

ANEMIA OF CHRONIC DISEASE: ILLNESS OR ADAPTIVE MECHANISM

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SUMMARY – The anemia of chronic disease (ACD) is the most prevalent anemia after iron deficiency anemia. It is associated with infectious, inflammatory and neoplastic disease. ACD is a medical condition caused by the release of cytokines which mediate inflammatory and immune response (tumor necrosis factor, interleukins 1 and 6, and interferon). Abnormal iron metabolism with iron trapping in reticuloendothelial cells is primarily the cause of this condition, making iron unavailable for erythropoiesis although iron tissue reserves are elevated. Disorder in erythropoietin secretion and shortening of red cell life span also play a role in the pathogenesis of ACD. The main therapy is treatment of the underlying disorder and red cell transfusions in severe anemia. In more severe (protracted) anemias that lead to impaired quality of life and have an impact on the mortality and survival rate, erythropoiesis stimulating agents are used. Recently, new possibilities are being evaluated in terms of therapy for ACD in defined conditions, such as chelating agents, as well as hepcidin antagonist and other erythropoiesis stimulating agents.

Key words: *Anemia – blood; Anemia – physiopathology; Anemia – therapy; Chronic disease; Inflammation*

Introduction

The anemia of chronic disease (ACD) is a result of body response to inflammatory or system disease¹. It was first described in 1930 and thoroughly described in 1950 by Wintrobe and Cartwright². ACD, usually a mild to moderate anemia, is the most prevalent anemia after iron deficiency anemia and also the most prevalent anemia in hospitalized patients. This anemia, first described in chronic infections, may be found in subjects with diseases involving acute or chronic immune activation and thus could be seen in a variety of inflammatory conditions, acute or chronic infections, rheumatologic disorders, autoimmune disorders and cancer³. Most patients with ACD do have

active infections, inflammatory conditions, or malignancy. In severe acute infection and sepsis, ACD can develop within few days⁴. Not only fever associated with infections has been shown to inhibit bacterial growth, but decreased iron concentrations (as seen in ACD) act synergistically with pyrexia to inhibit bacterial growth. Thus, attempt by hosts to withhold iron from the invaders has been termed ‘nutritional immunity’ and has been postulated to be an adaptive factor of ACD in infections. In malignant disease, the incidence of ACD can be as high as 70%, and even higher in patients treated with radiotherapy and chemotherapy⁵. Also, ACD can also be seen in severe trauma, alcoholic liver disease, congestive heart failure, thrombosis, chronic pulmonary disease, diabetes, or can be associated with a variety of medical problems. Besides other factors, age also influences the development of ACD.

It is considered that many factors have a role in the pathogenesis of ACD but it is still not fully understood.

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The multifactorial etiology of ACD involves not only block in iron reutilization by red blood cells (RBC) but also a decreased RBC lifespan, direct inhibition of hematopoiesis, and relative deficiency of erythropoietin. The severity and grade of ACD are related to the stage of underlying condition. Many studies have shown that the grade of anemia associated with underlying disease is an important prognostic factor, but it has not been elucidated whether treatment of ACD contributes to better prognosis⁶. ACD is characterized by decreased serum iron, decreased total iron-binding capacity and increased iron stores. Reduced level of plasma iron is the main laboratory finding in ACD. Therefore, differentiating between ACD and iron deficiency anemia can be diagnostically challenging. In both conditions, iron plasma level is reduced. However, in iron deficiency anemia, iron deficit is absolute, whereas in ACD it is functional and characterized by macrophage iron retention induced by cytokines and the master regulator hepcidin⁷. Thus, in ACD, iron body reserves are increased, but iron is unavailable for hemoglobin synthesis due to the increased reuptake of iron within reticuloendothelial cells (which are iron reservoir in human body). The increased release of cytokines, such as interleukin(IL)-1, IL-6, tumor necrosis factor (TNF)-alpha and transforming growth factor (TGF)-beta, which is indirectly mediated *via* interferon (IFN) alpha, beta and gamma, results in abnormal iron metabolism that is the central disturbance in the pathogenesis of ACD^{8,9}. Also, expression of the liver-derived acute phase protein hepcidin, the key regulator of iron homeostasis, is induced by both iron overload and inflammatory stimuli. Hepcidin binds to ferroportin, the only known iron export protein, resulting in the internalization and degradation of this transporter, which then blocks iron export from enterocytes and macrophages to the circulation¹⁰.

The aim of this article is to present new insights in the ACD pathogenesis, treatment options and treatment issues.

