Anaemia of critical illness – implications for understanding and treating rHuEPO resistance

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Abstract
The prospect of a shortage of blood for transfusions, increasing awareness of the adverse effects of transfusions, and the availability of human recombinant erythropoietin (rHuEPO) have stimulated interest in the pathogenesis of the anaemia of intensive care unit (ICU) patients. As in the anaemia of chronic illness or chronic renal failure (CRF), the anaemia of ICU patients is a multifactorial process. Blood loss, inappropriately low erythropoietin production, reduced red cell lifespan, reduced iron availability, and inhibition of erythropoiesis by cytokines all contribute to the anaemia of critical illness, although the contributions of the various elements differ depending on the disease aetiology. Evidence is accumulating that use of rHuEPO can induce stimulation of erythropoiesis in critical illness, but at doses that are usually several-fold higher than those used to define resistance to rHuEPO in the current guidelines for the management of anaemia in CRF. Available data suggest that these high doses are well tolerated, at least in the short term. These observations, as well as demonstrating the potential benefits of rHuEPO therapy in critically ill patients, have practical implications for non-ICU patients with CRF who do not respond sufficiently to the usual doses of rHuEPO. Although the risk–benefit ratio relationship for very high doses of rHuEPO needs further consideration, demonstration of rHuEPO efficacy in critical illness should result in a re-evaluation of the ‘dose–response relationship’ for rHuEPO in patients with less acute and severe illness, including CRF patients hyporesponsive to current dosing regimens.

Keywords: anaemia; chronic renal failure; critical illness; erythropoietin; resistance

Introduction
Anaemia generally results from one of three different causes or a combination thereof: increased blood loss, reduced red cell life span, or impaired red cell production. Red cell production can normally be increased up to 7-fold and thus blood loss and red cell destruction must exceed a critical level before anaemia develops. In patients with chronic renal failure (CRF) the overall success in correcting anaemia with recombinant erythropoietin (rHuEPO) indicates that inadequate red cell formation due to inappropriately low erythropoietin production is the predominant cause [1]. However, supraphysiological doses of rHuEPO are usually needed to maintain the haemoglobin (Hb) level in a subnormal range. Moreover, a significant number of patients do not achieve current target Hb levels despite receiving high doses of rHuEPO. Thus, additional factors other than erythropoietin deficiency clearly play a role in the pathogenesis of renal anaemia and their contribution appears to vary significantly among patients. In fact, red cell life span has long been known to be shortened in patients with renal failure [2] and patients treated with haemodialysis suffer continuous blood loss. Additional, albeit controversial, evidence exists for a decreased sensitivity of erythroid precursor cells towards erythropoietin in uraemia [1]. Among the various factors affecting erythropoietin responsiveness, chronic inflammation also seems to play an important role [3].

The terms ‘anaemia of chronic disease’ (ACD) or ‘anaemia of inflammation’ characterize a type of anaemia that occurs frequently in patients with chronic inflammatory, infectious, or neoplastic diseases in the presence of normal kidney function [4–6]. As in patients with renal disease, this type of anaemia is multifactorial. The erythropoietic response to a chronic reduction in Hb levels in these patients is not lacking as in CRF, but it is blunted; i.e. the relationship between serum concentrations and Hb levels is significantly less steep than in patients with pure iron deficiency anaemia. Thus, although the contribution of
different causes of anaemia varies, there is considerable overlap in the pathogenesis of ACD and the anaemia of renal failure (Figure 1). rHuEPO is also effective in treating the anaemia of cancer and chronic inflammatory disorders, but dose requirements are usually higher and response rates lower than in patients with CRF [7–9].

Although ACD by definition is associated with ‘chronic’ disorders, increasing evidence has been provided in recent years that the underlying causes are similar to those leading to the anaemia that develops rapidly in patients treated on intensive care units (ICU) [10,11]. In fact ‘anaemia of critical illness’ has been considered as an acute form of ACD [12].

Surprisingly, the causes and significance of anaemia of critical illness have so far received comparatively little attention, despite it being an obvious and frequent disorder, leading to a high usage of allogenic blood transfusions in ICUs. Recently, the prospect of a shortage in blood for transfusions, increasing awareness of the adverse effects of red cell transfusions and the availability of rHuEPO has greatly stimulated interest in the pathogenesis of the anaemia of ICU patients. Contributing to this interest has been the positive experience of anaemia management in patients with CRF. Conversely, increased attention to the anaemia of critical illness and its potential response to rHuEPO may provide important insights for understanding and managing anaemia in renal patients, who are hyporesponsive to rHuEPO.

