

Anaemia in the critically ill patient: monitoring of erythropoietin therapy

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INTRODUCTION

Patients who require the intensive attention of a physician because of various of medical emergencies (e.g. status after cardiac arrest, shock, bleeding, respiratory failure, postoperative complications) are defined as critically ill. Over 60% of these patients on a surgical intensive care unit develop anaemia with a haemoglobin concentration of <12 g/dL, which is associated with a greater risk of mortality. In addition to blood loss from the gastrointestinal tract or through drains and wounds, these critically ill patients also have an inadequate red-cell production [1]. Erythropoiesis is depressed because of alterations in iron metabolism, a reduced response to erythropoietin and increased inflammatory cytokines. Anaemia of the critically ill patient caused by these factors resembles anaemia of chronic disease (ACD) [2]. Conditions predisposing to ACD exist in every patient who develops an acute-phase response. Attempts should be made to limit the development of ACD whenever possible. Clinically, ACD is characterized by normocytic, normochromic anaemia, increased ferritin concentration, decreased transferrin saturation and a low reticulocyte count [3]. The major causes for ACD are a diminished stimulation of erythropoietin production at low haemoglobin concentration, and disturbances of iron distribution, resulting in functional iron deficiency (FID). Circulating iron concentrations are low despite evidence of increased iron storage, and thus less functional iron is available to meet the demands of erythropoiesis [4]. The bone marrow in many critically ill patients may respond to administration of exogenous recombinant erythropoietin (rHuEPO) and iron because of a weak erythropoietin

response and FID in the anaemia of these patients.

In surgical patients with anaemia, blood transfusions are frequently used at haemoglobin concentrations of <10 g/dL [5]. However, not only is there a shortage of banked blood in industrialised countries, but blood transfusions also have numerous disadvantages for the patient. Treatment with rHuEPO may be a solution for some of these problems. However, optimal haematological benefits will only be produced if a significant bone marrow response can be predicted and iron availability is able to keep pace with the iron demands of erythropoiesis enhanced by rHuEPO. It is therefore important to reliably test the erythropoietic state and monitor the iron demand of erythropoiesis from an early stage.

In this article we discuss some of these key issues from specific studies with the aim of answering the following questions: (i) For which of the critically ill patients is the administration of rHuEPO a therapeutic option? (ii) Which biochemical serum markers and haematological blood cell indices predict an early response to rHuEPO administration, and indicate iron demand in the bone marrow? (iii) Is it possible to use a predictive model which can be used to adequately monitor rHuEPO response and FID?

EVALUATION OF THE ERYTHROPOIETIC STATE IN CRITICALLY ILL ANAEMIC PATIENTS

As an alternative to red-cell transfusions, the administration of rHuEPO and iron has been well studied in many types of surgery, critically ill anaemic patients and in end-stage renal failure (ERF) [6–8]. For treating the critically ill patient with rHuEPO it is important to know if iron availability for erythropoiesis meets the demands. Most experience in this field is in patients with ERF

[8]. To evaluate the iron status of these patients requires analysis of ferritin as an indicator of stored iron, analysis of transferrin saturation and of the proportion of hypochromic red cells (%HYPO) as markers of FID [8]. In critically ill patients, ferritin and transferrin saturation do not represent iron metabolism and are not indicators of FID because they are influenced by the acute-phase reaction. Reticulocyte haemoglobin content (Ret-Hb) and the %HYPO have been widely accepted for assessing FID. Ret-Hb provides direct real-time evaluation of the bone marrow activity, reflecting the balance between iron availability and erythropoiesis. As an indicator for proliferation and iron availability to the bone marrow, the ratio of serum soluble transferrin receptor (sTfR) concentration to the logarithm of serum ferritin concentration (sTfR/log ferritin = ferritin index) is a valuable tool [9]. In healthy subjects, Ret-Hb is 28–35 pg and the ferritin index is <1.5 [10]. In critically ill patients with elevated C-reactive protein (CRP), the threshold for the ferritin index indicating hypoproliferative erythropoiesis and normal iron availability to the marrow is ≤ 0.8 . More recently Thomas and Thomas [10] developed a diagnostic plot combining Ret-Hb and the ferritin index, which allows the identification of four major erythropoietic states (Fig. 1): 1. Normal erythropoiesis with replenished iron stores (iron status in ACD); 2. Normal erythropoiesis with depleted iron stores but not yet in an iron-deficient erythropoietic state (latent iron deficiency); 3. Hypoproliferative erythropoiesis, depleted iron state and functional iron compounds (classic iron deficiency), decreased haemoglobinization of red cells; 4. Hypoproliferative erythropoiesis, FID in iron-replenished state (FID in patients with ACD), decreased haemoglobinization of red cells