The Pathogenesis of ACD

Anemia of chronic disease is anemia connected with inflammation or system disease. It is mediated by inflammatory cytokines TNF, IL-1, IL-6 and IFN. Studies on humoral mediators have shown an increased concentration of inflammatory cytokines in

chronic diseases and their relation with ACD. Proinflammatory cytokine activity contributes to iron metabolism dysregulation, decreased RBC production in bone marrow, shortening the RBC lifespan, and decreased erythropoietin secretion¹. This multifactorial etiology of ACD associated with inflammatory cytokines is present in underlying diseases and the most frequent causes and prevalence of ACD are listed in Table 1³.

Cytokine activity on disturbance in iron metabolism is the main feature of ACD. Iron plasma level is decreased, while the level of iron in the reticuloendothelial system is increased. Reduced availability of iron leads to restricted iron in erythropoiesis. Additionally, inflammatory cytokines stimulate iron storage into macrophages in multiple ways: stimulating receptors for erythrophagocytosis, stimulating expression of the protein divalent metal transporter (DMT-1) through which the transmembrane import of non-transferrin iron and inducing transferrin receptor (TfR) iron uptake in macrophages occur. The increased iron storage in macrophages and hepatocytes leads to increased ferritin expression^{8,9}.

Disturbance in iron metabolism can be explained by hepcidin activity. Hepcidin is a peptide synthesized in the liver. Normally, hepcidin synthesis is increased in iron excess and decreased in anemia and hypoxia. It is a systemic regulator of iron transport from iron storage cells into plasma due to its inhibitory effect on iron release from cells, by degradation of ferroportin, which is the only iron export protein. In inflammatory state induced by IL-6, hepcidin synthesis is increased leading to decreased iron release from macrophages and other iron storage cell, thus causing plasma hypoferrremia^{10,11}.

The mechanism of decreased RBC half-life in ACD was not understood for a long time. It is considered that inflammatory cytokine IL-6 activates mac-

Table 1. Underlying causes of anemia of chronic disease³

Underlying disease	Prevalence (%)
Infection (acute or chronic)	18-95
Neoplasm (hematologic or solid)	30-77
Autoimmune diseases	8-71
Chronic rejection after transplantation	8-70
Chronic kidney disease	23-50

rophages and leads to RBC hemolysis. The mechanism of hemolysis is explained in increased erythrophagocytosis, which is the normal pathway for degradation of old RBC and reutilization of iron from heme¹¹.

In ACD, the RBC production in bone marrow is impaired due to the inhibitory effects of TNF-alpha, beta and IL-1, which is indirectly mediated by IFN alpha, beta and gamma. The most potent inhibitory effect appears to be the one by IFN gamma. The mechanism involves induction of apoptosis or down-regulation of the expression of erythropoietin receptors or other hematopoietic growth factors. Acute phase proteins efficiently inhibit TfR and TfR mediated iron uptake in erythroid precursors^{12,13}. Also, in *in vitro* conditions, hepcidin has an inhibitory effect on the erythroid colony forming units¹⁴.

Serum erythropoietin level in ACD is inadequate for the degree of anemia, due to decreased renal production mediated by inflammatory cytokines. Erythropoietin response in ACD appears to be more inadequate if the activity of the underlying disease is more severe and if the levels of plasma cytokines, especially IFN gamma and TNF alpha, are higher. The inhibitory cytokine effects on erythroid colony forming units can be partially prevented by increased levels of erythropoietin¹⁵.

Diagnosis of ACD (Laboratory Findings)

The diagnosis of ACD is based on exclusion and is often difficult. Various laboratory tests have been suggested as helpful. The best way to diagnose ACD is to document anemia of underproduction (low reticulocyte index) with low serum iron and transferrin levels and elevated serum ferritin in a setting of systemic, usually

inflammatory illness. Other causes of anemia (hemolysis, nutritional deficiency, or sequestration) should be ruled out. A component of iron deficiency should be strongly considered in a patient with systemic inflammation and low or 'normal' serum ferritin. Often those other causes of anemia accompany ACD.

The anemia of chronic disease is usually normocytic and normochromic, and in some cases can be microcytic and hypochromic. Anemia is usually mild with hemoglobin concentration ≥ 100 g/L or moderate with hemoglobin in the range of 85-100 g/L; hemoglobin level of < 85 g/L can only be found in some patients.

Reticulocyte count is normal or low as well. Definitive diagnosis may be difficult to reach if there is coexisting blood loss, the effects of medication or hereditary defects of hematopoiesis such as thalassemia. Body iron status should be evaluated, so that iron deficiency anemia can be ruled out. In ACD and iron deficiency anemia, serum concentration of iron and transferrin saturation (Fe/TIBC ratio) are reduced, which indicates hypoferrremia due to higher storage in reticuloendothelial cells in the former and absolute iron deficiency in the latter (Table 2)¹⁵.

