British Journal of Anaesthesia **97 (3)**: 278–91 (2006)
doi:10.1093/bja/ael189 Advance Access publication July 27, 2006

BJA

REVIEW ARTICLE

Anaemia during critical illness

T. S. Walsh[1]* and Ezz-El-Din Saleh[1 2]

[1]*Anaesthetics, Critical Care and Pain Medicine, New Edinburgh Royal Infirmary, Little France Crescent, Edinburgh, Scotland EH16 2SA*
[2]*Present address: Department of Anaesthetics, Menoufia University, Egypt*
**Corresponding author: Anaesthetics, Critical Care and Pain Medicine, New Edinburgh Royal Infirmary, Little France Crescent, Edinburgh, Scotland EH16 2SA. E-mail: Timothy.Walsh@ed.ac.uk*

Br J Anaesth 2006; **97**: 278–91

Keywords: blood, erythrocytes; blood, transfusion; complications, anaemia; intensive care

Anaemia occurs frequently during critical illness. Recent studies have increased our understanding of how well critically ill patients tolerate anaemia. It is known that anaemia does not result simply from diagnostic and physical blood loss, but is multifactorial in origin. Recently, abnormalities in circulating red cell function have been described that are potentially relevant to efficient oxygen delivery. Potential new approaches to the management of the anaemic patient during critical illness have also been evaluated.

This narrative review considers methodological issues relevant to understanding the critical care literature on anaemia. We summarize current understanding of the prevalence of anaemia during critical illness, specifically among patients in intensive care units (ICUs), and discuss the various factors that contribute to its development. We consider how red cell function may alter during critical illness and the possible clinical relevance of these changes. The treatment of anaemia is discussed, with particular emphasis on haemoglobin triggers for allogeneic red cell transfusions among critically ill patients, with reference to clinically important subgroups. The place of erythropoietin, an emerging therapy for anaemia in this setting, is considered and key future research questions identified.

Definition of anaemia

Anaemia is a haemoglobin concentration in blood that is below the expected value, when age, gender, pregnancy and certain environmental factors, such as altitude, are taken into account.[23] It results in a reduction in red cell mass and a decrease in the oxygen-carrying capacity of the blood. The World Health Organization (WHO) defines anaemia as a haemoglobin <13 g dl^{-1} (haematocrit <39%) for adult males and <12 g dl^{-1} (haematocrit <36%) for adult non-pregnant females.[23] There are no universally agreed grades of severity for anaemia during critical illness. Several classifications specific to cancer, a condition in which recent studies link anaemia severity and its treatment to quality of life, have been proposed (Table 1).

Interpreting the critical care transfusion literature

Anaemia is assessed by measuring the haemoglobin concentration or haematocrit. It therefore reflects the relationship between circulating red cell mass and the plasma volume. During critical illness, many factors can change acutely both these factors, such that the presence of anaemia needs to be interpreted in relation to concurrent therapy and pathophysiology. This detail is often unclear from large studies, because it is difficult to measure, expensive to collect, and classification in a manner that enables statistical analysis is difficult.

Another major confounder to interpretation is transfusion practice. Prior to publication of the Transfusion Requirements in Critical Care (TRICC) trial there was wide variation in transfusion practice.[30] The TRICC trial compared a transfusion trigger of <7 g dl^{-1}, with a target level of 7–9 g dl^{-1} during ICU admission, with a trigger <10 g dl^{-1} and target of 10–12 g dl^{-1} in patients whose haemoglobin concentration had a value of 9 g dl^{-1} during the first 3 days in ICU.[29] The 30 and 60 day mortality were similar for these groups and significantly lower with the restrictive strategy among younger (<55 yr) and less ill (APACHE II score <20) patients. Studies carried out after publication of this landmark trial continue to show variation in transfusion triggers. As a result, the prevalence and incidence of anaemia among populations of critically ill patients needs to be placed in context by a description of the associated transfusion practice.

Prevalence of anaemia during critical illness

The prevalence of anaemia among critically ill patients is influenced by factors that include patient case mix, illness

© The Board of Management and Trustees of the British Journal of Anaesthesia 2006. All rights reserved. For Permissions, please e-mail: journals.permissions@oxfordjournals.org

Table 1 World Health Organization grading of the severity of anaemia for patients with cancer

Grade of cancer related anaemia, haemoglobin range (g dl^{-1})
0 (none) >11
1 (mild) 9.5–10.9
2 (moderate) 8.0–9.4
3 (severe) 6.5–7.9
4 (life threatening) <6.5

Table 2 Estimates of the prevalence of anaemia at admission to intensive care

Variable	Estimate of value or prevalence
Mean haemoglobin concentration at ICU admission	10.5–11.3 g dl^{-1}
Proportion of patients with	
Haemoglobin concentration <12 g dl^{-1}	60–70%
Haemoglobin concentration <9 g dl^{-1}	20–30%
Prevalence of pre-existing anaemia at ICU admission	13%

severity and pre-existing comorbidity. As noted above, the blood transfusion practice employed will inevitably influence the haemoglobin concentrations observed. The TRICC study has resulted in a more consistent use of restrictive triggers; typical median pre-transfusion haemoglobin values in recent studies have been 7.8–8.5 g dl^{-1}.[15 24 58 73 76]