**Frequency and extent of anaemia in critical illness**

Regardless of the heterogeneity of underlying diseases and complications necessitating ICU treatment, anaemia is a frequent and almost universal finding in this patient population. Many patients are already anaemic when admitted to the ICU. This holds true not only for post-operative admissions, but also for patients with medical diseases. In a prospective observational study of patients treated on a medical ICU for more than 3 days, we found a reduced Hb concentration on admission to the ICU in more than 50% of cases [13]. A subgroup analysis revealed that patients admitted to the ICU with a Hb level below 12 g/dL had a significantly worse prognosis than those admitted with higher Hb values [14].

Progression of anaemia during the period of ICU treatment is reflected by a further reduction in mean Hb levels and frequent blood transfusions. By ICU day 3, approximately 95% of patients have Hb concentrations below normal [12]. Depending on the type of ICU under investigation and inclusion criteria of studies, transfusion rates between 25 and 39% have been reported [13,15,16]. In one study including only patients treated on ICU for more than 1 week, the rate was 85% [17]. About 40% of these patients received transfusions during the initial week only, while the remainder were transfused after week 1, with an average of 2–3 U/week. Considering the individual change in Hb levels between admission and discharge or death, and the amount of blood transfused during the ICU stay, we estimated that the median blood loss of all patients treated in an ICU for more than 3 days amounts to approximately 0.7 L [13]. This figure increases to 3.1 and 4.3 L in patients with acute renal failure (ARF) or an adverse outcome (Figure 2) [13]. In patients with burn injuries comprising 25–65% of total body surface area, an average transfusion requirement of around 4.5 L has been reported [18].

**The pathogenesis of anaemia in critical illness**

In surgical intensive care patients, intra- and post-operative blood loss obviously plays a variable, but potentially important role (Table 1). However, both
Table 1. Causes of the anaemia of critical illness

- Blood loss
  
  Peri-surgical blood loss
  Acute bleeding episodes
  Iatrogenic diagnostic blood loss
  Occult gastrointestinal bleeding
  Renal replacement therapy
- Reduced red cell life span
- Impaired red cell production
- Inappropriately low erythropoietin production
- Inhibitory effects of inflammatory cytokines on erythropoietic stem cells
- Reduced iron availability

in medical and surgical ICUs, the majority of patients do not have overt bleeding episodes sufficiently severe to explain their degree of anaemia [19]. Approximately only a third of all transfusion events in ICU were found to be associated with acute blood loss [17] and the estimated overall blood loss in patients with and without episodes of acute bleeding is little different [13]. In patients with ARF, anaemia tends to be particularly severe and repeated blood loss into the extracorporeal circuit during intermittent or continuous renal replacement therapy can contribute to a significant degree [13,17].

Phlebotomies are another potentially important source of blood loss. The extent of ‘diagnostic blood loss’ depends partly on technical aspects (e.g. size of sampling tubes), but is mainly related to the frequency and awareness with which laboratory results are ordered. Thus, the contribution of diagnostic blood loss to total blood loss can vary considerably. Some studies suggest that iatrogenic blood loss is the major determinant of anaemia in critically ill patients [20,21]. However, more recent investigations indicate that diagnostic blood loss is not usually the predominant cause. Corwin et al. [17] estimated that phlebotomies correspond with 30% of transfused blood. We found that using a moderately restrictive regimen for blood sampling, diagnostic blood loss did not account for more than 20% of the total loss [13]. Minor procedures such as the insertion of arterial and venous catheters may further add to iatrogenic blood loss in ICU, but in most patients it should not be quantitatively relevant.

Taken together, these observations imply that ‘non-acute’ blood loss from other sources plays a significant role. It is likely, for example, that occult bleeding from the gastrointestinal tract occurs frequently. Although such losses are difficult to quantify, impairment of mucosal integrity, which increases the risk for continuous blood loss, can be found in many critically ill patients [22]. Gastrointestinal bleeding is likely to be facilitated by the frequent use of heparin and coagulation disorders. In animal experiments the administration of interleukin 6 (IL-6) was shown to cause anaemia by inducing intestinal blood loss [23].

Little is known about red cell life span during critical illness. Signs of haemolysis are not regularly found in intensive care patients [13], but in view of the systemic inflammatory response and complement activation, a premature destruction of red cells is probable. In particular, the survival of transfused red cells is likely to be reduced.

