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Review article

Erythropoietin Resistance in Hemodialysis Patients

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SUMMARY

Anemia is defined as blood hemoglobin concentration of less than 120 g/l in women and less than 130 g/l in men. The main cause of the development of anemia in patients treated with regular hemodialysis is the lack of endogenous erythropoietin, and its main clinical consequences are: progressive decline in residual renal function, development of cardiovascular disorders, disorders of cognitive functions and a decrease in the quality of life of these patients. Despite the administration of an appropriate dose of erythropoietin, in 5-10% of patients treated with regular hemodialysis, there is resistance to erythropoietin activity. The main risk factors for the development of resistance to the effects of erythropoietin are: iron deficiency, microinflammation, deficiency of vitamin D, secondary hyperparathyroidism, deficiency of vitamin C, and inadequate hemodialysis. The main side effects of erythropoietin are: hypertension, thrombosis of the vascular approach to hemodialysis, and the red blood cell precursor aplasia in the bone marrow. Early detection and elimination of risk factors, optimization and individualization of hemodialysis prescription prevent the development of resistance to erythropoietin activity, enable the achievement of target blood hemoglobin, reduce the development of cardiovascular morbidity, and improve the quality of life of these patients.

Key words: **anemia, erythropoietin resistance, hemodialysis, microinflammation, vitamin D deficiency**

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INTRODUCTION

Anemia is defined as blood hemoglobin concentration of less than 120 g/l in women and less than 130 g/l in men (1, 2). The main cause of the development of anemia in patients with chronic kidney disease is the deficiency of endogenous erythropoietin, and its main clinical consequences are: progressive decline in residual renal function, development of cardiovascular and cognitive disorders, and a decrease in the quality of life of patients treated with regular hemodialysis. It is present in 90% of patients who suffer from the advanced stage of chronic kidney disease (GFR < 25-30 ml/min/1.73 m^2) (1, 2). Erythropoietin should be administered when the blood hemoglobin level is less than 110 g/l, and the target hemoglobin level in patients treated with regular hemodialysis should be 110-120 g/l (Table 1) (1, 2). Despite the use of an appropriate dose of erythropoietin (the original formulation, biosimilar erythropoietin), in 5-10% (by some authors and up to 30%) of patients treated with regular hemodialysis there is resistance to erythropoietin activity (inability to reach the target hemoglobin concentration in the blood) (1, 2).

Table 1. **Types of agents that stimulate erythropoiesis: dose and frequency of administration (i.v. application)**

Type of erythropoietin	Initial dose	Frequency of maintenance dose
Epoetin-α	50 IU/kg, 3 x per week	1-3 x week
Epoetin-β	40 IU/kg, 3 x per week	1-3 x week
Epoetin-δ	40 IU/kg, 3 x per week	1-3 x week
Darbepoetin-α	0.45 μg/kg, 1 x per week 0.75 μg/kg, 1 x 2 weeks	1 x 2 weeks/ 1 x month
CERA	0.6 μg/kg, 1 x 2 weeks	1 x month

CERA - Continuous Erythropoietin Receptor Activator: Metoxy polyethylene glycol-epoetin beta

Resistance to erythropoietin effects

Resistance to erythropoietin activity is an independent risk factor for the development of cardiovascular morbidity (acute myocardial infarction, impaired cardiac failure, and stroke) and adverse outcome for patients treated with regular hemodialysis (3). The development of resistance to the effect of erythropoietin may indicate: a significant reduction in blood hemoglobin concentration in addition to a constant dose of erythropoietin, a significant increase in the dose of erythropoietin to maintain the target hemoglobin concentration, or an inability to increase the hemoglobin concentration at levels above 110 g/l despite administering erythropoietin at a dose of ≥ 500 IU/kg/week (3). According to European recommendations, resistance to erythropoietin activity is defined as the inability to achieve the target blood hemoglobin concentration (Hb = 110-120 g/l) using erythropoietin at a dose of ≥ 300 IU/kg/week (≥ 20,000 IU/week) or darbepoetin-a at a dose of ≥ 1.5 μg/kg/week (≥ 100 μg/week) or as a constant need for high doses of erythropoietin in order to maintain the target hemoglobin concentration (3). An alternative method for measuring the severity of resistance to erythropoietin activity is the Erythropoietin Resistance Index - ERI (3). It represents the ratio of a weekly dose of erythropoietin depending on body weight and blood hemoglobin (EPO/kg/weekly/Hb). The erythropoietin resistance index (ERI) > 0.02 μg/kg/week/g Hb indicates the presence of erythropoietin resistance (3).