Compared with the diagnostic plot, neither traditional biochemical indicators of iron metabolism (ferritin, transferrin saturation) nor haematological markers (complete blood count, reticulocyte count and red-cell indices)

allow highly accurate identification of FID in the critically ill patient [10,11].

A PREDICTIVE MODEL FOR ADEQUATELY IDENTIFYING CRITICALLY ILL PATIENTS WHO WILL RESPOND TO rHuEPO

The therapeutic implication of the diagnostic plot is to differentiate patients into groups that would benefit from administration of iron only, from administration of rHuEPO only or from the combination of rHuEPO and iron (Fig. 2). Iron supplementation only is adequate for anaemic patients in groups 2 and 3. Patients with adequate iron supplementation usually respond with a change from group 3 to group 2 within 10 days, and to group 1 after 4–20 weeks.

Anaemic patients in group 1 and 4 are given rHuEPO therapy, but the use of rHuEPO should be restricted to specific clinical situations that are not expected to improve by simply treating the cause of the critical illness. According to the diagnostic plot, patients in group 4 have FID requiring combined i.v. iron supplementation with their first rHuEPO dosage. Patients in group 1 should be treated primarily with rHuEPO only [3].

PREDICTION OF RESPONSE TO rHuEPO IN PATIENTS WITH A CRITICAL ILLNESS

Anaemia, especially in patients with ERF, with cancer-related anaemia and in critical illness after surgery, has been shown to be effectively reversed by rHuEPO, as the drug is capable of increasing the rate of erythropoiesis. The response of anaemia to rHuEPO is dose-related, varies among patients, and cannot always be predicted. Identifying significant haematological response may take months, because in most clinical settings the effectiveness of each sequential increase of rHuEPO dosage is evaluated by monitoring the increase in haemoglobin 4–5 weeks after increasing the rHuEPO dosage. Thus, it is useful to use laboratory tests that indicate a real-time haematological response to a higher rHuEPO dosage, and that can predict a pending erythropoietic response for a specific rHuEPO dose [12].

A lack of response to rHuEPO therapy may be related to either: (i) reduced iron availability, which may not keep pace with the increased

FIG. 1. Diagnostic plot for identifying different erythropoietic states of imminent iron deficiency, combining the biochemical marker for iron availability (ferritin index = sTfR/log ferritin) with Ret-Hb, the haematological indicator for the iron demand of erythropoiesis. The plot is also used for evaluating the erythropoietic state before starting rHuEPO therapy. A Ret-Hb of <28 pg indicates FID. In patients with CRP values of ≤5 mg/L, a ferritin index of > 1.5 indicates depleted iron stores, and of <1.5 indicates replenished iron stores. The threshold for the ferritin index is 0.8 in patients with infection and inflammation (CRP >5 mg/L). Ferritin index thresholds for the Dade-Behring sTfR assay are shown. From [10].