Under conditions where the intravascular lifespan of erythrocytes is abnormally low, either owing to external loss or to premature red cell destruction, the ability to increase red cell formation in the marrow becomes particularly relevant. One of the major elements in the pathogenesis of the anaemia of critical illness is a lack of this adaptive increase. Despite reduced Hb levels, reticulocyte counts are not increased and there is no shift towards more immature forms [13,24], normally a sign of stimulated erythropoiesis. At least three identifiable factors contribute to inappropriately low rates of red cell formation.

Firstly, an insufficient increase in endogenous erythropoietin production fails to compensate for the degree of anaemia. Blunted erythropoietin production has been observed independent of the presence of ARF, but can be aggravated by renal dysfunction [25]. Relative erythropoietin deficiency has been reported both in paediatric and adult patients and is largely irrespective of the underlying disorder causing critical illness [13,24,26–28]. Patients with sepsis can, under certain conditions, show a marked increase in erythropoietin levels that is unrelated to their Hb concentration [29]. However, the overall relationship between serum erythropoietin levels and Hb concentration is blunted in cases of sepsis compared with normal [26]. Studies with isolated perfused kidneys and hepatoma cells have shown that the pro-inflammatory cytokines IL-1β and tumour necrosis factor (TNF-α) inhibit erythropoietin production [30,31]. The mechanisms of this interaction are, as yet, unclear but do not seem to be related to an interference with hypoxia-inducible transcription factors that regulate erythropoietin in an oxygen-dependent fashion [32].

Secondly, inflammatory cytokines can inhibit red cell production through direct interaction with maturation and proliferation of erythroid progenitor cells. Interferons, TNF-α and IL-1 have been shown to prevent the growth of burst forming and erythroid colony forming units in vitro through different mechanisms [33–35]. Anaemia also results when cytokines are administered in vivo [10].

Thirdly, systemic inflammation is believed to impair iron availability for erythropoiesis [13,24,36–38], although this is difficult to assess, as ferritin levels are significantly increased and transferrin levels reduced as part of the acute-phase reaction. Knowledge of the interaction between systemic inflammation and iron availability is still limited, but effects of inflammatory cytokines on cellular iron uptake mechanisms seem to play an important role. Cytokines can down regulate transferrin receptors on cell membranes of erythroid and non-erythroid cells, thus impairing cellular iron uptake. Concomitantly, they enhance the expression of lactoferrin receptors, providing an alternative method of iron uptake by tissue macrophages [39]. As a net
consequence, iron is preferentially delivered to macrophages and its availability for Hb synthesis is reduced.

The relative importance of these three factors for the impairment of red cell production is difficult to assess. As inflammation and infection are also well-recognized causes of rHuEPO resistance in CRF patients treated with rHuEPO, reduced endogenous erythropoietin production does not seem to be the predominant cause. A priori, it appeared highly questionable whether the ‘inflammatory block’ of erythropoiesis could be overcome by therapy with rHuEPO. However, increasing evidence suggests that the erythropoietin resistance associated with inflammation is not absolute and that high doses of rHuEPO can induce stimulation of erythropoiesis in critical illness.

The use of rHuEPO in critically ill patients

Over the last 10 years a number of case reports, a few small trials and a single larger trial have been published on the use of rHuEPO in patients treated in ICU (Table 2). The idea of using rHuEPO therapy as an alternative to red blood cell transfusions was originally conceived as a way of treating Jehovah’s Witnesses, who refused to receive blood transfusions. Following the administration of high doses of rHuEPO, the majority of these reports demonstrated an increase in reticulocyte counts within a few days and a subsequent rise in Hb levels. Despite the natural limitations of uncontrolled case observations, these reports provided the first indication that rHuEPO can lead to effective stimulation of impaired red cell production under varied conditions of critical illness. The majority of these observations were made using doses of more than 1000 IU/kg a week.

Three small, randomized trials tested the efficacy of rHuEPO. One, which included patients with severe burn injuries, failed to demonstrate a significant difference in Hb or reticulocyte levels between rHuEPO- and placebo-treated patients [18]. In contrast, the other two trials, with 19 and 36 patients, respectively, confirmed the efficacy of rHuEPO by demonstrating increased rates of red cell production, as measured by a rise in reticulocyte counts or soluble transferrin receptor levels [24,37]. In the study by van Iperen et al. [24] patients treated with rHuEPO also received a moderate dose of i.v. iron (20 mg daily) and the trial included a treatment arm in which patients received i.v. iron only (Figure 3) [24]. High doses of rHuEPO led to a significant increase in reticulocyte counts, while in patients treated with i.v. iron only reticulocyte counts were not different from those of untreated controls. As a result of the lack of a rHuEPO-only arm, the effect of simultaneous iron supplementation on the response to rHuEPO remains unclear.

