Hematological System Diseases

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16.1 Polycythemia Vera

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Polycythemia vera (PV) is a clonal myeloproliferative disease characterized by erythrocytosis. This is pathologically characterized by the simultaneous proliferation of erythroid, granulocyte, and megakaryocytes in bone marrow. The count and the capacity of erythrocyte are significantly increased in clinical characteristics, accompanied by neutrophils and thrombocytosis, and a series of symptoms and signs caused by multiple blood and hyperviscosity. PV is often accompanied by splenomegaly. The onset of PV is insidious, in which the progress is slow and various transformations can occur in the late stage. Approximately half of the patients develop hypertension, usually with elevated systolic blood pressure.

16.1.1 Epidemic Characteristics

The incidence of PV is estimated at 1.9–2.6/100,000 per year, slightly higher in men than in women (2.8/100,000 per year vs. 1.3/100,000 per year), and is particularly prevalent among Ashkenazi Jews [1, 2]. The incidence rate increases with age. Among the 1545 patients analyzed by International Working Group for Myeloproliferative Neoplasms Research and Treatment (IWG-MRT), the median age of PV diagnosis was 61 years (18–95 years) [3].

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16.1.2 Etiology and Pathogenesis

The etiology of PV is unknown. Exposure to certain mutants, such as ionizing radiation and benzene, is considered a risk factor. Recent studies have shown that PV is closely related to JAK2 gene mutation, and jak2-mediated signal transduction plays an important role in promoting or regulating cell proliferation. In multiple studies, V617F mutation of JAK2 exon 14 was found in 95–97% of PV patients, and mutation of JAK2 exon 12 was found in about 3% of PV patients, which may lead to transitional expression of bcl-xl, a protein generated by red line progenitor cells through the jak-stat signaling pathway [2, 4–6]. The upregulation of bcl-xl or bcl-2 antiapoptotic proteins is an important mechanism to maintain the survival of red line progenitor cells. It has been proved that the phosphorylation of tyrosine kinase after JAK2 gene mutation promotes the overreaction of erythroid clones to cytokines and induces the proliferation of erythroid cells in mice. Normally activated JAK2 is the EPO—the EPO receptor pathway controls erythroid cell differentiation and apoptosis. The mutation leads to the spontaneous growth of PV erythroid clones without relying on EPO [6–11].

The pathogenesis of hypertension caused by PV: The number and capacity of erythrocytes are significantly increased in polycythemia vera due to abnormal proliferation of erythrocytes in bone marrow. The capacity and viscosity of blood are increased, so that the systolic blood pressure increases because of the increase in peripheral resistance, which is the main reason for rising blood pressure.

16.1.3 Pathology

PV lesions mainly involve bone marrow, spleen, and liver. The structure of bone marrow is almost normal. The erythroid hyperplasia is extremely obvious, and the granulocyte and megakaryocyte cell lines often proliferate at the same time or one of them proliferates, and some patients have erythroid hyperplasia alone. The immature erythrocytes are island-like hyperplasia near the sinus. The immature granulocytes in each stage diffuse hyperplasia around the trabecular and perivascular, and the megakaryocytes proliferate in the inter-trabecular region. The proliferating cells in the bone marrow are highly atypia and the sinusoidal expansion is significant. Iron storage cells in bone marrow and iron particles were significantly reduced, and about 80% of patients had negative iron staining. Fibroblasts and blood vessels proliferated obviously in the later stage of the disease, and big red blood cell hematopoietic islands appeared together with immature granulocytes and heterogeneous megakaryocytes. The reticular fiber staining indicates that the reticular fibers are highly proliferative, indicating that the bone marrow will be transformed or combined with the bone marrow fibrosis.

At early stage of disease, spleen sinus significantly dilated and hyperemia, the count of erythrocytes is increased, and accompanied by a small amount of immature erythrocytes. Three lines of hematopoietic cells can appear in the spleen at the late stage of the disease, which is similar to myeloid metaplasia. Several researchers

believe that splenomegaly is caused by spleen congestion due to the accumulation of mature erythrocytes and platelets in the spleen. Dilatation of the hepatic sinuses occurs in the enlarged liver, with cellular components similar to the splenic sinuses. Myeloidosis can also occur in the liver at the late stage of the disease.

The above-mentioned pathological changes of liver and spleen are also the pathological basis of portal hypertension and frequent upper gastrointestinal bleeding. If there is thrombosis in the larger blood vessels, the infarct can occur in the corresponding organs; others usually have no obvious pathological changes.

16.1.4 Clinical Manifestations

PV often develops insidiously, and some cases are found by routine blood cell tests. The symptoms are classified into the following groups:

1. Neurological symptoms: The symptoms include headache, fatigue, dizziness, and hyperhidrosis, which are associated with increased blood viscosity, thrombocytosis, and lacunar cerebral infarction.
2. Aquagenic pruritus is usually the chief complaint of PV patients and is described as "intolerable" by 15% of patients with this symptom. The symptom appears approximately 3 years before PV diagnosis on average and is the basis of suspected PV diagnosis in 15% of patients. The most common symptom areas are chest, back, medial arm, and ventral leg. Polyplasmic manifestations: accounts for 60%, such as conjunctival congestion, blush, purple lip, dark red tongue, and varicose blood vessels [12].
3. Erythromelalgia: Erythromelalgia or burning pain in the feet or hands accompanied by erythema, pallor, or cyanosis in the presence of palpable pulses is seen in 29% of patients with PV [13].
4. Thrombosis: Venous thrombosis and arterial thrombosis complications were found in 7 and 16% of PV patients, respectively, with the most common brain involvement, presenting as transient ischemic attack or cerebral infarction, and a few patients complicated with limb arterial thrombosis [3]. It has been reported that thrombosis of hepatic vein or inferior vena cava occurs in Budd–Chiari syndrome; PV is one of the important causes of this syndrome, accounting for about 10% [14]. In rare cases, blood clots form in the heart cavity, leading to refractory heart failure.
5. Polyplasmic manifestations: Accounts for 60%, such as conjunctival congestion, blush, purple lip, dark red tongue, and varicose blood vessels.
6. Hemorrhage: Accounts for about 40% of the total; there are often gingival bleeding, epistaxis, skin ecchymosis, and gastrointestinal bleeding, and a few patients can be complicated by intracranial hemorrhage [15].
7. Hepatosplenomegaly: Hepatomegaly accounts for about 24%, and splenomegaly accounts for about 87%. The liver is usually mild to moderately enlarged, while the spleen can be swollen and stretched to the pelvis with advanced fibrosis. Some patients may have discomfort or pain due to swelling of the liver and spleen.