Risk factors for the development of resistance to erythropoietin

The main risk factors for the development of resistance to erythropoietin activity are iron deficiency, inflammation, lack of vitamin D and secondary hyperparathyroidism, while other risk factors include: infec-

tion, malnutrition, chronic hemolysis, hemoglobinopathy, aluminum intoxication, deficiency of vitamin C, vitamin B12, folic acid and L-carnitine, as well as anti-EPO antibodies (3).

IRON DEFICIENCY

Iron deficiency can be absolute (saturation of transferrin with iron - TSAT < 20%, serum ferritin concentration - F < 100 ng/ml) and functional (saturation of transferring with iron - TSAT < 20%, serum ferritin concentration - F > 100 ng/ml) (3). Absolute iron deficiency is most commonly due to occult gastro-intestinal bleeding (uremic gastritis, anticoagulation of ventricular circulation), and the main causes of functional iron deficiency in patients treated with regular hemodialysis are: microinflammation, deficiency of vitamin D, secondary hyperparathyroidism and vitamin C deficiency (Table 2) (3).

Table 2. **Parameters for the evaluation of iron status in the patient's organism**

Parameters	Iron deficiency	Excess iron
TSAT (%)	< 20	> 50
F (ng/ml)	< 100	> 800
HYPO (%)	< 2.5 (< 10)	> 10
CHr (pg)	< 32.2	> 33
sTfR (mg/ml)	> 1200	< 1000

TSAT - saturations of transferrin by iron, F - serum ferritin concentration, HYPO - percentage of hypochromic erythrocytes, CHr - hemoglobin content in reticulocyte, sTfR - concentration of the solubil transferin receptor in the serum

According to the recommendations of KDIGO (Kidney Disease Improving Global Outcomes), i.v. iron should be applied in patients treated with regular iron hemodialysis when the saturation of transferrin with iron - TSAT is < 30%, and serum ferritin concentration is less than 500 ng/ml (4, 5). Intravenous iron administration provides a faster rise in blood hemoglobin concentration, and its main disadvantages are: blood vessel damage (difficulty in making arteriovenous fistula) and the appearance of serious adverse events - SAE (4, 5). Adverse reactions to the intravenous administration of iron may be allergic and toxic. Patients who have a high risk of developing serious adverse reactions should be identified, that is, those with: bronchial asthma, mastocytosis, earlier allergic reactions, and atopic constitution (4, 5). According to EMA (European Medicine Agency) recommendations, after i.v. administration of iron, patients should be monitored for 30 minutes. In addition to potential for allergic reactions, i.v. application of iron increases the risk of oxidative stress, infections (de novo infection, worsening of the existing infection) and the development of secondary hemochromatosis (intravenous iron should not be used in patients with active systemic infection) (4, 5). Oxidative stress (free oxygen radicals) accelerates the development of atherosclerosis and increases the risk of developing cardiovascular complications. Uncontrolled i.v. iron application can be accompanied by its accumulation in the liver, pancreas and the heart, and this results in the development of disorders of the function of these organs (saturation of iron transfer - TSAT ≥ 50%, serum ferritin concentration - F ≥ 800 ng/ml) (4, 5). The gold standard for the measurement of iron content in the organism of patients with secondary hemochromatosis (hemochromatosis associated with hemodialysis) is the measurement of the concentration of iron in the liver (the concentration of iron in the liver correlates with the total iron content in the organism of the patient with secondary hemo-chromatosis). Measurement of iron concentration in the liver is performed by nuclear magnetic resonance. In healthy subjects, the upper normal iron concentration in the liver is 32 μmol/g, and an increased concentration of iron in the liver indicates a concentration higher than 50 μmol/g and a concentration higher than 200 μmol/g indicates a heavy load

of the liver with iron (4, 5). The only available iron chelator is deferoxamine (Deferoxamine, Desferal®), used for the prevention of secondary hemochromatosis (haemhromatosis associated with hemodialysis) and for the treatment of organ function disorders due to iron precipitation (cardiac insufficiency, multiple endocrinology disorders, liver cirrhosis) (during IV infusion deferoxamine may show an allergic reaction) (4, 5).