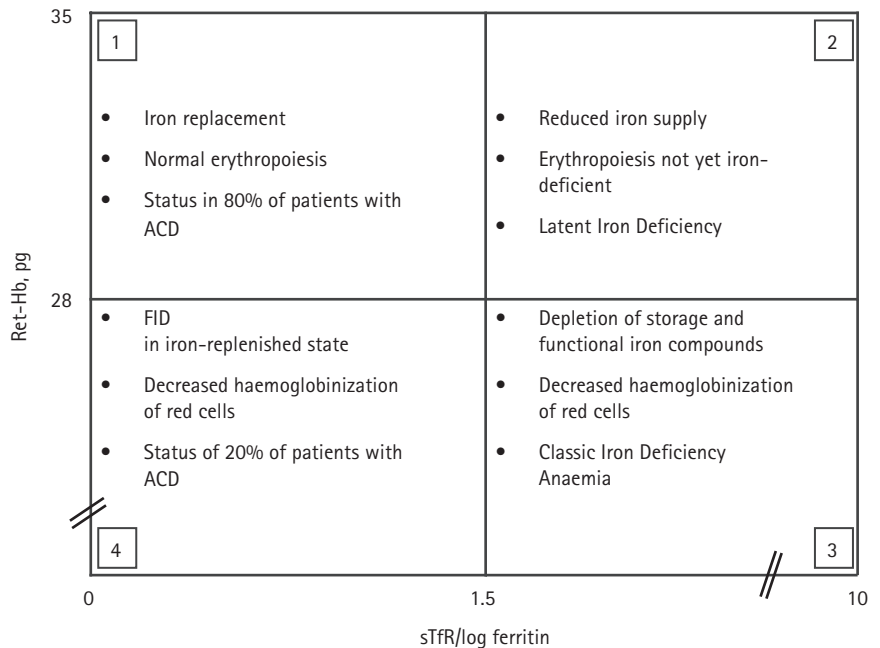


FIG. 2. Therapeutic implications for treating different phases of iron deficiency. From [10].

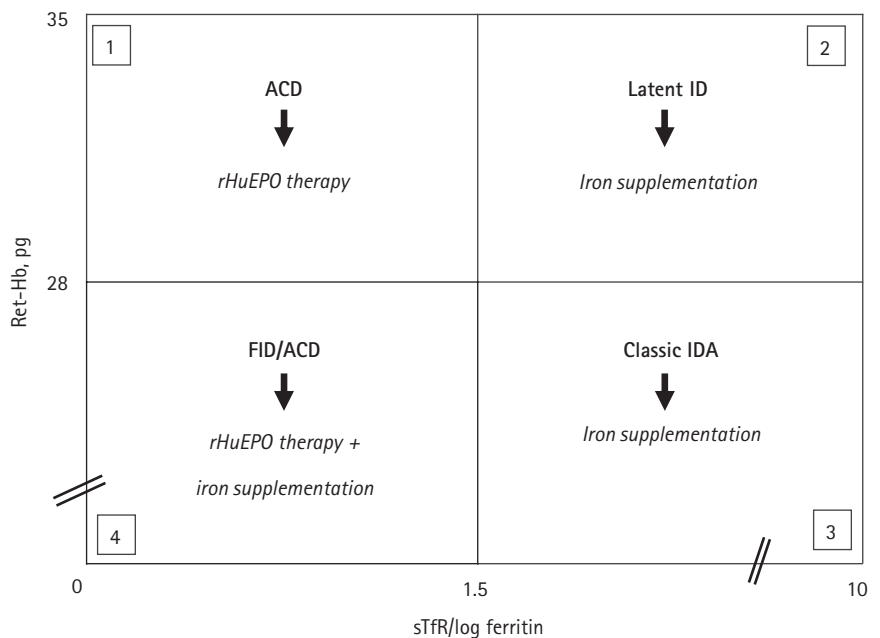
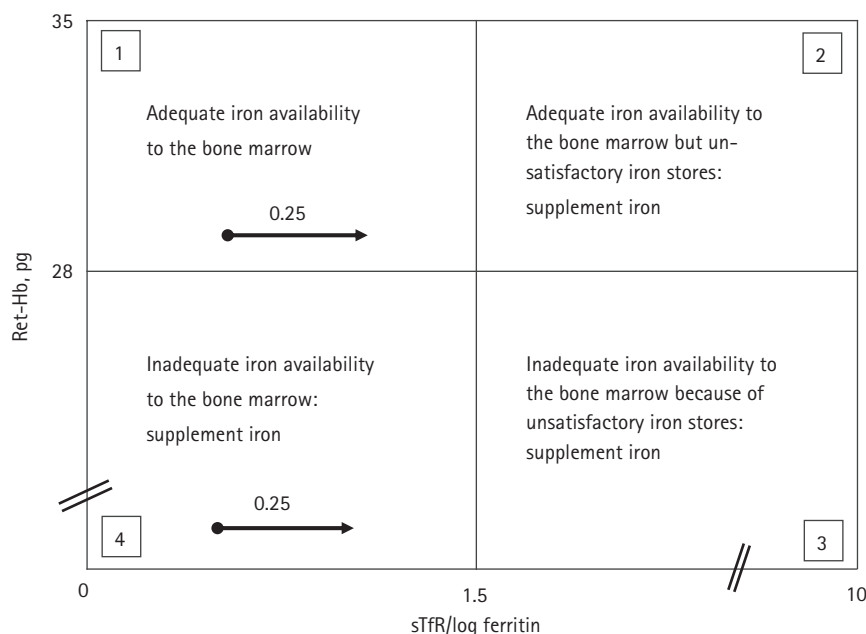