8. Hypertension: According to relevant statistics, about 78% of patients with PV have elevated blood pressure. About half of patients with general polycythemia have high blood pressure, mostly mild to moderate, mainly with elevated systolic blood pressure.
9. Hyperuricemia: Hyperuricemia is common in PV patients, some of whom have gout attacks in clinical practice.

16.1.5 Laboratory Inspection

16.1.5.1 Hemogram

1. Erythrocyte: Erythrocyte count >6 × 10^{12}/L, hemoglobin >180 g/L, hematocrit >50%, which are the hemographic characteristics of PV patients. If accompanied by repeated gastrointestinal bleeding and/or multiple venous bleeding treatments, low-pigmented microcytic anemia can be caused by iron deficiency, with saturation of serum iron, ferritin, and transferrin decreasing. In the late stage, combined with myelofibrosis and extramedullary hematopoiesis, the life span of erythrocyte was shortened, and the erythrocyte and hemoglobin gradually decreased from elevation to anemia. The increase of plasma volume caused by erythrocyte stasis in megaspleen and portal hypertension can lead to dilutional anemia. When complicated with extramedullary hematopoiesis, teardrop red blood cells, abnormal red blood cells with uneven coloration, and nucleated red blood cells can be found in peripheral blood smears.
2. Leukocyte: Leukocyte in peripheral blood increased in more than 80% of patients, usually up to (10–30) × 10^{9}/L. There were also a few neutrophils, late granulocytes, and a slight increase of basophils. In the late stage of myelofibrosis, the number of promyelocytes increased further, and even a small amount of primordial or promyelocytes appeared.
3. Platelet: More than 40% of patients had more platelets in peripheral blood. Giant platelets could be seen in blood smears. Some patients had abnormal platelet function, such as decreased aggregation and adhesion. The platelet life is still normal. In the late stage with myelofibrosis, platelets gradually decrease until thrombocytopenia.

16.1.5.2 Bone Marrow

Bone marrow aspiration smears showed active proliferation or obvious activity, mainly erythroid proliferation, often accompanied by granular and megakaryocyte proliferation. The proportion of cells in each stage was normal. Iron staining showed that both intracellular iron and extracellular iron are reduced or even disappear. Bone marrow biopsy revealed the aforementioned pathological changes.

16.1.5.3 Erythrocyte Volume

The erythrocyte volume measured by radionuclide labeling increased significantly (male >36 mL/kg, female >32 mL/kg). Erythrocyte volume measurement is an important index for the diagnosis of erythrocytosis. It has high repeatability, and the

error range is only ±5%. When complicated with portal hypertension, the increase of plasma volume may result in the false appearance of normal erythrocytic count, hemoglobin concentration and hematocrit. In addition, similar phenomenon may occur when iron is deficient. At this time, the detection of erythrocyte volume can be confirmed.

16.1.5.4 Others

1. Hemorheological examination showed that the blood viscosity was significantly increased and that the sedimentation rate was slowed down. The coagulation and fibrinolysis indexes were mostly normal. The release of vitamin B12 from granulocytes increased in about 40% of patients, so the level of serum vitamin B12 increased and that of folic acid often decreased. The levels of serum uric acid and lactate dehydrogenase increased. Blood gas analysis showed normal oxygen saturation. Serum EPO levels are often reduced.
2. Karyotype analysis of bone marrow chromosomes: about 30–40% of patients have acquired abnormalities, but no marker chromosomes. Trisomy 8 and 9 were the most common, among them, while the others were 20q-, llq-, and 13q-. Abnormalities such as 5q- and 7q- may also occur after chemotherapy, radiotherapy, or progression of the disease. The prognosis of patients with chromosomal abnormalities at diagnosis is poor [16, 17].
3. Echocardiography: About 77% of patients with PV have aortic or mitral valve lesions, such as valve thickening and vegetation, which is one of the pathological bases of thromboembolic complications.

16.1.6 Diagnosis and Differential Diagnosis

16.1.6.1 Diagnosis

The diagnostic criteria proposed by the WHO in 2016 [18]:

1. Main criteria:
   (a) Hb >185 g/L (male) or >165 g/L (female).
   Or male hematocrit >49%, female hematocrit >48%.
   Or increased red blood cell volume (RCM): >25% of the average normal predictive value.
   (b) Bone marrow biopsy showed age-adjusted three-line hematocytosis (full myelin hyperplasia), that is, significant erythroid, granulocyte, and megakaryocytic proliferation accompanied by pleomorphic, mature megakaryocytes (different sizes).
   (c) JAK2 V617F(+) or other functionally identical mutations such as JAK2 exon 12 mutation.
2. Secondary criteria:
   (a) Serum EPO is lower than the normal reference range.
   It can be diagnosed by meeting the three main criteria, or the first two major and minor criteria.

If Hb >185 g/L (male) or 165 g/L (female), HCT >52% (male) or 48% (female), JAK2 gene mutation is positive, and serum EPO is lower than the normal reference range, which met PV diagnostic criteria.

16.1.6.2 Differential Diagnosis

PV must be differentiated from secondary and relative polycythemia.

PV must be differentiated from secondary and relativistic polycythemia. Secondary erythrocytosis is caused by long-term and chronic hypoxia resulting in increased EPO, which stimulates the overreaction of bone marrow erythroid system, and can also be caused by EPO tumors. Relative erythrocytosis, also known as benign or pseudocytosis, is caused by reduced plasma volume, hence not true erythrocytosis. The three types of erythrocytosis are identified in Table 16.1.

