progress has been made in the diagnosis and treatment of PV, especially related to the implementation of immunohistochemical and molecular examinations, allogeneic stem cell transplantation and targeted chemotherapy. Nevertheless, the disease remains incurable in most cases, affecting patients' quality of life and life expectancy.

Preface

These methodical guidelines comprise the basic topics necessary for medical students that can assist in diagnosing PV, as well as elaborating the treatment principles and personalized therapeutic strategies. The methodical guidelines constitute an effort to make the subject issues on PV available, thus being perceived by the students. The major objective is to support the students of the Faculties of Medicine and Public Health. There have been defined the notions that will allow enriching the knowledge related to this field , as well as will provide useful data at all steps of knowledge assessment. An appropriate attention will be paid to the clinical activity of the students at the patient's bed, when carrying out practical skills, tests and clinical cases

on the relevant subject. In order to achieve a better understanding of the subject issues presented in these methodical guidelines, we opted for using graphical materials (tables, figures, and diagrams), images, clinical cases and assessments tests.

The aim of the seminar

To study the epidemiological patterns, etiology, pathogenesis, clinical features, laboratory tests and health care options applied for diagnosing PV, synthesis of treatment principles and customized strategies.

Duration of the seminar
The seminar lasts 5 hours.

Objectives of the seminar

1. To build-up knowledge on the epidemiology, etiology and pathogenesis of PV;
2. To develop knowledge on the clinical, hematological, morphological, immunohistochemical, cytogenetic and molecular features of PV;
3. To acquire practical skills in PV diagnosis;
4. To build-up knowledge on differential diagnosis of PV;
5. To develop general principles and personalized strategies of PV treatment.

The seminar will be proceeded

1. On Hematology discipline, at „Nicolae Testemitanu" SUMPh, in groups of students, by using study modules.
2. Within the Hematology units at the Hematology Department of the PMSI Institute of Oncology of the Republic of Moldova.
3. Within the hematology offices at the Consulting Diagnostic Centre of the PMSI Institute of Oncology of the Republic of Moldova.

Methods and Materials used for the seminar

Teaching methods to be used

The teaching methods and procedures, involved in the effective learning and achievement of the suggested objectives, are as following:

- Topic presentation by defining, describing, explaining and demonstrating;
- joint interactive discussion;
- problem-solving cases;
- data summarizing and synthesizing.

Various forms of independent, frontal, group, interactive activities are used during the seminars.

Methods of evaluation

- questioning on the study issue;
- problem-solving situations;
- analysis of clinical cases;
- single choice and multiple choice tests;
- individual work;
- assessment of practical skills;
- taking exam.

Materials used at the seminar

Teaching materials such as tables, schemes, algorithms, digital images, international guidelines are used for broader learning of PV. Power Point presentations are also applied during the seminars.

Questions for students' self-training

1. Epidemiology and etiology of PV.
2. Pathogenesis of PV.
3. Clinical features and complications of PV.
4. Diagnosis of PV.
5. Hematological features of PV.
6. The diagnostic value of the BM biopsy in PV.

7. The diagnostic value of immunohistochemistry in PV.
8. The value of cytogenetic and molecular examinations in diagnosing PV.
9. Differential diagnosis of PV.
10. Management principles and treatment options in PV.
11. PV evolution and prognosis.

Epidemiology of polycythemia vera

The reported worldwide annual incidence rate of MPNs ranges from 0.44 to 5.87 per 100000, with the lowest incidence being reported in Japan and Israel [12]. According to the data from the majority of bibliographic references, there is a stable incidence trend for PV of approximately 2.3 cases per 100000 [13, 14, 15]. The estimated incidence per 100000 population of PV varies between 0.4-2.8 cases in Europe and between 0.8-1.3 cases in the USA [16]. The reported median age upon diagnosis ranges from 65–74 years for PV cases. It is uncommon in individuals under 30 years old. The disease is slightly predominant in men, which increases in incidence after the 6th decade and occurs earlier in women. The occurrence of PV in children is not registered. PV is considered an orphan disease in the USA, since it affects less than 200000 people, regardless of the observation period [17]. Marketology researches have shown that in 2003 the prevalence was 22 per 100000 population in PV cases. The development and increased prevalence of CMPH in the elderly correlates with the demographic aging process in the USA and the European Union [18], in which the rate of the population over 80 years old will triple with a predictability between 2011 and 2060.

Etiology of polycythemia vera

The cause of PV is not fully known. Almost all patients with PV have a mutation of the JAK2 (Janus kinase 2) gene [1, 15]. This mutated gene plays a role in the onset of PV. However, its particular role as being the cause of the disease is still under study. Most patients with PV do not present a family history of the disease. However, occasionally there is more than one family member suffering from this specific disease. PV is more prevalent among Jews of Eastern European descendants than other Europeans or Asians.

Pathogenesis of polycythemia vera

The first-line evidence to support the stem cell origin of PV were the clonality studies [1, 15]. Using X-chromosome inactivation patterns (XCIPs) in the mid-1970s, Fialkow et al showed that neutrophils, erythrocytes and platelets originated from the same clone. Large studies have proved these findings so far. Erythropoiesis in PV is autonomous and does not rely on EPO. Its plasma concentrations are reduced in PV patients and PV progenitor cells. Unlike normalones, these can survive *in vitro* and give rise to erythroid colonies (BFU-E) in the absence of added erythropoietin (endogenous erythroid colonies and EECs). PV erythroid progenitors exhibit an increased sensitivity to EPO, as well as to other several growth factors, including insulin-like growth factor-1, thrombopoietin,interleukin-3 and granulocyte/monocyte colony-stimulatingfactor. In 2005, several groups identified a unique acquiredmutationin the cytoplasmic tyrosine kinase JAK2 in myeloid cells among most patients with PV [19]. JAK2 lies downstream of several cell-surface receptors including EPOR. Upon EPO binding to EPOR, JAK2 becomes phosphorylated and, in turn, phosphorylates downstream targets, most important of which are the STATs (signal transducers and activators of transcription), leading to stimulation of erythropoiesis *(Figure 1, 2).* Valine 617 is located in theJH2 domain of JAK2, which acts to repress its kinase activity. The V617F mutation leads to increased kinase activity, provides cytokine independence and results in erythrocytosisin a mouse transplant model. If appropriately sensitive methods are applied for the detection of the JAK2 V617F mutation, about 95% of PV cases are positive. Truncating mutations and deletions in a tumour-suppressor gene, TET2, have been reported in nearly 15–20% of patients with MPNs [20]. Recently published data suggest, that the order of acquisition mutations influences phenotype and therapy response.

Other abnormalities that have been described include (1) decreased levels of the platelet thrombopoiet in receptor, (2) deregulation of BCL-x, an inhibitor of apoptosis, (3) increased expression of protein tyrosine phosphatase activity by red cell precursors, (4) increased messenger RNA (mRNA) levels of the PRV-1 ("a receptor named polycythemia rubra vera 1") gene in granulocytes and (5) acquired loss-of-heterozygosity of chromosome 9p as a result of uniparenteral disomy [15, 22].