Anaemia at ICU admission

Several recent studies have documented the prevalence of anaemia on admission to ICU. A cohort study of 3534 patients admitted to 146 Western European ICUs with varying case mix (the ABC study) found that the mean haemoglobin concentration at ICU admission was 11.3 g dl^{-1}.[73] Sixty-three per cent of patients had a haemoglobin concentration <12 g dl^{-1} on ICU admission and 29% of patients had an admission haemoglobin concentration <10 g dl^{-1}. The study had a low risk of selection bias because all patients admitted to the participating ICUs over a 2 week period were included. In the study 13% of patients had a recent history of anaemia, and among these 37% had a haemoglobin concentration <10 g dl^{-1} on ICU admission. The study found that ~50% of those patients admitted to ICUs with a haemoglobin concentration <10 g dl^{-1} had no history of either acute bleeding or other documented causes of anaemia. Anaemia was more frequent and more severe in older patients. Approximately 40% of the patients in the study were elective post-operative admissions to ICUs and the overall illness severity was therefore lower than is typical for some countries (mean APACHE II score 14.8; SD 7.9).

A similarly designed study in the USA examined 4892 admissions to ICUs (the CRIT study).[15] In this study the mean haemoglobin concentration at ICU admission was 11.0 g dl^{-1}. Almost two-thirds of patients had a haemoglobin concentration <12 g dl^{-1} at ICU admission. In this study 20% of patients were post-operative, although it is unclear whether these were emergency or planned admissions. In addition, it is unclear what proportion of all ICU admissions to the 284 participating ICUs was studied. As the study took place over 9 months (averaging 2 enrolments per ICU per month), it is likely that the study group represented a subgroup of all admissions. The illness severity at ICU admission was higher than in the ABC study (mean 19.7; SD 8.2). As in the ABC study, 13% of patients had anaemia as a comorbidity on admission.

A cohort study of 1023 sequential admissions to 10 Scottish ICUs found that the median haemoglobin concentration at ICU admission was 10.5 g dl^{-1} (interquartile range 9.0–12.4 g dl^{-1}).[77] The illness severity of patients in this cohort was similar to those in the CRIT study (mean APACHE II score 19.8; SD 7.7). This study had complete data for >99% of patients admitted to the participating ICUs over the 100 day study period and therefore had a low risk of selection bias. The authors also showed that the patients studied represented 44% of all general adult ICU admissions nationally over the study period. At ICU admission, 25% of patients had a haemoglobin concentration <9 g dl^{-1} (range 16–34% across the 10 ICUs). Among ICU survivors and non-survivors 21 and 29%, respectively, of patients had an admission haemoglobin concentration <9 g dl^{-1} at ICU admission.

A summary of the epidemiology of anaemia on admission to ICU based on these large multicentre studies is shown in Table 2. Because of differences in case mix and study methodology, the prevalence of anaemia at ICU admission varies, but it appears that 20–30% of patients have moderate to severe anaemia (haemoglobin concentration <9 g dl^{-1}). Only 10–15% have documented pre-existing anaemia.

Anaemia during ICU stay

The prevalence and severity of anaemia during ICU admission is clearly linked closely with the transfusion practice used. The evolution of anaemia among non-transfused, non-bleeding, critically ill patients is difficult to study both ethically and in practice. Nguyen and colleagues[52] found that among non-bleeding ICU patients who did not receive red cell transfusions haemoglobin concentrations decreased by a mean 0.52 g dl^{-1} day^{-1}. On average, haemoglobin concentrations decreased by 0.66 g dl^{-1} day^{-1} for the first 3 days and by 0.12 g dl^{-1} day^{-1} thereafter. This early rapid decrease in haemoglobin values was also found in a prospective observational single centre cohort study of patients receiving >24 h of intensive care.[11] Fifty-two per cent of patients had a haemoglobin concentration ⩽9 g dl^{-1} on the first day of ICU care, increasing to 77% by day 2. In the CRIT study in US ICUs, the mean haemoglobin concentration in a cohort of non-transfused patients decreased from ~12 g dl^{-1} at admission to 11 g dl^{-1} by days 3–4, after which values reached a plateau among

Table 3 Haemoglobin transfusion triggers and transfusion rates in intensive care for recent large epidemiological studies of anaemia, blood transfusion or both in ICUs