PV also needs to be differentiated from other myeloproliferative diseases. In a small number of patients, the blood in the second and even the third line of the blood is significantly higher than normal, but none of them meet the criteria for diagnosis of PV or essential thrombocythemia (FT) or chronic myelogenous leukemia (CML). If one of the significantly increased ones involves red blood cells, it needs to be differentiated from PV. In principle, the diagnostic criteria for PV should be closely

Table 16.1 Identification of three types of polycythemia

	Polycythemia vera	Secondary polycythemia	Relative polycythemia
Pathogen	Unknown	Tissue hypoxia or abnormal EPO increased	Blood concentration
Skin and mucous membranes	Dark red	Common Cyanosis	No Cyanosis
Splenomegaly	More common	Rare	No
Hypertension	Common	No	No
Volume of erythrocytes	↑	↑	Normal
Volume of plasma	Normal or ↓	Normal or ↓	↓
Arterial oxygen saturation	Normal	Normal or ↓	Normal
White blood cell count	↑	Normal	Normal
Platelets count	↑	Normal	Normal
Neutrophil alkaline phosphatase concentration	↑	Normal	Normal
Bone marrow smear	Simultaneous proliferation of erythroid, granulocyte and megakaryocytes	Erythroid hyperplasia	Normal
EPO	↓or normal	↑	Normal
Serum vitamin B12	↑	Normal	Normal
EPO-free BFU-E growth	(+)	(−)	(−)

followed. If it is not met, it should be diagnosed as "myeloproliferative disease." Usually there is no need for treatment, and regular follow-up until the diagnosis is confirmed.

PV can be converted into myelofibrosis at later stage of disease. If patients visit a doctor at this stage, it can be misdiagnosed as primary myelofibrosis. The identification is mainly based on careful medical history. There is no other effective method.

16.1.7 Treatment

The goal of treatment is to reduce the risk of thrombosis and bleeding, to eliminate various symptoms and signs caused by erythrocytosis, to reduce the risk of transformation into myelofibrosis and acute leukemia and to reduce red blood cell capacity <0.55 [19].

1. First-line therapy
   (a) Prevention of thrombosis: Because embolism is the main cause of death in patients with PV, thrombosis prevention should be performed in patients diagnosed. Oral low-dose aspirin (100 mg/day) is preferred. Based on the evidence from the ECLAP study, it is recommended that patients with no specific contraindications should use low-dose aspirin [20].
   (b) Symptomatic treatment [21]: Venous bloodletting and myelosuppressive agents are often ineffective for skin itching. Since hot water bathing can aggravate skin itching, patients should be advised to reduce the frequency of baths or avoid bathing with overheated water. Aspirin and Cyproheptadine have a certain effect, but antihistamines do not. IFNα also plays a role, but with slower effect. Symptoms are usually relieved after controlling hemogram by chemotherapy and radiotherapy. Recent studies have shown that JAK2 inhibitors and mammalian rapamycin target protein inhibitors (mTOR inhibitors) are effective against refractory pruritus.
   (c) Venous bloodletting: Weekly bloodlets two to three times, each time 200~400 mL, until the hematocrit <0.45. This treatment can quickly relieve symptoms and reduce red blood cell volume, but cannot reduce the increase of white blood cells and thrombocytosis, nor can it alleviate the intractable skin rash and gout attack. Those who have heart or cerebrovascular disease or history of thrombosis should be careful in bloodletting. It should be no more than 200~300 mL each time, up to two times a week. To prevent thrombosis after bloodletting, low molecular dextran 500 mL should be infused intravenously after bloodletting, and ensure adequate intake. Erythrocyte monoharvesting can rapidly reduce HCT in a short period of time and can be used if necessary. Repeated venous bloodletting treatment may have associated symptoms and signs of iron deficiency, but generally no iron supplementation.

The treatment had the lowest proportion of leukemia conversion (1.5%) and secondary solid tumors and the least adverse reactions, and the median survival time was 12.6 years, similar to other treatments. However, the incidence of thromboembolic complications in the first 3 years of treatment alone was higher, and more patients were associated with myelofibrosis. It must be emphasized that even in patients who have only had bloodletting, their leukemia conversion is lower than other therapies, but it is still significantly higher than the matched normal population. The current consensus is that young patients with stable disease (<50 years old) and those who have no previous history of thrombosis are more suitable for bloodletting therapy and supplemented with low-dose aspirin.

(d) Decellular therapy: High-risk patients should receive decellular therapy. The patients who could not tolerate or needed frequent venous bloodletting, the patients with symptoms or progressive splenomegaemia, the patients with serious disease-related symptoms, PLT 1500×10^9/L and the patients with progressive increased leukocyte count (leukocyte count $>15\times10^9$/L) were all the patients treated with decellular therapy.

Hydroxylurea (HU) is most commonly used in Europe and America. The dose is 1.5~2 g/day. The blood level can reach the normal range within a few weeks, and then it is maintained at 0.5~1 g/day. The efficacy of HU is short-lived, and it often rebounds quickly after stopping the drug, so continuous medication is necessary. Once myelosuppression occurs, it can be recovered from days to weeks after stopping the drug. Acute leukemia occurred in 5.4% of patients treated with HU for a long time, although higher than venous bleeding, but the safety is relatively good. The occurrence of bone marrow fibrosis and mortality in HU is similar to that of venous bloodletting, and the thromboembolic complications are significantly reduced, only 6%. Therefore, HU often combines with venous bleeding to learn from each other.

For patients with ineffective treatment of HU, cyclophosphamide, busulfan, chlorambucil, (melphalan), and alkylating agents can be used.

The use of recombinant interferon alpha (IFNα) in the treatment of PV has a good effect [22]. It inhibits the proliferation of abnormally cloned hematopoietic progenitor cells and bone marrow fibroblasts, antagonizes platelet-derived growth factor (PDGF) and metastatic growth factor (TGF-β) to alleviate abnormal hematopoiesis and myelofibrosis. Because of the slow onset of IFNα, it should be used after the hemogram is obviously improved, as a long-term maintenance treatment. It can also be applied at the same time as other treatments to exert a superimposed effect. The dose of IFNα is 3 million U to 5 million U/time, three times a week, and the course of treatment is at least 6–12 months. IFNα also relieves intractable skin itching and is not associated with cytopenia. The conversion rate of long-term leukemia is lower than that of chemotherapy.

