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Anemia in Chronic Obstructive Pulmonary Disease

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death worldwide, and it is projected to be the third by 2020 or earlier. Patients with COPD frequently have other chronic diseases and systemic effects that worsen their clinical status and prognosis. The best recognized manifestations include the presence of concomitant cardiovascular disease, skeletal muscle wasting, osteoporosis and lung cancer. Although COPD is "traditionally" associated with polycythemia there is a growing body of literature on the relationship between anemia and COPD. Recent studies described that anemia in patients with COPD is more frequent than expected, with a prevalence ranging from 8 to 33%. Systemic inflammation may be an important pathogenic factor, but anemia in COPD can also be the result of a number of factors, such as nutritional and endocrine disorders, treatment with certain drugs (theophylline or angiotensin-converting enzyme inhibitors), acute exacerbations and oxygen therapy.
The level of hemoglobin in COPD patients is strongly associated with increased functional dyspnea, decreased exercise capacity as well as a poor quality of life. Moreover, some studies have showed that anemia is an independent predictor of mortality. Despite the possible clinical benefit of successfully treating anemia in these patients, evidence supporting the importance of its effect on the prognosis of COPD is limited.

2. Prevalence of anemia in COPD

The prevalence of anemia in COPD remains unclear and varies widely. This variability depends on the population under study (stable COPD or patients hospitalized for acute exacerbation), the tools to identifying anemic subjects, and the definitions used for anemia. Contrary to common thinking, recent studies have shown that anemia is a frequent comorbid associated disease in COPD, ranging from nearly 10 to 30% of patients, particularly in patients with severe disease, whereas polycythemia (erythrocytosis) is relatively rare (Barnes & Celli, 2009).The World Health Organization defines anemia in the general population as hemoglobin concentration of less than 13.0 g/dL in men and less than 12.0 g/dL in women (WHO 1968). However, when determining anemia using hemoglobin, it is important to account for the following aspects: firstly, the prevalence of anemia in the general population increases with age and COPD is a chronic disease that affects an aging

population; secondly, appropriate hemoglobin threshold for anemia definition in older post-menopausal females remains controversial (Cote et al, 2007) and finally, COPD patients could have a "relative anemia"—a term used to describe cases in which apparently normal hemoglobin values do not correlate with level of hypoxemia.

John et al., reported for first time anemia prevalence in a stable COPD population. They found that among 101 severe COPD patients (forced expiratory volume in one second [FEV_1]37 ±2% predicted) 13 were anemic, which means a prevalence of 13%. (John et al, 2005) The data extracted from large national database in France maintained by the Association Nationale pour le Traitement à Domicile de l'Insuffisance Respiratoire (ANTADIR study) showed a similar prevalence in a cohort of 2524 COPD individuals under long-term oxygen therapy (LTOT) (12.6% in males and 8.2% in females) (Chambellan et al, 2005). Cote and colleagues estimated a prevalence of anemia of 17% in contrast with 6% of polycythemia among 683 COPD outpatients. (Cote et al, 2007). In hospitalized patients, described prevalence in anemia rises up to 33%.John and colleagues compared the prevalence of anemia between hospital-admitted COPD and other chronic diseases (asthma, chronic heart failure, chronic renal insufficiency, and cancer).They found in a sample of 7,337 patients an overall prevalence of anemia in COPD of 23%. This was comparable to that in patients with heart failure, higher than in asthmatic individuals, but lower than that in the groups with cancer or chronic renal insufficiency (John et al, 2006). In another study, based on 177 COPD admitted patients due to acute exacerbation (AECOPD) the prevalence reported was 31%. The normocytic normochromic anemia was the most common morphological pattern in 32 cases (58%) and anemia of chronic disease (ACD)or anemia of inflammation was also the more frequent etiology founded. Ultimately, only 8 (4.5%) had polycytemia. (Portillo et al, 2007).

It is worthwhile saying that studying the prevalence of anemia in patients with acute syndromes may overestimate the real number of cases, however, the frequency of anemia during AECOPD is also a relevant issue, since it represents a state of augmented systemic inflammation which also could affect hemoglobin levels in COPD, as described later.