The two most important preparations for the intravenous use of iron are: ferric gluconate (Ferrlecit®) and iron sucrose (Venofer®) (have a low risk of adverse reactions) (6, 7). The recommended dose for ferric gluconate is 1000 mg, divided into eight doses (one dose after each individual hemodialysis: 62.5 mg/ml (125 mg/2 ml). Iron sucrose is a formulation widely used in the world and in the Republic of Serbia, mostly in the population of patients treated with hemodialysis [iron (III) - hydroxide saccharose complex: Ferrovin amp. 100 mg/5 ml, 0.9% NaCl sol. 100 ml + Ferrovin amp. 100 mg/5 ml = i.v. infusion 25 ml (25 mg), as test dose for 15 minutes, into the venous segment of the ventral circulation]. If no adverse reactions occur in this period, the infusion of the remaining solution should be continued at a rate not higher than 50ml over 15 minutes (slow i.v. infusion over one hour in the last hour of hemodialysis) (6, 7). The recommended dose for iron sucrose is 1000 mg, divided into ten doses (one dose after each individual hemodialysis: 100 mg/ml) (6, 7). The incidence of severe hypersensitivity reactions to the iron sucrose preparation is 0.6/1.000.000 patients, and on the preparation of ferric gluconate 0.9/1.000.000 patients (6, 7). Regardless of the small risk of hypersensitivity reactions, the doctor is obliged to inform the patient of the possible risk of the administration of the intravenous iron preparation (a test dose is recommended, the hemodialysis unit should have a complete anticoagulation therapy, it is recommended that iron be administered in small doses in the form of spray i.v. infusion, medical staff should be educated for identifying, evaluating and treating adverse reactions to iron) (6, 7).

MICROINFLAMMATION

Microinflammation (CRP > 5 mg/l) is a significant risk factor for developing resistance to erythropoietin activity. Chronic kidney disease is a chronic microinflammatory condition characterized by a constant mild increase in the concentration of proinflammatory cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNFα) (persistent microinflammatory low grade) (8). It is present in 30-50% of patients treated with regular hemodialysis, and its main causes are: increased production and decreased clearance of proinflammatory cytokines, oxidative stress, metabolic acidosis, vitamin D deficiency , chronic recurrent infection associated with vascular access (occult infection of vascular access for hemodialysis), chronic periodontal disease, bioincompatibility of venous circulation and membranes for hemodialysis, conventional solution for hemodialysis (microbiological quality of water and hemodialysis solution) (8). In addition to systemic microinflammation, there is local microinflammation in these patients, that is, the activation of the immune system cells in the bone marrow (mycroenvironment of the hematopoiesis: monocytes, T-lymphocytes) accompanied by increased formation and secretion of proinflammatory cytokines (8). Proinflammatory mediators exhibit a direct and indirect negative effect on the hematopoietic process. The direct negative effects include: blocking the proliferation and differentiation of the red cell precursor cells, blocking the secretion of endogenous erythropoietin, and the main indirect negative effect is the stimulation of the synthesis and secretion of hepcidin in hepatocytes (IL-6 stimulating the secretion of hepcidin) (8). Ultrafine solution for hemodialysis can slow down the residual kidney function, improve the nutriational status of patients, increase the sensitivity of erythropoietin, and reduce the cardiovascular mortality of patients with chronic renal failure of the kidney treated with hemodialysis (8). Optimization of dialysis treatment, use of dialysers with polysulphonic membranes and ultra-pure bicarbonate solution for hemodialysis reduce the serum CRP concentration, resistance to erythropoietin activity, and help achieving and maintaining the target hemoglobin concentration in the blood of these patients (8).