2. Second-line treatment: About 25% of patients are resistant or intolerant to hydroxyurea, and 20–30% of patients are intolerant to interferon. These patients can be treated with second-line therapy [23].
   (a) Radionuclide therapy: 32P is most commonly used, which inhibits hematopoiesis by releasing beta-rays to prevent nuclear division of bone marrow hematopoietic cells. After the first intravenous injection of 3~5 mCi, the hemogram returned to normal in 4 weeks, and the liver and spleen decreased. After 12–16 weeks, the second dose was 2~3 mCi. If the hemogram is not corrected, the second dose should be increased by 25%. A small number of patients need to be administered for the third time, but the total dose should not exceed 15 mCi within 1 year. 32P can also be administered orally, but the dose should be increased by 25%, divided into two times, 1 week apart. The remission rate of 32P treatment is 75~85%, the effect can last for 6 months to several years, and the thromboembolic concurrency can be significantly reduced. Its shortcomings is that the dose is difficult to control, too much dose can cause bone marrow suppression, too little dose is ineffective. In addition, the incidence of acute leukemia and solid tumor after treatment is significantly higher than that of venous bloodletting, especially the incidence of long-term acute leukemia is as high as 10–15%, mostly occurring 2–8 years after treatment. If chemotherapy is used after treatment, the incidence of acute leukemia is higher. In view of the above reasons, 32P is currently only used for elderly patients who need frequent bloodletting, long-term application of myelosuppressive drugs, and liver and kidney function. The median survival of the 32P treatment was 10.9 years.
   (b) Ruxolitinib [24]: In an international, randomized, open-label, multicenter phase III clinical trial, relying on venous bloodletting for PV patients with splenomegaly was randomized to receive Ruxolitinib (110 cases, starting dose 20 mg/day) or standard treatment (112 cases, physicians choose hydroxyurea, interferon, anagrelide, lenalidomide, thalidomide, or no treatment according to the situation), After 32 weeks of treatment, for Ruxolitinib group and standard treatment group, the HCT control rate (HCT <45%) was 60% and 20%, spleen volume reduced by 35% was 38% and 1%, complete hematologic remission rate was 24% and 9%, symptoms reduced by 50% were 49% and 5%, respectively. Based on this result, in December 2014, Ruxolitinib was approved by the FDA for the treatment of PV patients with poor or intolerable hydroxyurea. The recommended starting dose is 20 mg/day. Dosage adjustment is not performed for the first 4 weeks of treatment. The interval between dose adjustments should not be less than 2 weeks, and the maximum dose should not exceed 50 mg/day.

   The most common hematologic adverse effects of Ruxolitinib are grade 3/4 anemia, thrombocytopenia, and neutropenia, but rarely lead to treatment interruption. If peripheral blood PLT $<50 \times 10^9$/L or neutrophil absolute value $<0.5 \times 10^9$/L, and HGB <80 g/L, the treatment should be discontinued. The drug should be gradually reduced within 7–10 days. Avoid sudden

withdrawal. It is recommended to add prednisone (20–30 mg/day) during the withdrawal.

3. Antihypertensive treatment
   As the primary disease is controlled, hypertension can be ameliorated. Patients with elevated blood pressure may use vasodilators, calcium channel blockers, and vasoconvertase inhibitors to reduce blood pressure but diuretics are prohibited to avoid the decrease of blood volume and further increase of blood viscosity leading to thrombosis. At the same time, an anticoagulant is used in combination to prevent thrombosis.
4. Other treatments
   (a) In PV patients with marked increase in platelets, if hydroxyurea is ineffective, anagrelide can be used at a dose of 24 mg/day, which works within 1 week, with a response rate of 75%, but with adverse reactions such as headache, palpitations, diarrhea, and liquid retention.
   (b) In late-stage PV combined with myelofibrosis, which is the stage of PV failure, patients often have spleen, anemia, leukocytopenia, and thrombocytopenia, and the treatment is very difficult. Radiotherapy in the spleen area has been confirmed to be ineffective, and splenectomy can achieve temporary relief. Since the general condition of the patient is usually poor at this time, and the complications are many, the mortality rate is as high as 25%. Therefore, it should be carried out cautiously and fully prepared before surgery. Patients with severe anemia who need regular blood transfusions may also be treated with androgens. Iron supplementation should be cautious when iron deficiency occurs, which can promote the rapid increase of red blood cells in the short term and aggravate the condition.
   (c) Patients with PV have complications with surgical diseases, including tooth extraction, postoperative complications up to 47%, most of which are hemorrhagic or thromboembolic complications; the risk is greater. Preoperative venous bloodletting and hematocyte replacement before surgery are recommended. The blood level is obviously improved, and then the surgery is performed.

16.1.8 Prognosis

Most of PV is slow to develop, but the prognosis is poor. The average survival time of nontreated patients is about 18 months. According to relevant statistics, the median life expectancy of untreated patients is 1.5 years. After various treatments, the median survival period can reach 10–15 years. The hypertension caused by PV improves with the improvement of PV conditions.

The first cause of death of PV is thromboembolic complications, accounting for 30–40%, myocardial infarction accounted for 50%, stroke accounted for 31.5%, venous thrombosis accounted for 18.5%, and other causes of death were acute leukemia (19%), solid tumor (5%), and bleeding (5%). The remaining cases died of advanced bone marrow failure, including myelofibrosis, most of which were due to neutrophil deficiency, death from infection, followed by thrombocytopenia and death from visceral hemorrhage. PV can be converted to other myeloproliferative

diseases and/or acute leukemia during the course of the disease, and in some cases, there can be multiple transformations. Individual cases are converted to chronic lymphocytic leukemia. Those who are converted to acute leukemia have poor therapeutic effects and usually die within a few months.

As the primary disease is controlled, hypertension in PV patients can be improved. Patients with elevated blood pressure may use vasodilators, calcium channel blockers, and vasoconvertase inhibitors to reduce blood pressure, but diuretics are prohibited from reducing blood volume-induced thrombosis.

16.2 Anemia

Amin Shi

Anemia is a common clinical symptom, which can be caused by different reasons or diseases. Anemia can be a primary cause of hematopoietic organ disease or a concomitant symptom of some systemic diseases. Anemia can cause elevated blood pressure by itself, or it can coexist with hypertension as two manifestations of a disease, which requires careful identification and vigilance against the possibility of some systemic diseases.

16.2.1 Definition and Diagnostic Criteria

1. **Definition:** Anemia refers to a syndrome in which the erythrocyte volume of the human peripheral blood decreases below the lower limit of the normal range and insufficient oxygen is transported to the tissues. The concentration of hemoglobin in the peripheral blood per unit volume, RBC count, and/or hematocrit are lower than the normal standards of the same age, sex, and region.
2. **Diagnostic Criteria:** Becase the red blood cell volume measurement is complex, often in clinical hemoglobin (HB) concentration of red blood cell (RBC) count and/or hematocrit (HCT) to replace, but mainly by the hemoglobin concentration is the most important, it is generally believed in the sea areas in China, adult male HB <120 g/L, RBC <4.5 × 10^{12}/L, and/or HCT <42% and adult female HB <110 g/L, RBC <4.0 × 10^{12}/L, and/or HCT <37%, can be diagnosed with anemia. In foreign countries, it is generally based on the diagnostic criteria established by WHO in 1972, that is, in the sea level area, the diagnosis of anemia is made when the HB level is lower than the following levels: 110 g/L for children aged 6 months to less than 6 years; 120 g/L for children aged 6–14 years; 130 g/L for adult males; 120 g/L for adult females (130 g/L for postmenopausal women); and 110 g/L for pregnant women [25].