Based on preliminary results demonstrating the ability of rHuEPO to induce red cell production in critically ill patients, Corwin et al. [40] performed the first larger trial to investigate whether rHuEPO therapy could reduce the number of red blood transfusions in ICU patients. They included 160 patients in three interdisciplinary ICUs. Patients were randomized to receive either placebo or rHuEPO, 300 IU/kg s.c., daily between ICU days 3 and 7, and then every other day [40]. All patients initially received oral iron in a liquid preparation, but should be switched to parenteral iron if they were unable to tolerate oral iron or demonstrated an inadequate response (serum transferrin saturation < 20% and a decrease of serum ferritin to < 100 ng/ml). The cumulative number of units of red blood cells transfused was significantly less in the rHuEPO than in the placebo group (166 vs 305 U; P < 0.002). Despite a lower number of transfusions, the final haematocrit (Hct) concentration of rHuEPO-treated patients was significantly greater than that of patients receiving placebo (35.1 ± 5.6 vs 31.6 ± 4.1%; P < 0.01). However, the percentage of patients transfused, did not differ significantly between the two groups. There was no difference between the two groups in either mortality or in the frequency of adverse events. Thus, the study provided clear evidence that rHuEPO administration to critically ill patients was effective in raising Hct concentrations and in reducing the total number of transfusions required.

Conclusions and perspectives

Overall, the experience in ICU patients seems to indicate that, in the majority of patients, rHuEPO resistance related to systemic inflammation can be overcome using high, pharmacological doses of rHuEPO. However, it should be noted that weekly doses of rHuEPO shown to be effective in the critically ill (Table 2) are usually several-fold higher than the dose level used to define ‘resistance’ to rHuEPO in current guidelines for anaemia management in CRF [49,50]. Available data also indicate that, at least during short-term treatment, these high doses of rHuEPO are well tolerated and do not lead to any obvious adverse effects.

From a basic science perspective, such observations are interesting as they strengthen the predominant role of rHuEPO for the regulation of red cell production. Apparently, adverse conditions that inhibit red cell maturation and reduce the availability of iron can be overridden in the presence of supraphysiological concentrations of rHuEPO. This confirms and extends previous observations in patients with CRF indicating that an increase in rHuEPO dose can compensate for some degree of iron deficiency.

In the management of the critically ill, rHuEPO therapy has potential benefits beyond avoiding non-infectious and infectious risks associated with red cell transfusions. The capacity of transfused red blood cells to deliver oxygen is severely hampered [51].
<table>
<thead>
<tr>
<th>Publication</th>
<th>Patients</th>
<th>Underlying disease</th>
<th>rHuEPO therapy</th>
<th>Frequency</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>van Iperen <em>et al.</em> [24]*</td>
<td>2000</td>
<td>36</td>
<td>Interdisciplinary ICU</td>
<td>300 IU/kg s.c. plus i.v. iron (20 mg/d)</td>
<td>Every 2nd day (day 1,3,5,7, and 9)</td>
</tr>
<tr>
<td>Corwin <em>et al.</em> [40]</td>
<td>1998</td>
<td>160</td>
<td>Interdisciplinary ICU</td>
<td>300 IU/kg s.c.</td>
<td>Daily for 5 days, then every 2nd day</td>
</tr>
<tr>
<td>Gabriel <em>et al.</em> [37]</td>
<td>1998</td>
<td>19</td>
<td>Major abdominal surgery or trauma or multiple organ failure</td>
<td>600 IU/kg i.v.</td>
<td>3 times/week</td>
</tr>
<tr>
<td>Still <em>et al.</em> [18]</td>
<td>1995</td>
<td>40</td>
<td>Burn patients</td>
<td>300 IU/kg</td>
<td>Daily for 7 days</td>
</tr>
<tr>
<td>DeMeester <em>et al.</em> [41]</td>
<td>1994</td>
<td>1</td>
<td>Trauma patient‡</td>
<td>300 IU/kg i.v.</td>
<td>Daily for 3 days</td>
</tr>
<tr>
<td>Moghtader <em>et al.</em> [42]</td>
<td>1994</td>
<td>1</td>
<td>Burn patient‡</td>
<td>Then 150 IU/kg</td>
<td>Every 2nd day</td>
</tr>
<tr>
<td>Smith and Mihov [43]</td>
<td>1993</td>
<td>2</td>
<td>Paediatric, GI bleeding‡</td>
<td>50 IU/kg</td>
<td>Days 5 and 8</td>
</tr>
<tr>
<td>Kraus and Lipman [44]</td>
<td>1992</td>
<td>1</td>
<td>Trauma patient‡</td>
<td>~70 IU/kg</td>
<td>Daily for 7 days</td>
</tr>
<tr>
<td>Fleming <em>et al.</em> [45]</td>
<td>1992</td>
<td>10</td>
<td>Paediatric burn patient</td>
<td>300 IU/kg s.c.</td>
<td>Daily for 7 days</td>
</tr>
<tr>
<td>Boshkov <em>et al.</em> [46]</td>
<td>1991</td>
<td>1</td>
<td>Burn patient‡</td>
<td>300 IU/kg i.v.</td>
<td>Daily for 7 days</td>
</tr>
<tr>
<td>Law <em>et al.</em> [47]</td>
<td>1991</td>
<td>2</td>
<td>Burn patients‡</td>
<td>~370 IU/kg i.v.</td>
<td>For 3 days</td>
</tr>
<tr>
<td>Koestner <em>et al.</em> [48]</td>
<td>1990</td>
<td>1</td>
<td>Trauma patient‡</td>
<td>300 IU/kg</td>
<td>Daily for 3 days</td>
</tr>
</tbody>
</table>