Ferritin as a marker of body iron reserves is a general indicator of iron quantity in reversible reserves (stores). In iron deficiency anemia, ferritin level is lower than 30 ng/mL, whereas in ACD its level is normal or higher. The soluble transferrin receptors (sTfR) are fragments of membrane receptors that are increased when iron availability for erythropoiesis is low, which is the way how the body manifests iron deficiency. In ACD, the levels of sTfR are normal because inflammatory cytokines have negative effect on TfR expression. Some data indicate that sTfR offers

Table 2. Serum levels differentiating anemia of chronic disease (ACD) from iron deficiency anemia and combined states¹⁵

Variable	ACD	Iron deficiency anemia	Combined states
Iron	Low	Low	Low
Transferrin	Low or normal	High	Low
Transferrin saturation	Low	Low	Low
Ferritin	Normal or high	Low	Low or normal
Soluble transferrin receptors (sTfR)	Normal	High	Normal or high
sTfR/log ferritin index	Low (<1)	High (>2)	High (>2)
Cytokine levels	High	Normal	High

little advantage over conventional laboratory indicators of iron status⁶ and might not assess iron status in ACD patients. The ratio of sTfR (nmol/L) concentration and log of the ferritin level ($\mu\text{mol/L}$) (sTfR/log ferritin index) may be helpful. A ratio less than 1 suggest ACD, and ratio more than 2 ACD with co-existing iron deficiency^{7,15,16}. Bone marrow examination (cytochemistry) may also be helpful in differentiating ACD and iron deficiency anemia. Assessment of bone marrow aspirate stained with Perls' stain has been considered the gold standard for the diagnosis of iron deficiency anemia, but the results may vary greatly depending on the method of examination. In typical cases, extra-hemoglobin iron level is increased in ACD and decreased or absent in iron deficiency anemia. Bone marrow iron is almost never used for clinical decision in daily practice, and decisions are instead based only on peripheral iron indices¹⁷.

Treatment of ACD

Treatment of ACD is seldom needed. Correction of underlying condition or disease is therapy of choice for ACD. In most cases, termination of inflammatory process leads to correction of anemia. Blood transfusion therapy is an option as quick therapy in severe anemia. Iron as therapy option in ACD is not efficient, and may even be harmful because it is an essential nutrient for proliferating microorganisms as well as for tumor cells^{4,18,19}. Patients with ACD and absolute iron deficiency may receive iron supplementation. Reduced response to endogenous erythropoietin encouraged research into the usage of erythropoietin as a therapy option in ACD. In that case, recombinant human erythropoietin (rhEPO) is used for correction of anemia and its therapeutic effect has been shown in a large number of studies^{20,21}. The level of endogenous erythropoietin does not correlate with the response to rhEPO therapy, although in patients with a reduced level of endogenous erythropoietin, rhEPO therapy may lead to better therapeutic response. The dosage of rhEPO for treatment of ACD is several times higher than that used for anemia in chronic kidney disease. ACD does not need correction in every case, but always requires correction in conditions where it affects the quality of life, e.g., in patients with cancer or where it affects lifelong prognosis, as in patients with heart failure or chronic renal failure^{20,21}. Accord-

ing to guidelines, the target hemoglobin level is 110 to 120 g/L because higher levels can be associated with higher mortality²¹.

New findings on ACD pathophysiology will provide a new therapeutic approach for these patients. It is considered that iron chelation therapy can induce endogenous formation of erythropoietin, and hepcidin antagonist may prevent the retention of iron within the reticuloendothelial system²²⁻²⁴. Moreover, iron chelators such as deferoxamine have been shown in some studies to exert mild effect on ACD, perhaps also by decreasing free radicals and inflammation. New tests providing better distinction between the functional and absolute iron deficiency will enable better therapeutic regimen for ACD⁷.

Treatment Issues in ACD

The main question is whether ACD is neglected and underdiagnosed, and on the other hand, should we insist on treating mild or moderate ACD?

There is a hypothesis suggesting that ACD is in fact a protective and adaptive mechanism of the human body as a response to the underlying disease and that treatment of mild and moderate anemia leads to higher mortality²⁵. Under normal conditions, tissue oxygen supply is four times higher than the needs. Thus, in conditions of mild or moderate non-acute anemia, tissue is provided with an adequate amount of oxygen.

In many underlying conditions such as in patients with cancer, heart failure or chronic renal failure, anemia is associated with a higher mortality rate. However, the degree and severity of anemia only reflect the severity of the underlying disease.

A number of studies have identified anemia as an independent predictor of poor prognosis; however, in some studies, anemia was excluded as an independent prognostic factor if the variables such as C-reactive protein and the level of cytokines, which reflect the severity of inflammation were included⁹. In this case, if anemia is a marker of the underlying disease, therapy of anemia cannot improve the overall prognosis.