   The hemoglobin concentration of infants, children, and pregnant women is lower than that of adults, and the normal hemoglobin value of residents living in plateau areas is higher than that of residents living at sea level. Meanwhile, attention should be paid to the fact that when the plasma volume increases, the blood is diluted and the hemoglobin concentration decreases, which is easily misdiagnosed as anemia.

In dehydration or decreased circulating blood volume, anemia can be masked by increased hemoglobin concentration due to blood concentration.

16.2.2 Pathogenesis

1. **Physiological changes of human red blood cells**
   Red blood cells are derived from hematopoietic stem cells in the bone marrow. Under the influence of hematopoietic microenvironment (protein, erythropoietin, iron, folic acid, vitamin B12, etc.), hematopoietic stem cells first differentiate into erythroid oriented progenitor cells, and after multiple proliferation and differentiation, they become mature erythrocytes. After many proliferation differentiation, become mature red blood cells with the average life expectancy of 90–120 days. Aging red blood cells are destroyed by phagocytosis in the mononuclear macrophage system. About the same amount of red blood cells (1/120 or 0.8% of the whole body) are destroyed and born every day.
2. **Pathogenesis of Anemia**
   (a) Abnormal erythropoiesis anemia (hematopoietic stem progenitor cells, hematopoietic dysregulation, and hematopoietic raw materials lack or use disorder): Hematopoietic stem cell damage or the bone marrow microenvironment defect of congenital abnormal erythropoiesis anemia, Aplastic anemia are of ineffective hematopoiesis, and form of refractory anemia characterized by malignant clone hematopoietic system disease, such as myelodysplastic syndrome [26]. Myelopathic anemia resulting from myelofibrosis or infiltration of abnormal cells (such as leukemia or metastatic cancer). During the proliferation and differentiation of erythroid progenitor cells, folic acid and vitamin B12 are important coenzymes for the synthesis of cell DNA. If there is a lack of folic acid and vitamin B12, it can cause the stagnation of nuclear division, forming megaloblastic erythrocytes with unbalanced nuclear and plasma development, leading to megaloblastic anemia. The synthesis of hemoglobin began from early young red blood cells, iron first synthesis is blood red element and protoporphyrin, later is blood red element and globin synthesis of hemoglobin, iron deficiency or iron metabolic disorders can result in iron deficiency anemia, iron bead young cell anemia and chronic anemia, porphyrin metabolic disorders, can cause porphyrin disease, globin synthesis disorders can result in hemoglobin disorders and globin generation barrier anemia (Mediterranean anemia).
   (b) Erythrocyte destruction anemia: Hemolytic anemia occurs when certain external factors (including physicochemical infection or immunity) or erythrocyte internal factors (membrane defect, enzyme defect, abnormal hemoglobin structure, etc.) shorten the life span of erythrocytes and cause too much damage, which exceeds the compensation ability of bone marrow hematopoiesis.
   (c) Hemorrhagic anemia: Excessive loss of red blood cells, acute and chronic hemorrhagic anemia, including bleeding from ulcer disease, bronchiectasis, hemoptysis, hemorrhoids, and traumatic blood loss [26].

(d) Secondary anemia: Secondary anemia caused by various chronic diseases and systemic diseases (such as renal failure, liver disease, endocrine disease, gastrointestinal disease, etc.), such as renal insufficiency, pituitary or hypothyroidism, liver disease, etc., can be caused by insufficient erythropoietin and lead to anemia. Neoplastic diseases or certain viral infections can induce negative hematopoietic regulatory factors and inhibit hematopoiesis, leading to anemia [26].

In short, the pathogenesis of anemia is relatively complex and diverse. The same type of anemia may coexist with different pathogenesis. In aplastic anemia, in addition to bone marrow hematopoietic stem cell injury and microenvironmental defects, there are cellular immune mechanism factors. Certain tumor (be like lymphoma) besides encroach marrow outside still can cause autoimmune anemia.

3. **Anemia and Hypertension**

Anemia and hypertension concerns are complex. Anemia itself can cause hypertension. Primary lesions leading to anemia may be associated with hypertension, and anemia related drugs may cause high blood pressure.

(a) Anemia itself can cause elevated blood pressure: mainly occurs when anemia is compensated. First, when associated with anemia caused by hemodynamic changes, increased cardiac output, heart rate differential pressure of arteries and veins increases, leads to increase in systolic blood pressure second, anemia, when blood flow to the heart muscle of oxygen sensitive organs such as brain, and in the kidney, caused renal hypoxia ischemia, activation of the RAS system that can lead to high blood pressure, renal vasoconstriction. In addition, the higher incidence of hypertension in children with chronic hemolytic anemia (such as sickle cell anemia) may be associated with increased erythropoietin (EPO), increased blood viscosity, renal endothelin abnormalities, or other renal tubular sodium transport defects in chronic anemia [27].

(b) Secondary anemia, as one of the manifestations of some systemic diseases, may be associated with hypertension, common diseases listed below (Table 16.2), common in clinical renal disease lead to anemia and high blood pressure for see, mainly because the kidney is the important viscera of erythropoietin, regulate the production of the red blood cells, anemia and high blood pressure, kidney disease become easily happened.

(c) Some drugs used to treat anemia can raise blood pressure, drugs such as glucocorticoid cyclosporine erythropoietin can cause drug-induced hypertension.

16.2.3 Classify

There are a variety of classification methods of anemia, commonly used according to the red blood cell morphology, hemoglobin concentration, anemia etiology and pathophysiology and bone marrow proliferation or not and classification.

Table 16.2 Anemia associated with hypertension common diseases.