*Randomized controlled trial.  
‡Randomized, double-blind, placebo-controlled trial.  
§Jehovah’s witnesses.
Depending on storage time, tissue oxygenation does not always improve, and sometimes even worsens, following blood transfusions [52]. Therefore, it is an intriguing possibility that stimulation of endogenous erythropoiesis might improve tissue oxygen supply and patient outcomes. To this end, the use of rHuEPO may help to re-address the question of optimal Hb in acute illness, independent of confounding effects of red cell transfusions. Recent evidence has suggested that lowering transfusion thresholds is, to some extent, safe [53], but it may be important to distinguish between an ‘optimal transfusion threshold’ and the ‘optimal Hb level’. While the former reflects the Hb concentration at which the benefits of increasing oxygen-carrying capacity outweigh the risk of transfusions, the latter is likely to be higher if achieved by endogenous red cell production.

The observation that critically ill patients can respond to high doses of rHuEPO also has implications for non-ICU patients in renal failure, who do not respond to usual doses of rHuEPO. It implies that, in such patients, a significant dose increase may override resistance to rHuEPO. However, there are a number of limitations and open questions related to the use of very high doses of rHuEPO.

Firstly, at current prices, cost constraints are likely to limit the widespread use of very high doses of rHuEPO and it will be difficult, if not impossible, to demonstrate favourable cost–benefit relationships. Secondly, in such situations, optimal dosing regimens need to be further defined and the use of surrogate markers of erythropoiesis, such as reticulocyte kinetics and transferrin receptor levels, further evaluated. For example, ‘optimal’ dosing may imply withholding therapy (thus saving resources), until the most active phases of inflammation have been overcome. Thirdly, the issue of concomitant iron treatment is unresolved. Whether i.v. iron is effective and safe under conditions of severe inflammation and/or infection is of concern and difficult to evaluate. Fourthly, despite the favourable experiences so far, a theoretical safety issue remains with respect to the high concentrations of rHuEPO that may be needed to achieve efficacy in some patients. In more than 15 years of use, rHuEPO therapy has proven to be extremely well tolerated. In addition, patients with aplastic anaemias are known to have very high endogenous erythropoietin levels, without any recognizable adverse consequences. On the other hand several studies have reported effects of high doses of rHuEPO on non-erythroid cells [for example 54–56]. While the ‘usual’ doses of rHuEPO in CRF are unlikely to lead to tissue concentrations high enough to exert such effects, very high doses could be sufficient to stimulate erythropoietin receptors on non-erythropoietic cells. Extrarythropoietic effects do not necessarily lead to adverse consequences. Indeed, some animal experiments have shown high doses of rHuEPO to be neuroprotective [57]. Nevertheless, the risk–benefit relationship for very high doses of rHuEPO needs to be carefully considered.

In conclusion, despite several open questions remaining, the demonstration of rHuEPO efficacy in critical illness is exciting and will certainly lead to a reconsideration of the ‘dose–response relationship’ for rHuEPO in patients with less acute and severe illness, including CRF patients hyporesponsive to current dosing regimens.

References