FIG. 3. Diagnostic plot for monitoring rHuEPO therapy. An increase of the ferritin index of ≥ 0.25 indicates the effectiveness of the rHuEPO dosage, a Ret-Hb of ≥ 28 pg or an increase of Ret-Hb of ≥ 2 pg excludes FID, and a ferritin index of < 1.5 shows an adequate iron supply for red cell production. From [14].



iron demand of erythropoiesis enhanced by rHuEPO, i.e. FID; (ii) intrinsic unresponsiveness of the bone marrow. Laboratory tests designed to predict intrinsic unresponsiveness and FID have been recommended [13]. The simplest indicator of intrinsic unresponsiveness is a deficient increase in serum haemoglobin (< 1 g/dL at 4–8 weeks after starting rHuEPO therapy). FID is monitored by transferrin saturation (TfS) and a value of $< 20\%$ indicates FID, but TfS is not a reliable marker in the critically ill [13]. Until now no tests have been evaluated for differentiating between intrinsic unresponsiveness of the marrow and progression of FID in the critically ill, and in ACD in real time. Therefore valid strategies are still debated for these patients. To optimize rHuEPO therapy with proper laboratory management, we recommend the following procedure [10]: (i) Classify patients into four groups of erythropoietic state in accordance with Fig. 1 as the preliminary investigation. Patients in group 1 should be treated primarily with rHuEPO only, and patients in group 4 should be given i.v. iron supplements with their first dose of rHuEPO; (ii) Monitor rHuEPO therapy in accordance with the modified diagnostic plot at 2 and 6 weeks after starting therapy, as shown in Fig. 3 [14].

rHuEPO TREATMENT OF CRITICALLY ILL PATIENTS

The efficacy of the diagnostic plot in predicting rHuEPO response and detecting FID was shown in a randomized trial [14]. Twenty-six anaemic patients, who were critically ill after complications of surgery, were enrolled in the study. All patients had fulfilled the criteria of ACD for the previous 4–8 weeks and had not been treated with blood transfusions within the previous 2 weeks. Baseline patient characteristics included haemoglobin levels of < 10.5 g/dL for > 4 weeks, elevated CRP concentrations (median 137 mg/L, mean 154, SD 99) and an erythropoietic state in group 1 or 4. rHuEPO (NeoRecormon, Roche, Basel, Switzerland) doses of 150 U/kg s.c. were administered twice a week. The erythropoietic states and haemoglobin were evaluated at baseline, and monitored after the initial rHuEPO dosage twice weekly. The following conditions were defined to indicate an optimum response to rHuEPO: (i) Increase in haemoglobin of ≥ 1 g/dL; (ii) increase in the ferritin index as an indicator of stimulated erythropoietic activity; (iii) Increase in Ret-Hb of ≥ 2 pg at Ret-Hb concentrations of < 28 pg (Ret-Hb at ≥ 28 pg indicates absence of FID); (iv) No increase in the ferritin index to > 1.5 , which is the

threshold of ferritin concentration at which iron depletion is predictable.