Diseases	Disease name
Connective tissue disease	Rheumatoid arthritis Systemic lupus erythematosus Vasculitis
Endocrine disease	Hyperthyroidism Hypothyroidism Pheochromocytoma
Diseases of urinary system	Diabetic nephropathy Chronic urinary tract infection A variety of causes of kidney failure
Tumor	Multiple myeloma Lymphoma Small cell lung cancer Bronchial carcinoid
Other	Severe trauma Burns Thrombotic phlebitis

Table 16.3 Cytological classification of anemia

Type	MCV (fL)	MCH (pg)	MCHC (%)	Common diseases
Macrocytic anemia	>100	>34	32~36	Megaloblastic anemia
Normocytic anemia	80~100	27~34	32~36	**Aplastic anemia**
Hemolytic anemia				
Acute hemorrhagic anemia				
Microcytic hypochromic anemia	<80	<27	<31	Iron deficiency anemia Iron granulocyte anemia Globinogenesis anemia

Red blood cell morphological classification Anemia is divided into three categories according to mean red blood cell volume (MCV), mean red blood cell hemoglobin concentration (MCHC), and mean red blood cell hemoglobin content (MCH) (Table 16.3).

1. Macrocytic anemia: MCV >l00 fL, red blood cell diameter >10 m; most of this kind of anemia is normal pigment type and belongs to this type of anemia mainly due to folic acid and/or vitamin B12 deficiency caused by megaloblastic anemia, Hemolytic anemia occurs when the number of reticulocytes increases, Anemia of liver disease and hypothyroidism.
2. Normocytic anemia: MCV between 80 and l00 fL; most of this kind of anemia is normal pigment type, a few can have low pigment type and belongs to this kind of anemia mainly due to aplastic anemia, hemolytic anemia, acute hemorrhagic anemia, hypersplenism, and chronic renal failure caused by anemia.

Table 16.4 Classification criteria of anemia severity [25]

Hemoglobin concentration	<30 g/L	30~59 g/L	60~90 g/L	90~110 g/L
Red blood cell	$<1 \times 10^{12}$/L	$(1\sim2) \times 10^{12}$/L	$(2\sim3) \times 10^{12}$/L	$(3\sim4) \times 10^{12}$/L
Severity of anemia	Extremely severe	Severe	Moderate	Mild

3. Microcytic hypochromic anemia: MCV <80 fL, MCHC<31%; iron deficiency anemia, aplastic anemia (thalassemia), iron granule anemia, and some chronic anemia belong to this type of anemia.
   (a) Anemia was divided into mild, moderate, severe, and extremely severe anemia according to the concentration of hemoglobin and the number of red blood cells (Table 16.4).
   (b) According to the classification of the etiology and pathogenesis of anemia, anemia can be divided into the following categories: decreased erythropoiesis, including the lack of hematopoietic raw materials (iron folic acid, vitamin B12, etc.), and bone marrow diseases that affect the production of red blood cells; excessive destruction of red blood cells, anemia due to excessive destruction of red blood cells and insufficient compensatory capacity in the body; and hemorrhagic anemia.
   (c) According to the classification of bone marrow hyperplasia, anemia can be divided into hyperplastic anemia, including iron deficiency anemia, hemorrhagic anemia, and hemolytic anemia; dysplasia such as aplastic anemia.

   Clinical applications often combine several methods; erythrocyte morphological taxonomy can provide clues to the diagnosis of anemia, especially for iron deficiency anemia and megaloblyte anemia. Hemoglobin concentration has a certain practical value, can help determine the severity of anemia. However, according to the classification of etiology and pathogenesis, anemia caused by a variety of factors or with complicated mechanism cannot be classified, and it needs to be analyzed according to different conditions, such as chronic system diseases (cirrhosis, uremia).

16.2.4 Pathophysiology

1. The pathophysiological basis of anemia is a decrease in hemoglobin, the ability of the blood to carry oxygen is reduced, hypoxia changes in body tissues and organs, the body give play to the role of the corresponding compensation, such as pulse frequency increased faster heart beat with a breathing accelerate erythropoietin increase and a decreased hemoglobin affinity with oxygen, make more blood flow to the lack of oxygen sensitive organs such as brain heart [1]. The body's compensation for anemia includes a reduction in oxygen consumption, which is sometimes greater than normal due to the overload of the lungs and heart during anemia. Others, reduce the affinity between hemoglobin and oxygen: when anemia occurs, the production of 2,3-diphosphoglycerate (2,3-DPG) in red blood cells is increased, the PH value in red blood cells is increased, and the oxygen released in tissues is increased, so as to reduce hypoxia of tissues.

Redistribution of blood oxygen in tissues: blood flow is mainly to organs sensitive to hypoxia (such as heart and brain muscles) and is decreased in skin mucosa and kidney. With the increase of cardiac output, there were hemodynamic changes such as increased heart rate and pulse pressure difference. Respiratory hyperplasia: The increased production of erythropoietin by the kidney is up to 1000 times of normal and bone marrow hyperplasia is up to six to ten times of normal. These compensatory effects, coupled with inadequate oxygen supply, result in a range of clinical manifestations.

Anemia symptoms and severity depend on the causes of anemia and the primary disease, the rate of anemia occurred, the degree of anemia, body compensatory ability and the ability to adapt to oxygen in addition, also with the patient's age, with or without basic diseases such as cardiovascular disease and cerebrovascular disease and cardiovascular system of compensatory capacity if anemia occurred more rapidly, blood volume decreased significantly, older patients, with cardiopulmonary disease, clinical symptoms can be serious if the anemia is slow, the body has enough time to compensate, even more severe (Hb <60 g/L), the symptoms of anemia can be lighter.

2. Anemia itself can cause elevated blood pressure: mainly occurs when anemia is compensated. First, when associated with anemia caused by hemodynamic changes, increased cardiac output, heart rate differential pressure of arteries and veins increases, leads to increase in systolic blood pressure. When anaemia occurs, blood can flow to the heart, brain, muscle and other organs sensitive to hypoxia, and decrease in the kidney, cause renal hypoxia, ischemia, activation of RAS system so that renal vasoconstriction can cause blood pressure rise. In addition, chronic anemia with erythropoietin increased, the blood viscosity increases, also can cause high blood pressure.

   Secondary anemia, as one of the manifestations of some systemic diseases, may be complicated with hypertension. Anemia and hypertension caused by renal diseases are common. This type of anemia is mainly caused by a decrease in EPO due to impaired renal function, resulting in anemia. Anemia also causes renal hypoxia, ischemia, activation of the RAS system makes renal vasoconstriction can cause high blood pressure, high blood pressure in turn worsen kidney.