Two recent reports have provided data in large series of patients, obtained from ICD-9/10 code of the discharge diagnoses in order to analyze mortality and healthcare resource variables. In a study performed on US Medicare population, anemia was diagnosed in 21% of COPD patients (Halpern et al, 2006); whereas Shorr and co-workers identified 788 cases in a population of 2404 COPD patients (33%). Anemic patients were older, more likely to be male and non-caucasian, and had a greater co-morbidity burden than non-anemic individuals. (Shorr et al, 2008)

In summary, anemia seems to be common entity among COPD patients, but current available data about its frequency are provided from retrospective analysis or single-center studies, therefore, are subject to the general biases inherent in such designs. Efforts to determine the true prevalence of anemia as comorbid disease in COPD are needed.

3. Mechanisms of anemia in COPD

Increasing evidence indicates that COPD is a complex disease involving more than airflow obstruction (Barnes & Celli 2009).In many patients the disease is associated with several extra pulmonary manifestations that could be the expression of systemic inflammatory state of COPD. In the light of this and together with presence of normocytic anemia in some

reported series, it has considered that COPD is another disease likely to be associated with anemia of chronic disease or anemia of inflammation (ACD) (Similowski et al, 2006). In any case, besides the possible role that inflammation may play in the etiology of anemia in COPD, it should not forget that the aging process itself increases the prevalence of anemia as mentioned above and the hemoglobin concentration in COPD can also be influenced by intervention of other mechanisms (Fig. 1). There is a growing interest in the literature about this issue, but the evidence is still scarce. We briefly review the most cited pathophysiologic aspects of this association.

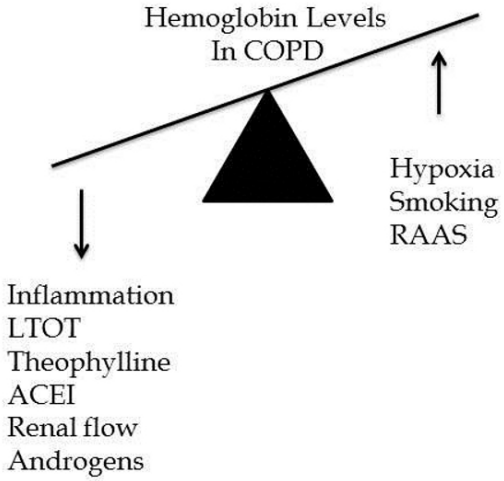

Fig. 1. Possible factors related to hemoglobin levels in COPD. ACEI indicates angiotensin-converting enzyme inhibitors; LTOT, long-term oxygen therapy; and RAAS, renin-angiotensin-aldosterone system.

3.1 Anemia of chronic disease

ACD is an immune disorder that has been reported in numerous diseases with an inflammatory component. Inflammatory cytokines exert various effects on pathogenesis of this form of anemia and ultimately interfere with the normal process of erythropoiesis. The underlying mechanisms are complex, including dysregulation in iron homeostasis and erythropoietin production, impaired proliferation of erythroid progenitor cells and reduced life span of red blood cells. (Weiss 2005). In addition, activation of these inflammatory mediators may stimulate the production of hepcidin, a polypeptide that is the principal regulator of extracellular iron homeostasis and is thought to play a key role of development of ACD.

ACD is usually normocytic, normochromic anemia, but it can become microcytic and hypochromic as the disease progresses. Characteristic changes in systemic iron distribution develop such that the serum iron concentration and transferrin saturation are low, while macrophage iron stores remain replete (Roy, 2010).

COPD is a disorder that could be related with ACD, due the existence of systemic inflammation documented in some patients with COPD. A wide variety of inflamatory markers are isolated in both peripheral blood and sputum in these patients and are higher

than controls (Gan et al, 2004). The most important mediators that have been identified are: C-reactive protein (CRP), fibrinogen, circulating leukocytes, and several interleukines (IL) such as IL- 6, IL-8 and tumor necrosis factor alfa (TNF-α) (Fig. 2). Increased of oxidative stress also have been demonstrated in COPD, especially during exacerbations. (McNee 2005).