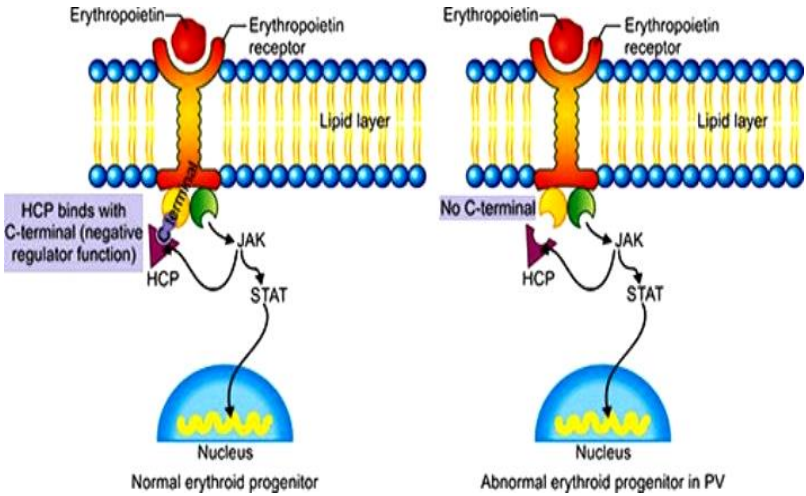

*Figure 1.***Pathogenesis of PV** [21]

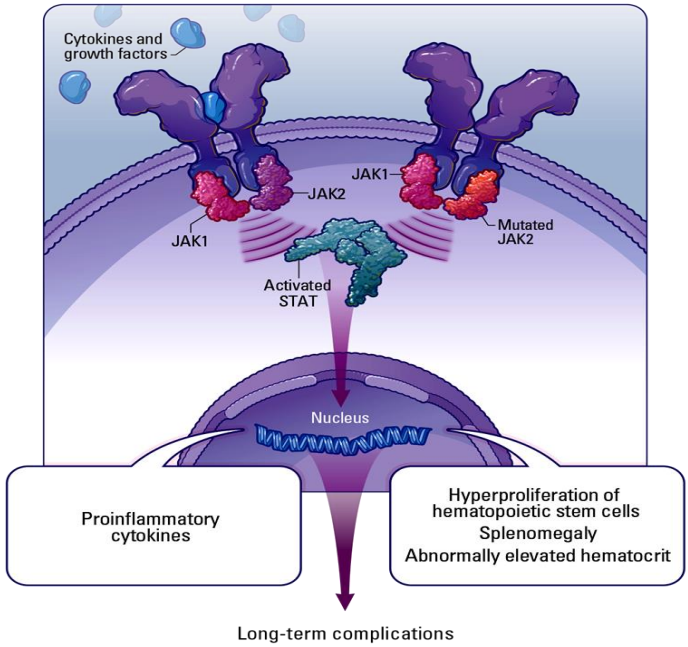

Figure 2. **Pathogenesis of PV**.

Clinical features, complications and staging of polycythemia vera

PV usually has an insidious onset, most commonly during the sixth decade of life, although the onset may occur in adolescence and develop until the old age [1, 15]. Presenting symptoms and signs include headaches, plethora, pruritus, thrombosis, and gastrointestinal bleeding, but many patients are diagnosed due to elevated hemoglobin and blood cell counts found on a routine medical examination [23]. Other cases may be uncovered during investigation for blood loss, iron-deficiency anemia, or thrombosis. Symptoms are reported by at least 30 percent of patients with polycythemia at diagnosis; the most common reported, in decreasing order of frequency, are the headaches, weakness, pruritus, dizziness, and sweating. PV generally occurs in older population; however, many of the vascular abnormalities (e.g., coronary artery disease) have a high prevalence due to age-related changes. Nevertheless, the prevalence of these events increase when complicated by PV. Palpable splenomegaly is reported in 30–50% of PV cases. It is unclear if its presence affects the prognosis, but it may be associated with an increased risk of progression to myelofibrosis. The arterial hypertension is more common in PV patients, as is hyperuricaemia that develops gout, last one being registered in about 5% of cases.

Thrombotic episodes are the most common and the most important complications of PV, occurring in about one-third of the patients. One half up to three-quarters of these events are arterial ones; ischemic strokes and transient ischemic attacks account for the majority of arterial complications [24]. In some studies, it has been stated that over a period of 10 years, 40 to 60% of patients develop at least one thrombotic event, showing an approximately equal annual incidence throughout this period. However, in prospective studies, thrombosis was most common just prior to and in the first few years after diagnosis. The most common serious complication is the cerebrovascular accident, which accounts for about one-third of the thrombotic events, followed by myocardial infarction, deep vein thrombosis and pulmonary embolism, based on their frequency. Bleeding and bruising is a common complication of PV, occurring in approximately one-quarter of the patients in some series. Although such episodes are usually minor, the gingival bleeding, nose bleeding, or easy bruising, serious gastrointestinal and other hemorrhagic complications with a fatal outcome also may occur.

Budd-Chiari syndrome is a catastrophic and often fatal complication of PV; it occurred in 10% of 140 patients in one series, but was less common in a European collaborative study. Budd-Chiari syndrome is caused by thrombosis of hepatic venous outflow leading to ischemia from reduced perfusion through hepatic arterioles and necrosis of hepatocytes. Budd-Chiari syndrome may present as ascites with or without right upper quadrant abdominal pain, hepatosplenomegaly and jaundice. The Budd-Chiari syndrome may be the first clinical manifestation of PV, preceding the elevated blood counts; endogenous erythroid colony formation and the *JAK2 V617* mutation have been described in many of these patients before clinical evidence of polycythemia occurred.

Pruritus occurs in approximately 40% of patients. It is usually aggravated when bathing or showering and may be so severe as to considerably compromise the patient's life quality. Its cause is unclear and it has been referred to an increased number of mast cells in the skin and to elevated histamine levels, although other studies have not reported these associations. Several patients have developed an uncommon skin condition, namely, the acute febrile neutrophilic dermatosis (Sweet syndrome).

Erythromelalgia is a syndrome characterized by hot extremities, painful and red phalanges, burning sensation, and erythema of the fingers and thumbs, associated with thrombocytosis, which typically shows a rapid response to low-dose aspirin therapy. In severe cases, it results in ischemic necrosis of the phalanges and may lead to their amputation. This syndrome occurs in less than 5% of PV patients and is not specific to PV or other myeloproliferative disorders. A study series conducted on 168 patients with erythromelalgia reported that less than 10 % of patients developed PV [25].

Portal hypertension, varices, and abdominal pain are common, being often caused by unrecognized splenic or hepatic vein thromboses [26]. The incidence of peptic ulcer is four to five times as great as in the general population. Gastrointestinal bleeding may be the first presenting symptom of PV, with iron deficiency caused by gastrointestinal blood loss often mimicking the erythrocytosis of PV.