   Medications for anemia can raise blood pressure, and medications such as glucocorticoids, cyclosporins, and erythropoietin can lead to drug-induced hypertension.

16.2.5 Clinical Manifestations

The clinical manifestations of anemia are associated with five factors which is the etiology of anemia (including the related diseases that cause anemia), the degree to which anemia leads to a decrease in oxygen-carrying capacity of blood, the degree to which blood volume drops during anemia, the rate of anemia, and the ability of the blood circulation and respiratory system to compensate for and tolerate anemia.

1. General manifestation: fatigue, fatigue is the most common and earliest symptom of anemia. Severe anemia can appear low thermal and basal metabolic rate increased pale skin and mucosa is the main sign of anemia, must pay attention to the temperature of the environment factors such as personal skin pigment and subcutaneous tissue water content will affect the color of skin to observe the nail bed palpebral conjunctiva of oral mucosa and tongue is more reliable.
2. The most common symptoms of cardiovascular system are palpitation, shortness of breath and hypertension. Patients often have a fast heart rate (more than 100 beats per minute) and a very strong heartbeat. Blood pressure increased, mainly systolic blood pressure increased, accompanied by increased pulse pressure (more than 50 mmHg). Severe anemia can appear angina, heart failure, physical examination may have heart enlargement, apex or bottom of the heart appear gentle systolic murmur, lower limb edema. ECG showed ST segment decrease, T wave flatness or inversion. These symptoms and signs disappear after anemia is corrected.
3. Central Nervous System: Headache, dizziness, dizziness, tinnitus, memory loss, inattention, and lethargy are common symptoms. Patients with severe anemia may experience syncope. Elderly patients may have confusion and mental abnormalities. Vitamin B12 deficiency can lead to limb numbness and sensory disorders.
4. Digestive System: Anorexia, abdominal distension, nausea, and other symptoms are more common; atrophy of tongue and mastoid process can be seen in nutritional anemia; jaundice and splenomegaly can be seen in hemolytic anemia.
5. Urogenital System: Anemia when the renal vasoconstriction and renal hypoxia can appear mild proteinuria and urine concentration function decline, the performance of nocturnal polyuria. Sexual desire changes and menstrual disorders were also common in women.
6. Others: Dry skin, dry hair, slow wound healing. Fundus pallor and retinal hemorrhage are rare.

16.2.6 Diagnosis

Diagnosis of anemia involves understanding the extent, type, and cause of anemia. The etiology diagnosis of anemia is the most important, only to find out the cause, can be reasonable and effective treatment of anemia.

1. Collect Medical History: Detailed questions should be asked about present and past history, family history, nutrition history, menstrual and reproductive history, and risk factor exposure. The history of present illness is an examination of the timing, speed, severity, complications, possible triggers, and response to intervention of anemia occured. The past history may provide clues to the cause of the disease. Family history provides the genetic background for anemia. Nutritional history, menstrual history and reproductive history are of auxiliary diagnostic value for anemia and hemorrhagic anemia caused by deficiency of

iron, folate or vitamin B12. A history of risk factor exposure is important for the diagnosis of anemia associated with hematopoietic tissue damage and infection [25]. It mainly includes acute or chronic bleeding, diarrhea, black stool, soy sauce urine menorrhagia, nutrition condition, history of exposure to chemical poisons, radioactive substances, or special drugs; Anemia in the family; A history of chronic inflammation, infection, liver and kidney disorders, connective tissue disease, and malignancies.

2. Physical Examination: Based on the general performance for anemia and influence on the system, carefully with general physical examination, should pay special attention to skin sclera for yellow dye, presence of bleeder skin and mucosa, liver and spleen enlargement and, lymph node, heart murmur, The anal finger examination has bloot. Flat or sunken nails are common in iron-deficiency anemia. Atrophy of the lingual papilla and deep sensory disturbance of the nervous system are seen in vitamin B12 deficiency.
3. Laboratory Examination: Laboratory examination is the main basis for the diagnosis of anemia, and it should be conducted from simple to difficult, including blood examination, bone marrow examination, and laboratory examination for the pathogenesis of anemia.
   (a) **Blood**: It mainly includes routine blood tests such as peripheral blood smear count and erythrocyte count.

   Routine Blood Tests: Hemoglobin and red blood cell count are reliable indicators for the determination of anemia. Cytological classification based on the mean red blood cell volume (MCV) calculated from the hemoglobin concentration red blood cell count and the hematocrit (MCH) and the mean red blood cell hemoglobin concentration (MCHC) is helpful for the diagnosis and classification of anemia.

   Peripheral Blood Smears: Peripheral blood smears can observe the changes in the number and morphology of red blood cells, white blood cells, and platelets, whether there are abnormal cells and malaria parasites, etc., which can provide diagnostic clues for the nature and type of anemia, and should be paid enough attention to, such as the size of red blood cells and the enlargement of the central pale staining area in iron deficiency anemia. Spherocytosis is seen in hereditary spherocytosis. Erythrocyte basophilic stipulation occurs in lead poisoning; target erythrocytes are found in globin-producing anemia. Lacrimal erythrocytes are seen in myelofibrosis. Rouleau was found in multiple myeloma. The possibility of microangiopathologic hemolysis is often suggested by various erythrocytes or fragments of erythrocytes. The occurrence of late and young red blood cells suggests that the proliferation of red blood cells is accelerated or anemia caused by myelopathy or hematopoiesis.

   Reticulocyte Count: It can help understand the proliferation of red blood cells and, as early indicators of anemia after treatment efficacy, should be as a routine examination in patients with anemia of normal adults reticulocyte accounted for 0.2~1.5% in the peripheral blood increased reticulocyte in hemolytic anemia after massive bleeding or after effective treatment, reticulocyte reduce in aplastic anemia.

(b) Bone Marrow Examination: Bone marrow smear classification reflects the degree of proliferation of bone marrow cells, cell composition ratio, and morphological changes, bone marrow biopsy reflects the degree of structural proliferation of bone marrow hematopoietic tissue cell composition and morphological changes [25]. Any unexplained anemia should be treated with bone marrow puncture, if necessary should also be treated with bone marrow biopsy. Examination of bone marrow specimens should first visually observe whether the bone marrow granule is rich, whether the fat droplets are too much. Under a microscope to observe the nucleated cell hyperplasia, proportion of each series of cell count, and presence of abnormal cells or parasites. Bone marrow examination results should be combined with outine blood and clinical manifestations for a correct diagnosis, sometimes needs a bone marrow biopsy or histochemical staining and chromosome examination.