DEFICIENCY OF VITAMIN D

The deficiency of vitamin D is a new risk factor for the development of erythropoietin resistance (9). In patients treated with regular hemodialysis, the normal concentration of 25(OH)D in the serum is 30-80 ng/ml, and the deficiency of vitamin D is defined as the concentration of 25(OH)D in the serum of < 30 ng/ml. A mild deficiency of vitamin D exists if the concentration of 25(OH)D is 20-30 ng/ml, the deficiency is moderate if the concentration of 25(OH)D is 10-20 ng/ml, and the severe deficiency of vitamin 25(OH)D is present if the concentration of 25(OH)D in the serum is less than 10 ng/ml (9). The main clinical consequences of vitamin D deficiency in patients with chronic kidney disease, including pati-

ents treated with hemodialysis include: development of secondary hyperparathyroidism, decreased bone density (osteoporosis), atherosclerosis and vascular calcification, cognitive function disorder, resistance to erythropoietin effect and anemia, progressive loss of kidney function and adverse outcome of patients (9). The mechanism of action depends on the local inflammation induced by vitamin D deficiency (the mechanism of action independent of blocking the secretion of parathormone) (9). Cells of the immune system in the bone marrow (monocytes, T-lymphocytes) on the surface of the membrane exhibit a vitamin D receptor - VDR. Due to the deficiency of vitamin D, monocytes and T-lymphocytes in the bone marrow increasingly produce and secrete proinflammatory mediators (interleukin-1, interleukin-6, tumor necrosis factor alpha, interferon gamma factor). The liberated proinflammatory cytokines block the proliferation and differentiation of red cell precursor cells and secretion of endogenous erythropoietin stimulate the secretion of hepcidin and the development of a functional iron deficiency. Hepcidin binds to ferroportin (receptor) on the surface of the macrophage of the reticuloendothelial system and blocks the release of iron (functional iron deficiency, deficiency of iron available for the erythrocytopoiesis process) (9).

In patients receiving hemodialysis, the deficiency of vitamin D should be treated with ergocalciferol (Ergocalciferol caps 1.25 mg = 50.000 IU) or cholecalciferol (Cholecalciferol amp 25.000 IU/ml, oral solution) over a period of 3-6 months (9). In the case of severe vitamin D deficiency, ergocalciferol is administered at a dose of 50.000 IU/week for the first month, and then continues at a dose of 50.000 IU/month for three months, so that the total dose is 350,000 IU for four months. In patients with vitamin D serum concentration of 10-30 ng/ml, ergocalciferol is administered at a dose of 50.000 IU/month for four months. According to the KDIGO recommendations, the use of ergocalciferol is indicated until the concentration of vitamin D in the serum is higher than 30 ng/ml (30-80 ng/ml) (9). In addition to ergocalciferol (vitamin D2), cholecalciferol (vitamin D3) can also be used. It is administered at a dose of 25.000 IU/week, and in patients treated with hemodialysis with a vitamin D concentration of less than 15 ng/ml, it is administered at a dose of 50.000 IU/week, for a period of 3-6 months, all until the target vitamin D concentration of 25(OH)D ≥ 30 ng/ml is reached in the serum (9). In patients with regular hemodialysis, the concentration of vitamin D in the serum should be measured once a year (9).

SECONDARY HYPERPARATHYROIDISM

Secondary hyperparathyroidism is a common complication in patients who are being treated with hemodialysis. The main factors triggering the development of secondary hyperparathyroidism are: deficiency of active metabolite of vitamin D [1.25(OH)2D3], hypocalcaemia and hyperphosphatemia, and its main clinical consequences are: bone diseases (renal osteodystrophy), cardiovascular diseases (vascular and valvular calcification) and the resistance to erythropoietin activity (10-13). High parathormone values (iPTH > 500 pg/ml) increase resistance to erythropoietin by their direct and indirect toxicity. Directly toxic effects include blocking of the secretion of endogenous erythropoietin, blocking of the proliferation and differentiation of red cell precursor cells and increased erythrocyte fragility (shortened erythrocyte life span), and indirectly, it includes bone marrow fibrosis - OF (Osteitis Fibrosis). Optimal control of secondary hyperparathyroidism is important for reducing the resistance to erythropoietin activity. The results of the studies conducted so far have shown that paracalcitol and cinacalcet reduce resistance to erythropoietin activity and contribute to better control of anemia in patients treated with regular hemodialysis (13-15). The use of paracalcitol is associated with lower values of the resistance index on the action of erythropoietin (15). In patients treated with cinacalcet over a nine-month period, there is a statistically significant increase in blood hemoglobin levels without a change in the dose of erythropoietin. The latest studies indicate that cinacalcet provides optimal control of anemia, reduces resistance to erythropoietin activity (indirectly via parathormone) and reduces the dose of darbepoietin (13, 14).