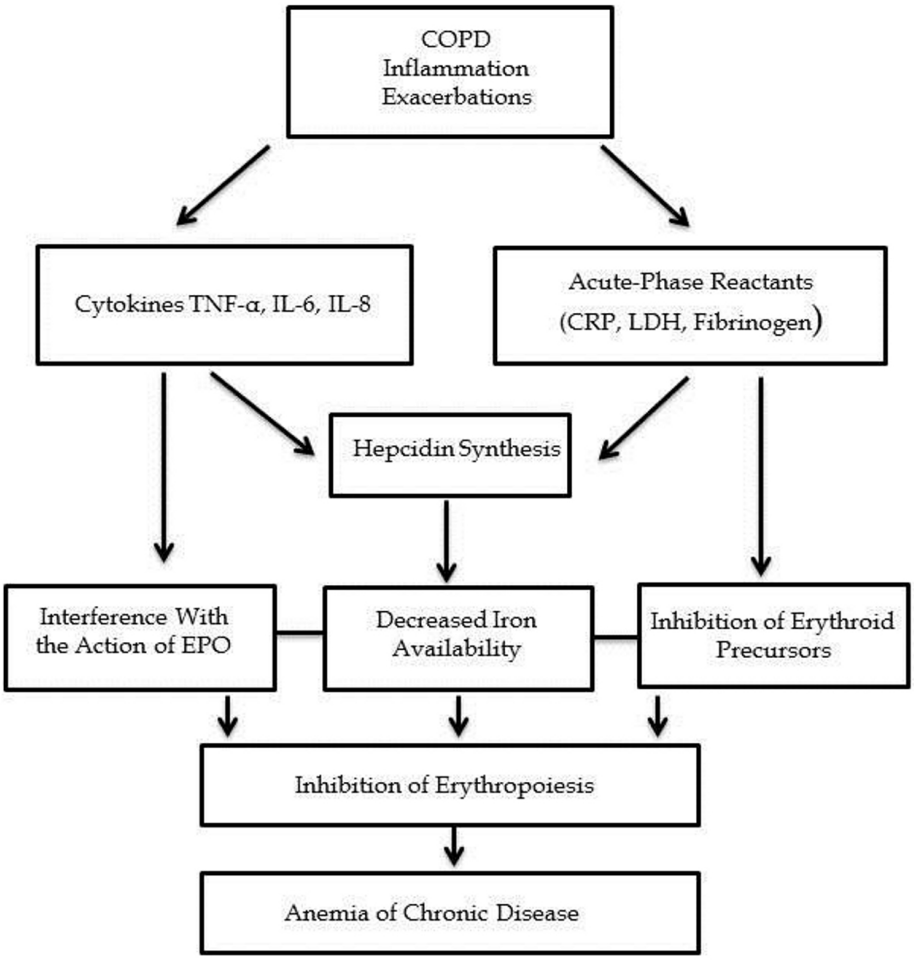

Fig. 2. Possible mechanisms of anemia of inflammation, or anemia of chronic disease, in chronic obstructive pulmonary disease (COPD). EPO indicates erythropoietin; IL, interleukin; LDH, lactate dehydrogenase; CRP, C-reactive protein; and TNF-α, tumor necrosis factor α. (Taken from Portillo, 2007)

One of the first studies that linked the ACD in patients with COPD was made by Tassiopoulos and co-workers, in 2001. Their initial objective was to evaluate the characteristics of anemia and compare the compensatory erythropoietic response in clinically stable patients with idiopathic pulmonary fibrosis and COPD individuals in respiratory failure. The assumption was that the hematologic mechanism would function differently in these two diseases and that the phenomenon of secondary erythrocytosis would be retained in COPD hypoxemic patients. However, they found that the expected response (an increase in red cell mass) was inconsistent in a subgroup of patients with COPD. These individuals had normal or below normal hemoglobin values in spite of higher than normal concentrations of erythropoietin (EPO) in plasma, a suggestion that inflammation was probably the cause of the inconsistent response (Tassiopoulus et al, 2001). These observations were confirmed later by the previously mentioned study performed by John and colleagues. In these patients, the serum levels of CRP and IL-6 were significantly higher than in a group of control subjects. CRP was significantly higher in the anemic subgroup than in non anemic patients as well the level of serum EPO. Moreover, an inverse correlation was showed between hemoglobin and EPO levels, an indication of the existence of a certain resistance to the action of this hormone. These results, together with the lack of any correlation between anemia with nutritional abnormalities present in these patients (weight loss and cachexia), led to the conclusion that the development of anemia in some patients with COPD may fulfilled the criteria for ACD. (John et al, 2005).