(c) Etiological Examination: Etiological examination items were selected according to patients' different conditions, including routine urine biochemical immunology fecal occult blood and parasite eggs examination, various special hemolysis tests, X-ray examination, gastroscopy, histopathology, and nuclide examination.

16.2.7 Treatment

The treatment of anemia and hypertension is mainly aimed at the symptoms of anemia and hypertension. While improving the symptoms of anemia, appropriate antihypertensive drugs should be selected for antihypertensive therapy to actively clarify the causes of anemia and hypertension.

1. Symptomatic Treatment: Treatment is mainly to relieve severe anemia in patients with fatal effects, improve symptoms of anemia, improve patient hemoglobin content, improve the symptoms of oxygen in the body, to find the reason that anemia and high blood pressure and treatment time, such as blood transfusion, blood transfusion can quickly relieve or correction of anemia, anemia is symptomatic treatment of the main measures in acute blood loss, blood transfusion can quickly restore blood volume and correction of anemia of chronic anemia have obvious symptoms in hypoxia, blood transfusion can make its ease symptoms. However, over a long term, a large number of blood transfusions may cause iron overload and appear secondary blood disease, therefore for some chronic refractory anemia should try to use a small amount of multiple transfusions in order to reduce blood transfusion on the cardiovascular system load and the transfusion reaction caused by repeated blood transfusion, should try to use red blood cells composition blood transfusion due to blood transfusion may be serious transfusion reaction increase hepatitis, malaria, syphilis, and AIDS chance of infection, therefore, must strictly grasp the indications of blood transfusion anemia with bleeding or infection, should according to the specific situation at the same time be bleeding or anti-infection treatment [25].

2. Etiological Treatment: Eliminating the cause of anemia is the first principle in treating anemia. The nature of the cause of anemia determines the therapeutic effect of anemia. There are three main treatments for anemia, depending on the cause: drugs, splenectomy, and bone marrow transplantation.
   (a) **Medication for Anemia**: Different medications are used for different causes of anemia. Therefore, it is necessary to understand the pharmacological properties and effects of various drugs and strictly grasp the indications. Before the cause of anemia is clear, medicines should not be taken casually, otherwise can make the situation complicates, cause the difficulty on diagnosis, and delay treatment. The following drugs are commonly used to treat anemia:

   Iron agent: Commonly used ferrous preparation, such as ferrous succinate, ferrous fumarate, ferrous gluconate, etc., is only effective for iron deficiency anemia, and it is not suitable for long-term application of iron agent for non-iron deficiency anemia.

   Folic acid and vitamin B12: Only for the deficiency of these two vitamins of megaloblastic anemia. Hemolytic anemia occurs because the need of folic acid is increased, also can compensatory folic acid.

   Glucocorticoid: The good curative effect to the autoimmune hemolytic anemia, may also be used for hemorrhage tendency of the patient.

   Androgen: Commonly used is a synthetic derivative of testosterone, long-term application (>3–6 months) can make aplastic anemia reduce some of the chronic refractory anemia which also has a certain effect, the application process to monitor the liver function, or add the use of hepatoprotective drugs.

   Cyclosporine-A: An immunosuppressant commonly used in organ transplantation. In recent years, it has been used in the treatment of aplastic anemia and has achieved good results. Some people have tried it in myelodysplastic syndrome and paroxysmal sleep hemoglobinuria.

   Erythropoietin: A recombinant human EPO gene that corrects renal anemia and is often used in conjunction with hemodialysis. It can also be used for anemia of chronic diseases, improve the hemoglobin level, and improve the quality of life of patients, but long-term application can cause increased blood pressure.

   (b) **Splenectomy**: The spleen is the main site of destruction of red blood cells and is also involved in the production of antibodies. Splenectomy can reduce red blood cell destruction and anemia in patients with hereditary spherocytosis and hypersplenism. Splenectomy is also effective in patients with autoimmune hemolytic anemia who cannot maintain the therapeutic effect with glucocorticoid.

   (c) **Bone Marrow Transplantation**: Bone marrow transplantation is mainly used for severe aplastic anemia and some severe aplastic anemia. Bone marrow transplantation requires high technical conditions, and the patient is no more than 45 years old, so donors with HLA matching are needed. Moreover,

the high medical cost limits the wide application of bone marrow transplantation, and it is difficult to carry out generally at present.

3. Treatment of Anemia with Hypertension
   (a) First, treatment should be targeted at basic diseases. Blood pressure caused by anemia itself can be decreased after anemia is corrected.
   (b) Anemia and hypertension caused by systemic diseases should be treated on the premise of primary disease. Meanwhile, the selection principle of correct anemia and anti-hypertensive therapy for anti-hypertensive drugs depends on the specific primary disease. For example, alpha-receptor blockers are preferred for hypertension caused by pheochromocytoma. Beta blockers are preferred for hypertension caused by hyperthyroidism. Hypertension caused by renal failure should be carefully treated with ACEI or ARB class antihypertensive drugs, calcium antagonist diuretics can be selected; Diuretics should be avoided in patients with severe burn injuries, where blood volume is often inadequate, and blood viscosity in multiple myeloma is often significantly elevated.
   (c) For hypertension caused by anemia drugs, EPO is the first-line treatment for renal anemia recommended by domestic and foreign guidelines. Long-term use of EPO is usually associated with elevated blood pressure, but there is no need to stop or discontinue erythropoietin treatment because of high blood pressure, except for uncontrolled hypertension. The Japanese guidelines recommend that mild elevated blood pressure caused by EPO should be considered a response to improve anemia rather than an adverse reaction. Patients' HB level should be closely monitored, and EPO dosage should be adjusted according to the appropriate HB target value, so as to ensure that patients with CKD can use EP0 reasonably, so as to achieve the goal of correcting anemia and effectively control the fluctuation of blood pressure [28].

16.2.8 Prognosis

The prognosis of anemia depends on the cause. Dystrophic anemia and hemorrhagic anemia have good prognosis. Except for tumors, secondary anemia has good prognosis. Systemic diseases with anemia have poor prognosis. Hypertension caused by anemia itself can be recovered after correction of anemia, but if combined with hypertensive heart disease, blood pressure control is relatively difficult and may require long-term drug treatment.

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