STAGING SYSTEM IN POLYCYTHEMIA VERA:

I. The initial stage, or a moderate plethora (Hemoglobin ≤ 170 g/L).

II. The stage of unfolded clinical and hematological manifestations (Hemoglobin 170-230 g/L).

This stage is divided in:
stage IIA – without myeloid metaplasia of the spleen,
and
stage IIB – with myeloid metaplasia of the spleen.

III. The anemic stage, or the stage of hematological transformations of PV.

Progression to myelofibrosis, the so-called post-PV myelofibrosis (PPV-MF), occurs in around 10–20% of PV cases within 15 years after diagnosis. Transformation often occurs gradually over many years, which is thought to reflect an accumulation of additional mutations, being associated with an increased risk of leukaemic conversion. The management of these patients is similar to that of PMF.

Patients with PV have an increased risk of developing leukemia [1, 15]. The risk of developing acute leukaemia in PV patients treated only with venesection is thought to be low in the short terms (1–3%). This risk, however, increases considerably (more than tenfold) when radioactive phosphorus (^{32}P), chlorambucil or irradiation are used as treatment. The mean time interval between the first starting therapy and the development of acute leukaemia ranges between 5–8 years. Acute leukemia, which is usually myelogenous, might be an invariably fatal complication of PV. A European multicenter observational study conducted on 1638 patients reported a 6.3% relative risk of developing leukemia within 10 years after the PV diagnosis was confirmed. In a PV Study Group-01 randomized trial, the incidence of acute leukemia at 18-year follow up was 1.5% on the phlebotomy-only treatment arm, 10% on the ^{32}P treatment arm, and 13% on the chlorambucil treatment arm [27]. The measurable increase in acute leukemia incidence with ^{32}P therapy does not occur until 5 millicuries have been administered. Acute leukemia as the terminal PV event may arise from either the *JAK2V617F*-positive clone or, more frequently, from a hematopoietic cell that does not carry *JAK2* mutation.

Diagnosis of polycythemia vera

The diagnosis of PV is based on the CBC findings (increased haematocrit count > 49% in men and >48% in women), histopathological examination of the BM and molecular-genetic investigations for the detection of *JAK2* V617F mutation. The WHO Working Group on

Myeloproliferative Neoplasms identified major and minor diagnostic criteria for PV [28].

2016 World Health Organization diagnostic criteria for polycythemia vera include:

Major criteria:

1. Hemoglobin > 16.5 g/dL (in men), Hemoglobin > 16.0 g/dL (in women)
   or Hematocrit > 49% (in men), Hematocrit > 48% (in women)
   or increased red cell mass (RCM);
2. BM biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size);
3. Presence of JAK2 or JAK2 exon 12 mutation.

Minor criteria:

Subnormal serum erythropoietin level.

The diagnosis of PV requires the inclusion of either all 3 major criteria, or the first 2 major criteria and one minor criterion. Patients will be rarely negative for bothV617F and exon 12 *JAK2* mutations. This group of truly *JAK2*-negative PV is very rare (≈5%), whereas secondary erythrocytosis, idiopathic erythrocytosis and relative erythrocytosis are all much more likely to be diagnosed in this clinical setting.

Hematological features of polycythemia vera

Relevant changes in CBC include the elevated hemoglobin levels and erythrocyte counts, mild or moderate leukocytosis, with deviation to the left to myelocytes, metamyelocytes in stage IIB [1, 15]. An absolute neutrophilia occurs in about two-thirds of the patients. Occasional myelocytes and metamyelocytes are present in the blood and considerable degrees of immaturity are present in patients with long-standing, advanced disease. Platelet count ranges from normal values to hyperthrombocytosis ($\geq 1000x10^9$/l). The platelet count is increased in approximately 50% of patients at the time of diagnosis, and in approximately 10% if it is greater than $1000x10^9$/L. In contrast to normal individuals in whom phlebotomy results in an increased platelet count, platelet levels may not be affected by phlebotomy in patients with PV. There are no consistent abnormalities of thrombopoietin levels. The presence of eryt-

hroid and myeloid precursors in the peripheral blood (leucoerythroblastic picture), anisocytosis and poikilocytosis of erythrocytes, erythrocaryocytes, giant platelets and megakaryocyte fragments may be detected in CBC in stage III with post-PV myelofibrosis.

The diagnostic value of bone marrow biopsy in polycythemia vera

BM trephine biopsy is essential for diagnosis of PV. Initial stages are characterized by the BM hypercellularity due to the excessive proliferation of erythrocaryocyte, less commonly granulocyte and megakaryocyte cell lines, in association with a disorganization of marrow architecture and the presence of large megakaryocytes [1, 15]. Some publicshed data suggest that the marrow in PV patients with exon 12 mutations is morphologically normal. Marrow morphology in the related myeloproliferative disorder ET was unreliable as a criterion for diagnosis. Absent or decreased iron stores are found in the marrow of most PV patients. In stage III with post-PV myelofibrosis, fibrosis may be determined within some marrow cavities as reticulin and collagen fiber deposition. BM fibrosis becomes increasingly dominant and progressively replaces hematopoiesis. BM aspiration may yield a dry-tap or a haemodilute sample, which shows a limited diagnostic value in stage III with post-PV myelofibrosis. Immunohistochemical staining using antihemoglobin and anti-MPO reveals the marked erythroid hyperplasia and relative decrease of granulocytic precursors. The CD61 stain shows an increased number of atypical megakaryocytes with predominant smaller forms. The uniformly weak pattern of c-mpl immunostains complements BM histopathology in distinguishing PV from non-clonal causes of erythrocytosis.

The diagnostic value of cytogenetic and molecular examinations in polycythemia vera

The following investigations are mandatory for diagnosis and differential diagnosis of PV: cytogenetic and molecular examinations of venous blood with determination of molecular-genetic markers of tumor clones by FISH, nested / multiplex PCR or RT-PCR (quantitative detection of JAK2 V617F mutation). If adequately sensitive methods are applied for the detection of the JAK2 V617F mutation, then nearly 95% of

PV cases are likely to be positive. There are no characteristic cytogenetic findings, but occasional clonal chromosomal changes, none of which is very specific for PV, are revealed in a minority of patients. Truncating mutations and deletions in a tumour-suppressor gene, TET2, have been reported in nearly 15–20% of patients with PV [20]. Recent references suggest, that the order of acquisition mutations exerts an effect on phenotype and therapy response.

Differential diagnosis of polycythemia vera

The pathologic conditions with an increased red cell mass, not related to clonal proliferation of hematopoietic progenitors, are included under this heading. They can be conveniently subclassified into primary and secondary eythrocytoses. In primary eythrocytosis, the defect is intrinsic to the red cell precursors, which are hypersensitive to erythropoietin. In secondary eythrocytosis, the defect is upstream of the red cell precursors. The latter group can be further subdivided into eythrocytoses with the presence or absence of systemic hypoxia. The small group of patients, who do not fit any of these categories, are diagnosed with idiopathic erythrocytosis.