3.2 Exacerbations

One of the inherent characteristics of COPD is the occurrence of exacerbations, (AECOPD) which succeed in the curse of the natural history of disease. During AECOPD typically occurs an amplification inflammatory response, both locally and systemically. It has been postulated that the existence of this increased systemic inflammation may worsen some of extrapulmonary manifestations of COPD including anemia. (Portillo 2007; Soler- Cataluña et al, 2010)

Two recent reports assessed the role of inflammatory mechanisms over hemoglobin levels during AEPOC with dissimilar results regarding EPO response. Sala et al., compared the plasma levels of EPO and CRP in patients hospitalized because of AECOPD (n = 26; FEV_1: 48 ±15% predicted), patients with clinically stable COPD (n = 31; FEV_1 :49 ± 17% predicted), smokers with normal lung function (n = 9), and healthy never smokers (n = 9). The main findings were: 1) EPO plasma levels were significantly lower during AECOPD and 2) in COPD group EPO was significantly related to CRP ($r = -0.55$, $p < 0.0001$) and with circulating neutrophils ($r = -0.48$, $p < 0.0001$). Finally, in a subset of 8 COPD patients who could be studied both during AECOPD and clinical stability, EPO levels were significantly higher in stability compared to those recorded during the AECOPD ($p < 0.0001$). These observations suggest that EPO is downregulated during AECOPD related to the burst of systemic inflammation. (Sala et al, 2010)

In the other study, hemoglobin, EPO and serum biomarkers of systemic inflammation (CRP, TNF-α, fibrinogen and IL-6]) were measured at three time points (admission, resolution and stable phases) in a selected cohort of 93 COPD patients. Hemoglobin levels were significantly lower on admission compared to resolution and stable phases ($p=0.002$), whereas EPO was significantly higher on admission compared to resolution

and stable phases. EPO and hemoglobin were negatively associated during AECOPD. This association was related to increased IL-6 levels, indicating a possible EPO resistance through the mechanism of increased systemic inflammatory process (Markoulaki et al, 2011).

3.3 Macrocytosis

An increase in mean corpuscular volume (MCV) has been reported in patients with COPD, although the cause is still poorly understood. Tsantes et al., investigated this phenomenon among 32 hypoxemic COPD patients and 34 healthy volunteers. They evaluated the following parameters: complete blood count, percentage of F-cells (erythrocytes containing fetal hemoglobin), arterial blood gases, and EPO levels. Red cell macrocytosis (defined as MCV>94 fL) was found in almost half of the patients with COPD (43.75%), and 37% of this group had erythrocytosis. The EPO response was not associated with the degree of hypoxemia, erythrocytosis, or macrocytosis, and in some cases the phenomenon occurred independently. The F-cell percentage was significantly higher in the patients with COPD, and this parameter correlated with MCV values. Based on their findings, the authors hypothesized that erythropoietic stress occurs repeatedly in COPD as a result of exacerbations and nocturnal or exercise-related desaturation. This may triggers a compensatory mechanism, as the release of immature cell forms in the bone marrow to optimize oxygen carrying capacity. Even when they are within the normal range, hemoglobin concentrations can be suboptimal in these patients given the severity of their baseline hypoxemia (Tsantes et al, 2004). Garcia-Pachón et al., also reported macrocytosis in COPD patients but without respiratory insufficiency. It was present in 17 of the 58 stable COPD patients (29%). The most interesting finding, was a significant correlation between macrocytosis, dyspnea, and FEV_1 in a subgroup of 9 COPD (36%), that presumably reflects a correlation between macrocytosis and a deterioration in the clinical situation (García-Pachón & Padilla-Navas 2007).

3.4 Renin-angiotensin-aldosterone system

There are some clinical and experimental studies demonstrating that COPD causes neurohumoral activation, which presumably contributes to a self- maintaining pathogenic cycle that may be related to the systemic effects of the disease (Andreas et al, 2005). An increase in EPO secretion has been observed in experimental animals after administration of renin or angiotensin II. Thus, administration of angiotensin converting enzyme inhibitors is accompanied by a reduction in EPO and hematocrit values. Vlahakos et al., analyzed the degree to which activation of renin-angiotensin system (RAS) was associated with the development of compensatory erythrocytosis in hypoxemic COPD individuals. Renin and aldosterone levels were 3 times higher in the patients with erythrocytosis than in the control group of hypoxemic COPD patients who did not have erythrocytosis. Therefore, it has been contemplated that the alteration in the activation could, partially, help to explain the differences found in the values of hemoglobin in patients with COPD with the same degree of hypoxemia (Vlahakos et al, 1999).

3.5 Renal flow

As EPO is synthesized primarily in the kidney, any impairment of renal hemodynamics—a comorbidity also reported in COPD as a consequence of decreased renal blood flow—causes

an imbalance in the supply and demand of oxygen that affects the production of this hormone possibly as a result of an effect on the oxygen sensor (Pham et al, 2001).