DEFICIENCY OF VITAMIN C

Patients treated with regular hemodialysis have a deficiency of vitamin C due to reduced dietary intake (fresh fruits and vegetables in addition to vitamin C also contain significant amounts of potassium) and its elimination during hemodialysis (low molecular weight - MW = 176.1 Da, in a small percentage it is bound to plasma proteins - PB = 25%, hydrosoluble vitamin) (16, 17). During the hemodialysis session, from 100-300 mg of vitamin C is removed (the concentration of vitamin C after the hemodialysis session is reduced by 30-50%) (16, 17). Normal serum vitamin C concentration is 30-60 μmol/l, and patients who are treated with regular hemodialysis often have a severe deficiency of vitamin C

(serum vitamin C concentration < 10 μmol/l) and require replacement of this vitamin. The results of the tests done so far have shown that the oral dose of vitamin C in patients treated with regular hemodialysis should be 100-200 mg/day, and the i.v. dose should be 300-500 mg, 3 x weekly, after each hemodialysis session, with appropriate monitoring for early detection of systemic oxalosis (16, 17). Systemic oxalosis is manifested by the deposition of oxalate crystals in the retina, skin, joints and interstitium of myocard (16, 17). Intravenous use of vitamin C reduces the concentration of ferritin and proinflammatory mediators in serum, and reduces resistance to the effect of erythropoietin in patients who are treated with regular hemodialysis (16, 17).

Choice of modality of dialysis in patients with resistance to erythropoietin activity

Results of studies show that on-line hemodialysis reduces resistance to erythropoietin activity and its consumption (optimal control of anemia) (18, 19). Reducing resistance to erythropoietin activity results from increased hepcidin removal during hemo-diafiltration session (there is a statistically significant positive linear correlation between the erythropoietin resistance index and the hepcidin effect in the serum) (18, 19). Hepcidin, as a medium molecular weight substance (MW = 2791 Da), is moderately removed during the standard hemodialysis session with a *"high-flux"* membrane, while the highest rate of removal is achieved during the on-line hemodiafiltration session as a result of convective transport (18, 19). A significant reduction in the concentration of hepcidin in the serum is achieved after 3-6 months of online treatment by hemodiafiltration. Online hemodialysis reduces inflammation, increases the availability of iron for erythropoiesis (improves "functional" iron deficiency) and reduces the destruction of red blood cells in the circulation (18, 19). The results of the clinical study REDERT show that online hemodiafiltration statistically significantly reduces inflammation, oxidative stress, the concentration of β2-microglobulin and serum hepcidin, and erythropoietin resistance versus patients who are treated with "low-flux" bicarbonate hemodialysis (18, 19). Patients who undergo hemodiafiltration online over a period of three to six months have a statistically significantly lower concentration of CRP and interleukin 6 (IL-6) in serum compared to patients treated with standard bicarbonate "low-flux" hemodialysis (18, 19).

Dialysis with a polysulfone membrane containing vitamin E statistically significantly reduces resistance to erythropoietin activity and provides better control of anemia in patients treated with regular dialysis versus standard dialysis (20-23). Polysulphonic membranes containing vitamin E have an antioxidant effect, reduce lipid peroxidation and block the formation of free radical oxygen (reduce oxidative stress). In addition to the antioxidant effect, these membranes reduce the concentration of the inflammatory median (anti-inflammatory effect), all of which result in the prevention of cardiovascular disease development, lower resistance to erythropoietin activity and better control of anemia in patients treated with regular hemodialysis (20-23). The results of the conducted clinical studies show that six months after treatment with dialysate with semi-voluptial membranes containing vitamin E, there is a statistically significant increase in hemoglobin concentration in the blood, reduction of the resistance index to erythropoietin activity, decrease in the concentration of C-reactive protein, interleukin-1 and interleukin 6 in serum, and serum oxLDL lipoprotein concentrations, compared to patients treated with regular dialysis, with no vitamin E-containing polysulfone membranes (20-23).

Adverse effects of erythropoiesis stimulating agents

The main side effects of erythropoietin include: hypertension, thrombosis (increased risk of thrombosis of the vascular access for hemodialysis) and Pure Red-Cell Aplasia - PRCA (creation of anti-EPO antibodies) (24-26). Hypertension is due to an increase in peripheral vascular resistance, and prevention involves a gradual increase in blood hemoglobin (≤ 0.3-0.4 g/dl /week). The risk of thromboembolism is associated with an increase in blood hemoglobin levels (24-26).