CLASSIFICATION OF SYMPTOMATIC ERYTHROCYTOSES:

I. Relative erythrocytoses:
   1. Stress-erythrocytosis;
   2. Geisböck's disease in arterial hypertension, obesity;
   3. Dehydration erythrocytosis.

II. Absolute erythrocytoses:
   1. Primary hereditary erythrocytosis.
   2. Secondary erythrocytoses:

A. Due to hypoxia and hypoxemia

- Elevated carboxyhemoglobinemia (Smoker's erythrocytosis)
- Alveolar hypoventilation (Pickwickian syndrome – sleeping apnea, obesity);
- Congenital cardiac defects.

B. Increased erythropoietin production

- Renal diseases (hypernephromatosis, cyst and hydronephrosis);
- Extrarenal tumours (hypophysial adenoma, pheochromocytoma, massive uterine leiomyoma, cerebellar hemangioblastoma, etc.).

BM biopsy does not reveal hypercellularity due to excessive proliferation of erythrocaryocytes, granulocyte and megakaryocyte cell lines.

PV should be differentiated from Vaughan type of PMF. This is a MPN, which emerges due to a clonal myeloid proliferation as a result of malignant transformation of the stem cell. The disease is characterized by splenomegaly, BM fibrosis, extramedullary hematopoiesis, slow tendency to cachexia and blastic transformation.

Management principles and treatment options in polycythemia vera

Up-to-date treatment of PV is focused on increasing the survival and patients' quality of life, preventing and combating thromboembolic and hemorrhagic complications and control of systemic symptoms [1, 15, 29].

Identification of the JAK2 V617F mutation has generated many regards to the development of therapeutic JAK2 inhibitors. As patients with PV currently show a very good prognosis, new agents will have to display an excellent safety profile.

In the absence of leucocytosis or thrombocytosis, progressive splenomegaly or thrombosis, regular venesection (phlebotomy) remains the mainstay of treatment for PV in patients who can tolerate it *(Figure 3).* A target hematocrit of ≤ 45% is widely used, following the demonstration that, in patients with PV, higher hematocrit values are associated with a significantly increased risk of thrombosis. This has been confirmed in a randomized controlled trial CYTO-PV. Phlebotomy has short-term impact on the haematocrit. The aim of regular phlebotomy is to reduce the blood volume and to induce iron deficiency, so that the hematocrit remains chronically below the target threshold of 45%. Thus, typical venesection regimens start with phlebotomy every 2–3 weeks until the hematocrit is controlled. Thereafter, phlebotomy is generally needed every 1–3 months, depending upon factors such as dietary iron intake and erythropoietic activity.

Cytoreductive therapy is recommended for patients unable to undergo phlebotomy and those with marked thrombocytosis, leucocytosis, and either progressive splenomegaly or prior thrombosis. Hydroxycarbamide (hydroxyurea) is the most commonly used drug, it is orally bioavailable and generally very well tolerated, which will re-

duce both the hematocrit, leucocyte and platelet counts. The commonest complications include leucopenia or thrombocytopenia, which are dose-dependent and can usually be prevented by thorough management of the blood count when the drug is first administered. The common dose is 0.5–2 g daily.

IFN-α is effective in controlling both the platelet and leucocyte counts, as well as the haematocrit. Moreover, there are some data showing that it may significantly reduce the burden ofV617F-positive cells in the blood. It is not widely used because of its cost, route of administration (subcutaneous injection) and its side effects (including fatigue, flu-like symptoms, depression, and autoimmune phenomena). It can be useful in young patients, who are reluctant to take other cytotoxic agents, in pregnancy and in patients with intractable pruritus. The usual doserange is 3–5 mU three times per week. There is an increasing interest in pegylated formulations of interferon that may be bettertolerated.

Anagrelide can be useful in controlling the platelet count and may be combined with Hydroxycarbamide, allowing lower doses of both agents. Approximately 10% of patients are completely unresponsive to Anagrelide. The usual dose is 1–2 mg daily, however, occasional patients may require doses of up to 8 mg daily. Its side effects are mainly secondary to its inotropic and vasodilatory properties.

Ruxolitinib has been approved for PV patients resistant or intolerant to Hydroxycarbamide, though its effects on thrombosis and transformation are unclear. Busulfan is sometimes used in elderly patients or when the other treatment approaches are not tolerated. It is very convenient, as it requires only intermittent administration, though it may increase the risk of leukaemia. The usual dosage is 2–4 mg daily for 7–14 days and then repeated every 4 weeks until the target blood count is reached.

Low-dose Aspirin (75–100mg daily) reduces thrombotic complications in PV and is used in most of patients without contraindications to this drug. Its use was supported by a randomized study (ECLAP).

Considering the age of most patients and the relatively benign evolution of PV, BM transplantation is not recommended for stable disease.

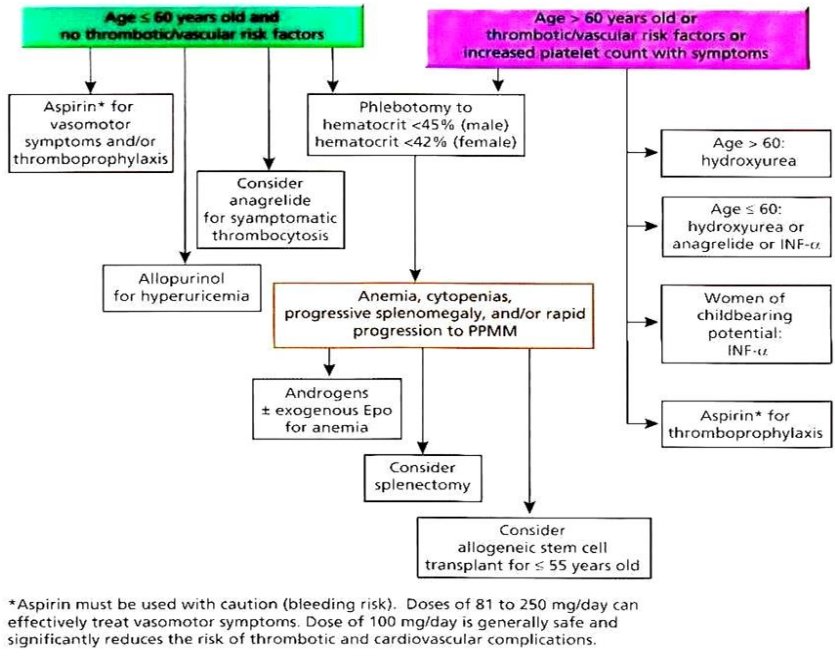

Figure 3. **Treatment algorithm used in polycythemia vera** [20].