3.6 Androgens

Androgens can also stimulate erythropoiesis directly by stimulation of erythroid progenitors or indirectly by activating the renin-angiotensin-aldosterone system; in fact, anemia is a common finding in men who have hypogonadism or are receiving antiandrogenic treatment. Furthermore, testosterone levels decline with age. There is evidence that testosterone concentrations are low in men with COPD (Casaburi et al, 2004).Various predisposing factors for these low values have been proposed, including hypoxia, corticosteroid treatment, and the chronic nature of the disease. A published study of a sample of 905 patients over 65 years of age concluded that low testosterone levels are associated with a higher risk of developing anemia (Ferrucci et al, 2003).

3.7 Other factors

It has been observed that, like the angiotensin-converting enzyme inhibitors, which reduce hematocrit values, theophylline also gives rise to a reduction in the production of red blood cells. The suppression mechanism is complex and in principle may be the result of direct inhibition of erythropoiesis through apoptosis induced by this drug rather than any effect on EPO (Tsantes et al, 2003).

Oxygen therapy can theoretically blunt hypoxia-driven erythropoyiesis, (Similowski et al, 2005) while smoking habit might exert negative effect on folate status and oxygen carrying capacity through tendency to increase red blood cell mass.

4. The effects of anemia in COPD

The relationship between anemia and adverse clinical outcomes is wide recognized in other chronic disease states. The hemoglobin is the principal oxygen transport molecule. Any decrease in hemoglobin levels results in a corresponding reduction in the oxygen-carrying capacity of the blood. Thus, while arterial oxygen pressure may remain normal, the absolute amount of oxygen transported per unit blood volume declines. Impairment of this mechanism exerts a negative impact on clinical status. Although there are few related studies, those published so far it appears that anemia plays an important role in various domains and outcomes of disease including mortality.

4.1 Symptoms, exercise tolerance

It is well known that anemia is a cause per se of dyspnea and that it contributes to functional limitation in the anemic individual. Fatigue is also a common finding among COPD and is the primary symptom of anemia. In fact, anemia is one of the most treatable causes of fatigue in general. Cote and colleagues demonstrated that anemia was independently associated with increased dyspnea, by means modified Medical Research Council dyspnea scale (MRC) and reduced exercise capacity measured by 6- min walk distance in a cohort of stable COPD patients (Cote et al, 2007). Recently, another study was aimed to investigated specifically the impact of ACD on dyspnea and exercise capacity utilizing cardiopulmonary exercise testing (CPET) in a group of 283 COPD patients. The results of these report also showed a negative effect of low hemoglobin on

breathlessness. COPD patients whom fulfilled criteria of ACD had higher MRC dyspnea score compared to controls and lower exercise capacity (lower peak oxygen uptake[VO2], peak work rate, peak VO2/heart rate, as well a trend for lower anaerobic threshold) (Boutou et al, 2010).

There is only restrospective study that analyzed the relationship between anemia in COPD and health related quality of life (HRQL) based on general population (n=2704). Among patients with COPD (n = 495) physical functioning (PF) and physical component summary (PCS) scores from Short Form-36 questionnaire were significantly lower in individuals with anemia compared to those without. In conclusion, anemia associated with COPD was an important contributor to poor quality of life. (Krishnan et al, 2006)

4.2 Health resources

COPD generates a large consumption of resources that involves a significant economic burden worldwide due to its high prevalence and morbidity. Moreover, presences of comorbidities in COPD appear to be a cost multiplier. (Shorr et al, 2008)

The ANTADIR study founded that a reduced hematocrit level was associated with more frequent hospitalizations and a longer mean hospital stay (Chambellan et al, 2005).Two studies mentioned above have been measured the economic impact of anemia in COPD based on large sample of patients. Both documented that anemia significantly and independently contributes to the cost of care for COPD. (Halpern et al, 2006; Shorr et al, 2008).

4.3 Mortality

There is some evidence available to suggest that anemia is associated with a reduced survival in COPD. In cohort of stable COPD used to described the BODE index (body mass index, airflow obstruction, dyspnea and exercise capacity) Celli and colleagues showed that patients who died were found to have significantly lower hematocrit levels than those who survived (Celli et al, 2004).