The use of erythropoietin (EPO) can be accompanied by the formation of antibodies (anti-EPO antibodies) and the PRCA (24-26) red cell precursor plasma aplasia. The incidence of PRCA is 0.02-0.03/10,000 patients per year, and in the last decade it is decreasing (most PRCA cases was evidenced in 2002/2003) (24-26). The risk factors that contribute to the development of PRCA include: erythropoietin-related factors (formulation stabilizers, protein aggregation, and erythropoietin length) and factors associated with the patient (age, gender, immune status, comorbidities) (24-26).

PRCA is the most severe complication of erythropoietin administration, characterized by the complete absence of precursor of red blood cells in the normal bone marrow, and clinically it manifests as a severe, progressive and isolated anemia with a sudden onset. The complete absence of red blood cell production is follow-

ed by a very low reticulocyte count (< 10.000/mm^3). The degree of decline in hemoglobin concentration of approximately 0.1 g/dl/day (~ 1.0 g/dl/week) may indicate the development of PRCA. It is necessary to do a biopsy of the bone marrow and determine the number of reticulocytes. In patients with reticulocyte counts less than 10 x 10^9/l, in the absence of erythrocyte precursor cells (absence of erythroblasts), the concentration of anti-EPO antibodies should be measured. Diagnosis of PRCA caused by erythropoietin is demonstrated by the absence of precursors of red blood cells in the bone marrow and by the proving anti-EPO antibodies (24-26). Treatment of PRCA consists in interruption of the use of erythropoietin, transfusion of deplasmated erythrocytes (~ 1 U/week, patients become dependent on transfusion of deplasmated erythrocytes), corticosteroid administration (0.5-1.0 mg/kg/day) and immunosuppressants (cyclosporin 200 mg/day or cyclophosphamide) (24-26). Biosimilar epoetin should be supplemented as well as comparative effectiveness and safety (biosimilars vs. Originators) in patients with renal anemia on hemodialysis.

CONCLUSION

In patients treated with regular hemodialysis, there is resistance to erythropoietin activity. The main risk factors for the development of resistance to the effects of erythropoietin are: iron deficiency, microinflammation, deficiency of vitamin D, secondary hyperparathyroidism, deficiency of vitamin C and "low-flux" hemodialysis. Early detection and elimination of factors that cause erythropoietin resistance can help achieve the target hemoglobin value, reduce the amount of erythropoietin, reduce treatment costs, reduce the development of cardiovascular morbidity and mortality, and improve the quality of life of patients treated with regular hemodialysis.

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Rezistencija na eritropoetin kod bolesnika na hemodijalizi

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SAŽETAK

Anemija se definiše kao koncentracija hemoglobina u krvi manja od 120 g/l kod žena i manja od 130 g/l kod muškaraca. Glavni uzrok razvoja anemije kod bolesnika koji se leče redovnom hemodijalizom je nedostatak endogenog eritropoetina, a njene glavne kliničke posledice su: progresivno opadanje rezidualne renalne funkcije, razvoj kardiovaskularnih poremećaja, poremećaj kognitivnih funkcija i smanjenje kvaliteta života ovih bolesnika. i pored primene odgovarajuće doze eritropoetina, kod 5-10% bolesnika koji se leče redovnom hemodijalizom postoji rezistencija na dejstvo eritropoetina. Glavni faktori rizika za razvoj rezistencije na dejstvo eritropoetina su: nedostatak gvožđa, mikroinflamacija, nedostatak vitamina D, sekundarni hiperparatireoidizam, nedostatak vitamina C i neadekvatna hemodijaliza. Glavna neželjena dejstva eritropoetina su: hipertenzija, tromboza vaskularnog pristupa za hemodijalizu i aplazija prekursora crvenih krvnih ćelija u koštanoj srži. Rano otkrivanje i uklanjanje faktora rizika, optimizacija i individualizacija preskripcije hemodijalize sprečavaju razvoj rezistencije na dejstvo eritropoetina, omogućavaju postizanje ciljne vrednosti hemoglobina u krvi, smanjuju razvoj kardiovaskularnog morbiditeta i popravljaju kvalitet života ovih bolesnika.

Ključne reči: **anemija, rezistencija na eritropoetin, hemodijaliza, mikroinflamacija, nedostatak vitamina D**