Prognosis

In the first half of the twentieth century, untreated PV had a dismal prognosis, exhibiting a 50% survival of less than 2 years. However, an adequate treatment of PV, nowadays, provides a relatively benign natural history with a life expectancy of over 11 years, considering that the average age of onset is 60 years [1, 15]. The Polycythemia Vera Study Group found that the median survival since the start of treatment was 13.9 years for those who underwent phlebotomy alone, 11.8 years for ^{32}P-treated patients, and 8.9 years for chlorambucil-treated patients. Thrombotic complications are the dominant cause of morbidity and mortality in patients with PV (≈31% of cases), followed by the transformation into acute leukemia (≈19% of cases). The predictive factors of poor prognosis and increased complication rates in PV include *JAK2* mutation burden and white cell count upon diagnosis, both factors probably serving as surrogate markers of disease activity.

Clinical case studies

Clinical case 1

A 70-year- old woman presented with general weakness, discomfort and pain in the left upper abdominal quadrant, redness of the face and neck, headaches, painful fingers. She has been considered ill for two years. She was treated from chronic hepatitis and arterial hypertension by a therapist.

Physical exam: Severe patient's condition. ECOG-WHO score 3. Hyperemic skin. Peripheral lymph nodes are not palpable. Lung exam: a vesicular murmur is determined. Rhythmical and loud heart sounds. Apical systolic murmur is detectable. Pulse rate is 88 beats/min. Blood pressure -160/95 mm/Hg. The liver is palpable +3 cm below the costal margin. The spleen is palpable at the umbilical line.

Peripheral blood count: Hb – 202 g/l, RBC – $6{,}0x10^{12}$/l, WBC – $17.5x10^{9}$/l, reticulocytes –12‰, PLT – 528.0 $x10^{9}$/l, promyelocytes – 3%, myelocytes – 37%, metamyelocytes – 4%, bands – 12%, segm. – 35%, eos. – 2%, bas. – 4%, lymph. – 1%, mon. – 2%, erythrocyte sedimentation rate – 1 mm/h.

Biochemical test: uric acid – 615 μmol/l, unconjugated bilirubin – 25 mcmol/l, total bilirubin – 29 mcmol/l, LDH – 587 U/H, all the other parameters are within the normal limits.

Pyrosequencing and droplet digital PCR of the venous blood: quantitative detection of JAK2 V617F mutation – 34,7%.

Bone marrow aspiration: Hypercellular. Red cell line – 35%. An increased number of megakaryocytes.

Abdominal ultrasound: Splenomegaly: 26x12 cm, homogenous structure. Hepatomegaly: RL 17 cm, LL 11 cm, diffuse changes.

1. What diagnosis would you determine?
2. Could you develop an investigation plan?
3. What is the treatment plan?

Clinical case 2

A 52- year-old man presented with periodical headaches, left upper abdominal quadrant discomfort, pruritus after water contact, painful fingers, headaches, redness of the face. The patient has been considered ill for one year, with gradual appearance of the above-mentioned sings. His condition has worsened within the last 3 months.

Physical exam: ECOG-WHO score 2. Hyperaemic face, arms and upper torso. Lung exam: a vesicular murmur is determined. Heart sounds are rhythmical and loud. Pulse rate is 96 beats/min. Blood pressure 165/95 mm/Hg. The liver is palpable at the level of costal margin. The spleen is palpable +4 cm below the left costal margin.

Peripheral blood count: Hb – 180 g/l, RBC – $5.8x10^{12}$/l, WBC – $14.2x10^{9}$/l, reticulocytes –12‰, PLT – 490.0 $x10^{9}$/l, myelocytes – 1%, metamyelocytes – 2%, bands – 5%, segm. – 67%, eos. – 2%, bas. – 1%, lymph. – 10%, mon. – 4%, erythrocyte sedimentation rate – 2 mm/h.

Biochemical test: uric acid – 570 μmol/l, LDH – 537 U/H, all the other parameters are within the normal limits.

Bone marrow aspiration: Hypercellular. Red cell line – 32%. Number of megakaryocytes is increased.

Abdominal ultrasound scan: Splenomegaly: 18.5x9 cm, homogenous structure. Liver: RL 14.5 cm, LL 7 cm, diffuse changes.

1. What diagnosis would you determine?
2. Could you develop an investigation plan?
3. What is the differential diagnosis in this case?
4. What is the treatment plan?

Clinical case 3

A 41- year-old man presented with fatigue, left upper abdominal quadrant discomfort, headaches, redness of the face, pruritus after water contact. The patient has been considered ill for one year, with gradual appearance of the above-mentioned sings. His condition has worsened within the last 2 months.

Physical exam: ECOG-WHO score 1. Hyperaemic face, arms and upper torso. Lung exam: a vesicular murmur is determined. Rhythmical and loud heart sounds. Pulse rate is 92 beats/min. Blood pressure 160/90 mm/Hg. The liver is palpable at the level of costal margin. The spleen is palpable +3 cm below the left costal margin.

Peripheral blood count: Hb – 165 g/l, RBC – $5.4x10^{12}$/l, WBC – $12.2x10^{9}$/l, reticulocytes – 12‰, PLT – 470.0 $x10^{9}$/l, myelocytes – 1%, metamyelocytes – 2%, bands – 5%, segm. – 66%, eos. – 2%, bas. – 1%, lymph. – 10%, mon. – 4%, erythrocyte sedimentation rate – 2 mm/h.

Biochemical test: all parameters are within the normal limits.

Bone marrow aspiration: Hypercellular, Red cell line – 32%. Increased number of megakaryocytes.

Pyrosequencing and droplet digital PCR of the venous blood: quantitative detection of JAK2 V617F mutation – 24, 7%.

Abdominal ultrasound: Splenomegaly: 17.5x9 cm, homogeneous structure. Liver: RL 14.5 cm, LL 7 cm, diffuse changes.

1. What diagnosis would you determine?
2. Could you develop an investigation plan?
3. What is the differential diagnosis in this case?
4. What is the treatment plan?

Clinical case 4

A 70- year-old woman presented with general weakness, discomfort and pain in the left upper abdominal quadrant, paleness of the face, weight loss of 7 kg. She was diagnosed with polycythemia vera and has been followed up by a haematologist for 15 years. She was initially treated with a SAChT and phlebotomy.

Physical exam: Severe patient's condition. ECOG-WHO score 3. Pale and subicteric skin. Not palpable peripheral lymph nodes. Lung exam: a vesicular murmur is determined. Rhythmical and quiet heart sounds. Apical systolic murmur is detectable. Pulse rate is 92 beats/min. Blood pressure 110/75 mm/Hg. The liver is palpable +3 cm below the costal margin. The spleen is palpable at the umbilical line.

Peripheral blood count: Hb – 98 g/l, RBC– $3.2x10^{12}$/l, WBC – $19.5x10^{9}$/l, reticulocytes – 47‰, PLT – 528.0 $x10^{9}$/l, promyelocytes – 3%, myelocytes – 37%, metamyelocytes – 4%, bands – 12%, segm. – 35%, eos. – 2%, bas. – 4%, lymph. – 1%, mon. – 2%, erythrocyte sedimentation rate – 25 mm/h.

Biochemical test: unconjugated bilirubin 26 mcmol/l, total bilirubin 31.5 mcmol/l, total protein 54 g/l, LDH 587 U/H, all other parameters are within the normal limits.