According to the hypothesis that anemia is an adaptive mechanism of the human body in response to the underlying disease, iron retention in macrophages is one of the mechanisms that limit the amount of iron available to microorganisms and cancer cells, as iron

is an essential nutrient for their growth^{4,19}. A meta-analysis of 51 randomized studies has shown higher mortality associated with the use of erythropoiesis-stimulating agents (ESAs) in order to achieve normal hemoglobin level rate compared to lower hemoglobin level in patients with cancer²¹. Studies involved patients with neck and head tumors, non-small lung carcinomas and breast carcinoma. This result is attributed to a higher rate of thromboembolic incidents in patients with a higher level of hemoglobin and to stimulation of tumor growth³².

If ACD is a protective mechanism, then attempts to treat it should have negative effects on the human body. This hypothesis has been supported in many studies that monitored the impact of RBC transfusion or use of ESA²⁶⁻³⁰.

Two observational studies have proven that RBC transfusion can be a predictor of lethal outcome in critically ill patients (sepsis, congestive heart failure, severe pancreatitis) if administered under less rigorous conditions (Hb <100 g/L) than according to conservative criteria (Hb <70-80 g/L). Mortality rate was significantly higher in the group of patients that received transfusion under less rigorous criteria compared with those that received transfusion under conservative criteria (16.1% *vs.* 8.7%)²⁷⁻³¹. A higher mortality rate due to the treatment of anemia was demonstrated in three observational studies in patients with acute coronary syndrome²⁹.

According to a meta-analysis, the use of ESA has no benefit in terms of overall mortality rate in critically ill patients regardless of the reduced transfusion usage²⁶⁻³⁰. In patients with chronic renal insufficiency anemia, there are two important components: anemia due to erythropoietin deficiency and ACD. The use of ESA in the treatment of anemia in chronic kidney disease resulted in great benefit because the higher hemoglobin level decreased comorbidities and development of system disease, thus reducing the component of ACD. In these patients, the higher mortality rate (hazard ratio 1.10) due to the use of ESA, when a higher hemoglobin level has been attained, is in correlation with the higher incidence of thromboembolic incidents (7.5% *vs.* 4.9%)^{31,32}.

Currently, there are no published studies reporting the results of ACD treatment with ESA in patients with rheumatoid arthritis and inflammatory bowel

disease, which would be very informative for the hypothesis that anemia is an adaptive response and that if treated it may worsen rather than improve clinical outcome.

Conclusion

There has been progress in the understanding of the pathophysiology of ACD. This refers to new findings in the understanding of iron homeostasis and its disturbances, particularly to the action of hepcidin that binds to ferroportin resulting in iron block in macrophages. These new insights have contributed to the development of new recommendations for the treatment of ACD. As for now, treatment of ACD includes therapy for the underlying disease, RBC transfusion, and in some cases erythropoietin usage. In the future, strategies could include the use of iron chelator therapy, which induces endogenous erythropoietin synthesis; hepcidin antagonist which would prevent iron retention in the reticuloendothelial system; and inflammatory cytokine antagonists^{23,24}. A recent hypothesis and studies have raised the issues of the usefulness or harmfulness of ACD treatment, especially when it is mild or moderate.

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Sažetak

ANEMIJA KRONIČNE BOLESTI: BOLEST ILI ADAPTIVNI MEHANIZAM

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Anemija kronične bolesti je iza sideropenične anemije najraširenija vrsta anemije. Pojavljuje se uz infekcije, upale i zloćudne bolesti. Nastaje kao posljedica lučenja upalnih citokina koji posreduju u upalnom i imunom odgovoru (faktor nekroze tumora, interleukin-1 i interferoni). Glavni poremećaj se sastoji u poremećenom metabolizmu željeza koje ostaje zarobljeno u stanicama retikuloendotelnog sustava i nije na raspolaganju eritropoezi iako ga u tkivnim rezervama ima u suvišku. Također je poremećeno lučenje eritropoetina i skraćen je poluživot eritrocita. Liječenje se sastoji u terapiji osnovne bolesti, transfuzijama eritrocita kod teže anemije, a kod dugotrajnih anemija koje ugrožavaju kavalitetu života i imaju utjecaj na ukupnu smrtnost i možda preživljenje terapija se po određenim definiranim uvjetima može provoditi tvarima koje stimuliraju eritropoezu. U novije vrijeme se razmatraju i druge mogućnosti liječenja poput kelirajućih tvari.

Ključne riječi: *Anemija – krv; Anemija – patofiziologija; Anemija – terapija; Kronična bolest; Upala*