Sixteen of the 26 patients responded to rHuEPO and had a significant increase in haemoglobin and ferritin index within 2 weeks. Six of the 12 responders with an erythropoietic state of 4 had FID, and most of the group 4 responders progressed to a ferritin index of 1–1.5, indicating that an iron-depleted state would soon develop. Ten patients, all with a ferritin index of < 0.25 , did not respond to rHuEPO.

From the data of this trial, the following preliminary predictions can be made for rHuEPO therapy of the critically ill: (i) An increase of ≥ 0.25 in the ferritin index for erythropoietic states (groups 1 and 4) indicates erythropoietic activity in response to rHuEPO; (ii) a decrease in Ret-Hb to 35–28 pg indicates imminent FID and a Ret-Hb of < 28 pg shows persistent FID; (iii) Iron depletion is predictable if the ferritin index exceeds the threshold of 1.5, as corresponding ferritin concentrations are 20–200 $\mu\text{g/L}$.

The question arises as to the advantages of the diagnostic plot over serum-haemoglobin measurements and known predictive models for monitoring rHuEPO response, which are mainly recommended for patients with ERF [8]. The combination of ferritin index and Ret-Hb determines the erythropoietic state as a baseline study and allows, in the early stage of rHuEPO treatment, differentiation between FID, intrinsic unresponsiveness of the bone marrow and inadequate rHuEPO dosage. An increase in Ret-Hb indicates the absence of FID. A decrease in Ret-Hb occurs within 2–4 days in FID [15]. The responsiveness to rHuEPO is indicated by an elevation in the ferritin index to > 0.25 at 1–2 weeks earlier than an increase in haemoglobin. Table 1 shows the conditions for adequate and inadequate responsiveness to rHuEPO, and further treatment recommendations.

In conclusion, anaemia in the critically ill patient resembles anaemia in chronic disease, an erythropoietic state with reduced production of red cells. Currently, patients with a haemoglobin level of < 10 g/dL are transfused with banked blood. Treatment with rHuEPO is a new alternative, but the optimum benefits will only be produced if a significant bone marrow response can be predicted and iron is available to keep pace with the iron demands of erythropoiesis enhanced by rHuEPO. The

TABLE 1 Conditions for optimal responsiveness to rHuEPO. The variables should be measured at 2 and 4 weeks after starting rHuEPO therapy

Variable	Result	Treatment
Ferritin index	≥0.25	Adequate rHuEPO dosage
	<0.25	Increase rHuEPO dosage
Ret-Hb	≥28 pg or increase of ≥2 pg	No FID
	<28 pg or increase <2 pg	FID; supplement iron
Ferritin index	<1.5	Adequate iron stores
	≥1.5	Inadequate iron stores, supplement iron
Haemoglobin increase	≥1 g/dL	Adequate response
	<1 g/dL	Inadequate response, supplement rHuEPO until week 4, if no increase, increase rHuEPO dosage or stop rHuEPO therapy

diagnostic plot described here can be used as a predictive model to adequately identify patients who respond to rHuEPO according to their erythropoietic state.

CONFLICT OF INTEREST

None declared.

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Abbreviations: ACD, anaemia of chronic disease; CRP, C-reactive protein; ERF, end-stage renal failure; FID, functional iron deficiency; %HYPO, proportion of hypochromic red cells; Ret-Hb, reticulocyte haemoglobin; rHuEPO, recombinant human erythropoietin; sTfR, soluble transferrin receptor; TfS, transferrin saturation.