Bone marrow aspiration: Hypercellular. Myeloid cell line – 81%. Number of megakaryocytes is increased. Erythroid cell lineage exhibits the signs of megaloblastic hematopoiesis.

Abdominal ultrasound: Splenomegaly: 26x12 cm, homogeneous structure. Hepatomegaly: RL 17 cm, LL 11 cm, diffuse changes.

1. What diagnosis would you determine?
2. Could you develop an investigation plan?
3. What is the treatment plan?

Assessment tests

S Which of the following clinical signs is true for the diagnosis of polycythemia vera in cases of increased hemoglobin values:

A. Hepatomegaly
B. Splenomegaly
C. Generalized lymph nodes enlargement
D. Skin infiltration by blast cells
E. Telangiectasias

Correct answer: **B.**

S In the unfolded stage of polycythemia vera, the most common complications are:

A. Infectious complications
B. Autoimmune hemolytic anemia
C. Venous and arterial thromboses
D. Autoimmune thrombocytopenia
E. Sepsis

Correct answer: **C**.

S Which of the following statements is true for the diagnosis of policythemia vera:

A. The skin becomes gradually reddish
B. Sometimes venous and arterial thromboses are the initial manifestations of the disease
C. Skin itching after exposure to water
D. Infectious complications that lead to death
E. Bone marrow examination shows hyperplasia and marked increase of megacaryocytes

Correct answer: **D.**

S The first-line treatment option in young males diagnosed with polycythemia vera is:

A. Radioactive phosphorus
B. Blood exfusions
C. Chlorambucil
D. Busulfan
E. Combined chemotherapy

Correct answer: **B**.

S Which of the following hematopoietic cells is primarily involved in polycythemia vera:

A. Blast cell
B. Stem cell
C. Myeloid cell precursor
D. Erythroblast
E. Erythrocyte

Correct answer: **C.**

S The morphological substrate of the tumor in polycythemia verais composed of:

A. Hyperplasia of two hematopoietic cell lines
B. Hyperplasia of three hematopoietic cell lines
C. Blast cell infiltration of the bone marrow
D. Absence of red cell line proliferation
E. Absence of megacaryocyte cell line proliferation

Correct answer: **B.**

S In polycythemia vera, the main clinical syndrome is:

A. Neurologic
B. Infectious
C. Lymph nodes enlargement
D. Plethoric
E. Sideropenic

Correct answer: **D.**

S Which of the following statements is true for the diagnosis of polycythemia vera:

A. Abrupt onset and accelerated evolution
B. Increased morbidity of young individuals
C. Frequent infectious complications
D. Peripheral lymph nodes enlargement is possible
E. The diagnosis may be proved only by bone marrow biopsy followed by histological examination

Correct answer: **E.**

S The diagnosis of polycythemia vera is confirmed if the bone marrow biopsy reveals:

A. Fibrosis
B. Panmyelosis

C. Reduced number of hematopoietic cells in the bone marrow
D. Replacement of the bone marrow by adipocytes
E. Replacement of the bone marrow by cancer metastases
Correct answer: **B.**

S Polycythemia vera–related skin itching is caused by:
A. Allergic reaction
B. Specific involvement of the skin
C. Development of infectious complications
D. Hemolytic syndrome
E. Increased histamine production by basophils and mastocytes
Correct answer: **E.**

S The diagnosis of polycythemia vera is definitely confirmed by the:
A. Lymph node biopsy
B. Bone marrow aspiration
C. Determination of the increased red cell sedimentation rate
D. Bone marrow biopsy
E. Computerized tomography scanning
Correct answer: **D.**

S Which of the following statements on the diagnosis of polycythemia vera istrue:
A. Arterial hypertension is a common symptom of the unfolded stage of polycythemia vera
B. The initial stage is manifested only by the increase of red cell count
C. Plethoric syndrome is the major clinical syndrome of polycythemia vera
D. Skin itching occurs frequently after having shower
E. The diagnosis of polycythemia vera may be proved on the basis of analysis of bone marrow aspiration fluid
Correct answer: **E.**

C Polycythemia vera may evolve with the following complications:
A. Myocardial infarction
B. Necrosis of fingers
C. Autoimmune hemolysis

D. Cholelithiasis
E. Common infectious complications
Correct answer: **A, B.**

C Which of the following drugs are more efficient in the treatment of polycythemia vera:
A. Imifos
B. Hydroxyurea
C. Cyclophosphamide
D. Vincristine
E. Chlorambucil
Correct answer: **A, B.**

C The following criteria should be considered to confirm the diagnosis of polycythemia vera:
A. Blast cells in the peripheral blood
B. Lymphocytosis in the peripheral blood
C. Pancytosis in the peripheral blood
D. Accelerated ESR
E. Panmyelosis in the bone marrow biopsy sample
Correct answer: **C, E**.

C In polycythemia vera, thrombosis are caused by:
A. Blood hyperviscosity
B. Neurologic syndrome
C. Thrombocytosis
D. Functional disorder of the gastrointestinal tract
E. Osteomedullary syndrome
Correct answer: **A, C**.

C In polycythemia vera, microcirculation disorders are manifested by the following signs:
A. Funicular myelosis
B. Paramyloidosis
C. Erythromelalgia
D. Sensorial neuropathy
E. Epileptiform convulsions
Correct answer: **C, E.**

C In polycythemia vera, hemorrhagic complications result from:

A. Paraproteinemic syndrome
B. Functional disorders of thrombocytes
C. Blood hyperviscosity
D. Splenomegaly
E. Erythromelalgia

Correct answer: **B, C**.

C The clinical manifestations of polycythemia vera are:

A. Transient hyperemia of the face
B. Constant hyperemia of the face
C. Skin itching after warm shower
D. Gingival hyperplasia
E. Head pressure feeling

*Correct answer***: B, C, E**

C Which are the indications for phlebotomy as a first-line treatment in polycythemia vera:

A. Benign evolution of polycythemia vera
B. Reproductive age of patients
C. Polycythemia vera with leukocytosis, thrombocytosis and splenomegaly
D. Patient's severe condition
E. Recurrent polycythemia vera following a cytotoxic treatment associated with constant decrease in platelet and leukocyte counts

Correct answer: **A, B, E.**

C The terminal phase of polycythemia vera is manifested by:

A. Posterythremic myelofibrosis
B. Acute leukemia
C. Chronic lymphocytic leukemia
D. Chronic myeloid leukemia
E. Sarcomatous growth

Correct answer: **A, B, D**.