In survival data derived from the ANTADIR study, multivariate analysis proved that hematocrit was important independent predictor of survival in COPD patients receiving LTOT and showed that the survival rate at three years was 24% in patients with hematocrit <35%, and 70% in patients with hematocrit > 55%(Chambellan et al, 2005).These findings are consistent with a recent report also conducted on patients under LTOT in which 67% had a diagnosis of COPD. Hemoglobin and hematocrit were significantly lower in the nonsurvivor group. Multiple regression analysis demonstrated that the main risk factors for mortality after three years of follow-up were male gender, lower values of hemoglobin, hematocrit and carbon dioxide pressure more intense hypoxemia and dyspnea sensation. The cut-off point associated with higher mortality in this study was hemoglobin ≤ 11 g/dl (sensitivity 95% specificity 85%) or hematocrit ≤33%(sensitivity 97% specificity 89%)(Lima et al, 2010).

In the National Emphysema Treatment Trial, in which randomized patients to be treated medically or surgically, also found that the decrease in hemoglobin acted as an independent predictor of mortality (Martinez et al, 2006).

Lastly, Rasmussen and co-workers analyzed the effects of anemia in critically ill patients with COPD admitted to the intensive care unit (ICU) requiring invasive mechanical ventilation. With a cutoff point of hemoglobin to define anemia of 12g/dL, it found that low

hemoglobin levels were associated with substantially increased mortality within the first 90 days following admission (Rasmussen et al, 2011).

5. Should anemia be treated in COPD?

Throughout this review we have discussed some clinical and pathophysiological aspects that would justify therapeutics efforts to correct anemia in COPD. However, the degree of uncertainty in fundamental aspects, as well limited available evidence do not establish whether the treatment of this condition will result in improvement in COPD outcomes.

Schonhofer et al., published the only two studies in the literature on this subject. After treating anemia by blood transfusion in 20 patients with severe COPD in an ICU, it documented a statistically significant reduction in minute-ventilation and work of breathing, with unloading of the respiratory muscles (Schonhofer et al, 1999) The earlier study involved 5 COPD patients in whom weaning from invasive mechanical ventilation had proved difficult. By increasing hemoglobin levels to over 12 g/dL by blood transfusion, the physicians were able to extubate satisfactorily (Schonhofer et al, 1998)

Another treatment options to correct anemia as used in other chronic disease such congestive heart failure, cancer or chronic kidney disease have not been explored in COPD (i.e. erythropoietic agents, iron supplements or combined therapy). Is not known whether treating the underlying inflammation could improve the hematological values. Future prospective trials are needed to establish the appropriate threshold for initiation treatment and effect of improvement of hemoglobin on clinical outcomes in COPD population.

6. Conclusions

Anemia seems to be a common feature in COPD, although its real prevalence remains to be determined. While the mechanisms involved in the genesis of anemia in COPD are poorly studied and the evidence is scarce, we can talk about an imbalance in hemoglobin levels because there are factors that stimulate erythropoiesis as well as others that blunt this process.

Recent data support that low hemoglobin and hematocrit concentrations can have a detrimental impact on certain respiratory variables in COPD, including mortality. Whether the treatment of anemia will result in improvement in functional outcome measures remains uncertain. However, before a treatment strategy can be devised, the influence of anemia on the natural history of COPD should be properly evaluated in further prospective studies.

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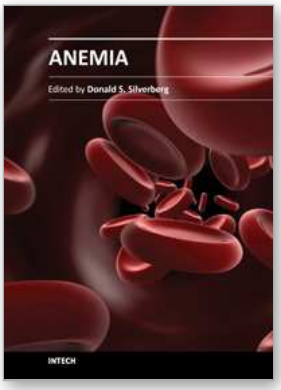

Anemia

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This book provides an up- to- date summary of many advances in our understanding of anemia, including its causes and pathogenesis, methods of diagnosis, and the morbidity and mortality associated with it. Special attention is paid to the anemia of chronic disease. Nutritional causes of anemia, especially in developing countries, are discussed. Also presented are anemias related to pregnancy, the fetus and the newborn infant. Two common infections that cause anemia in developing countries, malaria and trypanosomiasis are discussed. The genetic diseases sickle cell disease and thalassemia are reviewed as are Paroxysmal Nocturnal Hemoglobinuria, Fanconi anemia and some anemias caused by toxins. Thus this book provides a wide coverage of anemia which should be useful to those involved in many fields of anemia from basic researchers to epidemiologists to clinical practitioners.

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