C In polycythemia vera, plethoric syndrome is manifested clinically by:

A. Lymph nodes enlargement
B. Skin hyperemia
C. Scleral injection

D. Skin pallor
E. Positive Cuperman symptom
Correct answer: **B, C, E.**

C The following options might confirm the diagnosis of early polycythemia vera :
A. Dispensarization and dynamic follow-up
B. Dynamic peripheral blood count
C. Bone marrow biopsy
D. Bone marrow aspiration
E. Lymph node puncture
Correct answer: **A, B, C.**

C The following hematological transformations of erythremia in the terminal stage may occur:
A. Anemia, thrombocytopenia
B. Acute leukemia
C. Posterythremic myelofibrosis
D. Hodgkin lymphoma
E. Chronic lymphocytic leukemia
Correct answer: **A, B, C.**

C The peripheral blood analysis in stage IIB polycythemia vera reveals:
A. Erythrocytosis
B. Thrombocytopenia
C. Leukocytosis
D. Shift to the left of the leukocyte count
E. Elevated ESR
Correct answer: **A, C, D.**

C In polycythemia vera, cytotoxic chemotherapy is indicated in:
A. Leukocytosis
B. Thrombocytosis
C. Fertile age of patients
D. Splenomegaly
E. Inefficient phelebotomy treatment
Correct answer: **A, B, D, E.**

C The following statements are true regarding the initial stage of polycythemia vera:

A. Indolent evolution of fatigue and dizziness
B. Mild skin hyperemia
C. Absence of splenomegaly
D. Absence of vascular complications
E. Lymph nodes enlargement

Correct answer: **A, B, C, D.**

C In patients with polycythemia vera, microcirculation disturbances may lead to the development of:

A. Skin itching after exposure to water
B. Erythromelalgia
C. Gangrene of the fingers
D. Stenocardia
E. Abdominal pain

Correct answer: **B, C, D, E.**

C The following criteria are true for the differential diagnosis of stage IIB and stage IIA polycythemia vera:

A. Spleen size does not decrease after phlebotomy
B. Leukocytosis with the left shift up to myelocytes in the peripheral blood
C. Presence of erythrocaryocytes in the peripheral blood
D. Plethoric syndrome
E. Fibrosis in bone marrow biopsy sample

Correct answer: **A, B, C, E.**

C The complications of polycythemia verainclude:

A. Trombosis of the cerebral vessels
B. Myocardial infarction
C. Splenomegaly
D. Arterial hypertension
E. Phlebothrombosis

Correct answer: **A, B, D, E**.

S Which of the following statements regarding erythremia is true:

A. It is a polyclonal tumor;
B. The substrate of the tumor is composed of blast cells;
C. It develops only in females;

D. It is a lymphoproliferative process;
E. It is a myeloproliferative process
Correct answer: **E.**

S Reactive thrombocytosis develops in:
A. Megaloblastic anemia
B. After phlebotomy
C. Acute leukaemia
D. Immunodeficiency
E. Hiatal hernia
Correct answer: **B.**

S Stage I erythremia is characterized by:
A. Splenomegaly
B. Severe clinical symptoms
C. Hematocrit < 40%
D. Hematocrit = 50–55%
E. Hepatomegaly
The correct answer: **D.**

S Which of the following statements about stage I erythremia is true:
A. The spleen is palpable and increased by 3 cm;
B. The spleen is not palpate;
C. Hemoglobin -200 g/l;
D. Thrombosis is indispensable;
E. Trepanobioptate is within the normal range
The correct answer: **B.**

S A patient showed the following values of Hb 185 g/l, erythr. $6{,}5x10^{12}$/l, Ht 70%, leukocytosis with moderate thrombocytosis. These data support the following:
A. Idiopathic erythrocytosis
B. Secondary erythrocytosis
C. Erythremia
D. Acute leukemia
E. Medullary aplasia
Correct answer: **C.**

S In erythremia, diffuse cephalea, memoryloss and intellectual work capacity loss might occur due to:

A. Decrease in blood viscosity
B. Increase in blood viscosity
C. Anemia
D. Splenomegaly
E. Renal failure

Correct answer: **B**.

S The treatment applied in stage I erythremia is:

A. Single-agent chemotherapy
B. Combined chemotherapy
C. Phlebotomy
D. Large amounts of fluid intake
E. Splenectomy

Correct answer: **C.**

S Purplish-red color of face, injected sclera and the presence of the Cuperman symptom suggest the diagnosis of:

A. Acute leukemia
B. Lymphoproliferative process
C. Erythremia
D. Multiple myeloma
E. Solitory myeloma

Correct answer: **C.**

S The conclusive diagnosis of erythremia is made based on:

A. Cytological examination of bone marrow
B. Histological examination of bone marrow
C. Biochemichal blood test
D. ECG
E. Blood counts

Correct answer: **B.**

S The level of leukocytes in stage IIA erythremia is:

A. Normal
B. $< 15.0x10^9/l$
C. $> 15.0x10^9/l$
D. Leukopenia
E. The leukocyte level does not depend on the stage of erythremia

Correct answer: **B**.

S Stage II erythremia lasts for:

A. 10 months
B. 10-15 years and more
C. One month
D. One year
E. None of the above mentioned is correct

Correct answer: **B.**

S The hemoglobin level in the phase of clinical and hematological manifestations of erythremia is:

A. 180-240 g/l
B. 120-140 g/l
C. 140-160 g/l
D. 100-120 g/l
E. 80-100 g/l

Correct answer: **A.**

S The differential diagnosis of erythremia is carried out with:

A. Acute leukemia M_6
B. Chronic granulocytic leukemia
C. Erythrocytoses
D. Non-Hodgkin's lymphoma with spleen injury
E. Multiple myeloma

Correct answer: **C.**

S In patients with symptomatic erythrocytosis, the complete blood count shows:

A. Pancytosis
B. Pancytopenia
C. Anemia
D. Increase in the hemoglobin and erythrocytecounts
E. Thrombocytopenia

*Correct answer***: D.**

S The aim of phlebotomy is:

A. To increase the hemoglobin values
B. To increase the erythrocyte values
C. To decrease the hematocrit values

D. To increase the hematocrit values
E. To increase the circulating blood values
Correct answer: **C.**

S Which of the following is indicated in the treatment of symptomatic erythrocytosis:
A. Large amounts of fluid intake
B. Detoxification
C. Splenectomy
D. Cytostatic preparations
E. Phlebotomy
Correct answer: **E.**

S Erythrocytapheresis is indicated in case of:
A. Decreased hematocrit
B. Normal hematocrit
C. Increased hematocrit due to the increased count of erythrocytes
D. In all cases mentioned above
E. In none of the cases mentioned above
Correct answer: **C.**

S Which of the following is indicated to decrease blood viscosity in patients with erythremia:
A. Antiplatelet drugs (antiaggregants)
B. Phlebotomy
C. Anticoagulants
D. Antiaggregants and anticoagulants
E. Large amounts of fluid intake
Correct answer: **B**.

C Erythremia is a:
A. Type of acute leukemia
B. Lymphoproliferative tumor
C. Myeloproliferative tumor
D. Polyclonal pathology
E. Monoclonal pathology
Correct answer: **C, E.**

C The plethora syndrome develops as a result of:

A. Blood hyperviscosity
B. Decrease of hematocrit
C. Increase of the circulatory blood volume
D. Decrease of the circulatory blood volume
E. All mentioned above

Correct answer: **A, C**.

C Which of the following signs might reveal in stage I erythremia:

A. Giant splenomegaly
B. Hemoglobin value 160-170 g/l
C. Hemoglobin value >170 g/l
D. The spleen is not palpable
E. Thrombotic complications are common

Correct answer: **B, D.**

C The plethora syndrome is caused by:

A. Increased blood viscosity
B. Decreased blood viscosity
C. Increased hematocrit
D. Decreased hematocrit
E. Hematocrit is not changed

*Correct answer:***A, C.**

C Stage I erythremia is also called the:

A. Initial stage
B. Stage of erythremia proper
C. Stage of erythrocytosis
D. Moderate plethora
E. Anemic stage

Correct answer: **A, D.**

C The treatment applied in stage I erythremia is:

A. Multiple
B. Large amounts of fluid intake
C. Phlebotomy
D. Erytrocytophoresis
E. Blood donation

Correct answer: **C, D.**

C The differential diagnosis of erythrocytosis and erythremia is carried out by:

A. Bone marrow aspiration
B. Trephine biopsy
C. Blood count
D. Biochemical test
E. Electrocardiogram

Correct answer: **B, C.**

C Stage III erythremia is also called:

A. Blast crisis
B. Sarcomatization
C. Blast transformation
D. Anemic
E. Primary myelofibrosis

Correct answer: **D, E.**

C Which of the following therapies should be indicated to patients during phlebotomy:

A. Disaggregation drugs
B. Anticoagulants
C. Antacids
D. Diuretics
E. Fresh frozen plasma

Correct answer: **A, B**.

C Erythromelalgia is found in:

A. Erythroleukemia M_6
B. Hairy cell leukemia
C. Erythremia
D. Erythrocytosis
E. In all mentioned above

Correct answer: **C, D**.

C In erythremia, the lifespan of erythrocytes is:

A. Common one
B. Increased
C. Decreased
D. About 120 days
E. Over 120 days

Correct answer: **A, D.**

C Phlebotomy impacts the:

A. Erythrocyte count
B. Leukocyte count
C. Thrombocyte count
D. Hematocrit
E. All mentioned above

Correct answer: **A, D.**

C The following statements regarding erythremia are true:

A. Increase in the total blood volume
B. Frequent hemorrhages
C. Higher risk of thrombosis
D. Hyperviscosity
E. Hypoviscosity

Correct answer: **A, C, D.**

C Which of the following might occur in erythremia:

A. Hemolysis of erythrocytes
B. Overproduction of erythrocytes
C. Increase of erythrocyte lifespan
D. Increase of blood viscosity
E. Increase in the number of erythrocytes, thrombocytes, leukocytes

Correct answer: **B, D, E.**

C Clinical stages of erythremia are:

A. Stage I
B. Stage II
C. Stage II B
D. Stage III A
E. Stage III B

Correct answer: **A, B, C.**

C The presence of the plethora syndrome helps in diagnosing:

A. Malignant lymphoma
B. Erythremia
C. Idiopathic erythrocytosis
D. Secondary erythrocytosis
E. Cardiovascular failure

*Correct answer***: B, C, D**.

C In erythremia, the increase in the arterial blood pressure readings is caused by:

A. Increase in the circulatory blood volume
B. Decrease in the circulatory blood volume
C. Increased peripheral resistance
D. Ischemia of renal tissue
E. Splenomegaly

Correct answer: **A, C, D.**

C Stage II erythremia diagnose is based on all the following symptoms, except for:

A. Giant splenomegaly
B. Splenomegaly is reduced after phlebotomy
C. Leukocytosis < $15.0x10^9$/l
D. Leukocytosis > $15.0x10^9$/l
E. Absence of splenomegaly

Correct answer: **A, D, E**.

C Stage II B erythremia is characterized by following spleen manifestations:

A. It is massive
B. It is firm
C. It does not reduce unless cytostatics are used
D. Size does not depend on the stage of erythremia
E. It has a normal size

Correct answer: **A, B, C.**

C The complete blood count of the patient with stage III erythremia shows:

A. Leukocytosis $10.0\text{-}15.0x10^9$/l
B. Leukocytosis $20.0\text{-}30.0x10^9$/l
C. Anemia
D. Thrombocytopenia
E. Normal values

Correct answer: **B, C, D.**

C Stage III erythremia is characterized by the development of:

A. Bone marrow fibrosis
B. Spleen fibrosis

C. Liver fibrosis
D. Metaplasia of the bone marrow with adipocytes
E. Renal anaemia
Correct answer: **A, B, C.**

C The diagnosis of erythremia is confirmed based on:
A. Pancytosis of peripheral blood
B. Pancytopenia of peripheral blood
C. Plethora syndrome
D. The absence of diseases accompanied by erythrocytosis
E. The presence of diseases accompanied by erythrocytosis
Correct answer: **A, C, D.**

C Secondary erythrocytosis develops due to:
A. Hypoxia
B. Increased secretion of erythropoietin
C. Malignant extrarenal tumors
D. Severe dehydration
E. Hyperthermia
Correct answer: **A, B, C.**

C Phlebotomy as the only method of treatment is recommended in:
A. Individuals of reproductive age
B. Absence of thrombocytosis
C. Erythrocytosis
D. Anemia
E. All cases mentioned above
Correct answer: **A, B, C.**

C The treatment of erythremia depends on the:
A. Age
B. Haematocrit values
C. Liver size
D. Blood count
E. Disease staging
Correct answer: **A, B, D, E.**

C Stage I erythremia is characterized by the following symptoms, except for:

A. Splenomegaly
B. Severe clinical symptoms
C. Hematocrit > 60%
D. Mild clinical symptoms
E. Hepatomegaly

Correct answer: **A, B, C, E.**

C Erythremia is treated with:

A. Combined chemotherapy
B. Single-agent chemoterapy
C. Hydroxycarbamide
D. Busulfan
E. IFN-α

Correct answer: **B, C, D, E.**

C In erythremia, phlebotomy can be replaced with the following methods, except for:

A. Fluid infusion
B. Erythrocytapheresis
C. Hemodialysis
D. Plasmapheresis
E. None of the mentioned above

Correct answer: **A, C, D, E.**

C Erythremia is characterized by:

A. Uric diathesis
B. Plethoric syndrome
C. Arterial hypertension
D. Splenomegaly
E. Hemolytic syndrome

Correct answer: **A, B, C, D.**

C In erythremia, the following changes in blood pressure values can occur:

A. There is no change
B. The changes depend on the values of erythrocyte sedimentation rate

C. The changes depend on the sex of the patient with erythremia
D. There is a tendency to increase
E. There is a tendency to decrease

The correct answer: **A, B, C, E.**

C Erythromelalgia can develop in the following diseases except for:
A. Acute leukemia
B. Megaloblastic anemia
C. Hemolytic anemia
D. Chronic lymphocytic leukemia
E. Erythremia

Correct answer: **A, B, C, D.**

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