Study (reference)	Study acronym	Study size	Case mix	Mean (SD) population APACHE II score	Transfusion trigger	Proportion of admissions transfused (%)
Vincent and colleagues[73]	ABC study	3534	Mixed multicentre ICUs	14.8 (7.9)	Mean 8.4 (SD 1.3)	37
Rao and colleagues[58]	None	1247	Mixed multicentre general ICUs	Transfused patients 19.0 (8.8) Non-transfused patients 16.3 (9.3)	'haemorrhage' 8.5 (IQR: 7.8–9.3) 'low haemoglobin' 8.5 (IQR: 7.8–8.9)	53
Corwin and colleagues[15]	CRIT study	4892	Mixed multicentre ICUs	19.7 (8.2)	Mean 8.6 (SD 1.7)	44
Bellomo and colleagues[24]	None	1808	Mixed general ICU	Not given	Mean 8.2 (range: 4.4–18.7)	19.8
Walsh and colleagues[76]	ATICS study	1023	Mixed adult general ICUs (excluding cardiac)	19.8 (7.7)	Median 7.8 (IQR: 7.3–8.5)	39.5

patients remaining in the study.[15] The normal mean baseline haemoglobin concentration of this cohort suggest that these observations may not be generalizable to all intensive care admissions, but confirm the early rapid onset of anaemia in many critically ill patients. Several factors contribute to the decline in haemoglobin concentration, considered later in this article. Another way of assessing the prevalence of anaemia in ICU is to examine transfusion rates in conjunction with a measure of illness severity and the haemoglobin transfusion triggers used. A summary of the findings of recent large multicentre epidemiological studies (Table 3) indicates that 39–53% of patients receive blood transfusions in ICUs when the transfusion triggers range from 7.8 to 8.6 g dl^{-1}.[15 24 58 73 76] Based on all admissions, each patient typically receives on average 2–4 red cell units per admission while in the ICU, depending on the case mix and transfusion practice present. In the two largest studies (ABC and CRIT studies), in which mean transfusion triggers were high (mean 8.4–8.5 g dl^{-1}) relative to the value used in the TRICC trial, the authors followed the cohorts for up to 28–30 days. Irrespective of baseline haemoglobin concentration or blood transfusions mean values converged on a value of 9.5–10.5 g dl^{-1} over time.[15 73] The CRIT study investigators also published an analysis of the subgroup of patients with trauma (12% of the total cohort).[65] Among these patients, 55% received transfusions in the ICU at a mean haemoglobin transfusion trigger of 8.9 g dl^{-1}. The mean haemoglobin decreased rapidly over the first 1–4 days in the ICU after which it remained between 10 and 10.5 g dl^{-1} over the 30 day follow-up period. This suggested a significantly more liberal use of transfusions during ICU care than was used in the TRICC trial, despite most patients falling into the subgroups who had better outcomes with restrictive transfusion practice, namely lower APACHE II scores (mean 16.9) and being young (mean 44.1 yr). The reason that more liberal transfusion triggers were used was not clear.

In the ATICS study, the median transfusion trigger was 7.8 g dl^{-1} and only 25% of transfusions were associated with haemoglobin values >8.5 g dl^{-1} for non-haemorrhage transfusions.[76] Among ICU survivors, 21% had an admission haemoglobin concentration <9 g dl^{-1} and a further 27% developed a haemoglobin concentration of <9 g dl^{-1} on at least one occasion during ICU stay. Of patients who died in the ICU, these proportions were 29 and 31%, respectively. Forty-six per cent of male and 53% of female ICU survivors had at least one haemoglobin concentration measured <9 g dl^{-1} during their ICU stay.[77] A single centre UK cohort study of patients requiring >24 h of ICU care documented a median (interquartile range) transfusion trigger 7.8 (7.4–8.4) g dl^{-1}. With this practice, the haemoglobin concentration was ≤9 g dl^{-1} on 45% of all patient days in ICU.[11] An analysis of the ATICS dataset examined the 766/1023 patients who survived to ICU discharge.[77] Among the 317 females and 449 males discharged alive from intensive care, 80 and 87%, respectively, were anaemic compared with laboratory reference ranges. Twenty-eight per cent of females and 24% of males had a haemoglobin concentration <9 g dl^{-1} at the time of ICU discharge. The authors developed a logistic regression model to analyse factors associated with the presence of significant anaemia, defined as a haemoglobin concentration <9 g dl^{-1}, at ICU discharge. Unsurprisingly, the first haemoglobin concentration in the ICU was strongly associated with significant anaemia at ICU discharge, particularly given the restrictive transfusion strategy documented in the study. After including this factor the only other variables examined that were independently associated with significant anaemia at ICU discharge were the presence and severity of renal failure during ICU stay and the presence of thrombocytopenia.

Together, these data show that the 'hit' of critical illness frequently results in acute anaemia, which is present at ICU admission or develops within the first 24–48 h. Once present, anaemia persists in most patients until ICU discharge unless modified by blood transfusion practice.

In summary, despite differences in case mix and transfusion practice the prevalence of moderate to severe anaemia (haemoglobin concentration <9 g dl^{-1}) at some time during ICU stay appears to be 40–50% among most ICU populations. If anaemia is not present at the time of ICU admission it develops rapidly during the first 2–3 days in most patients.

Once present anaemia tends to persist until ICU discharge unless modified by blood transfusions.

Anaemia after ICU discharge

There are few data concerning anaemia after intensive care treatment, particularly when restrictive transfusion triggers have been used. Although the ABC and CRIT studies followed patients for up to 28–30 days the authors did not report anaemia outcomes specifically for the post-ICU recovery period.[15 73] During the period between ICU and hospital discharge and in the period after discharge home, many patients suffer fatigue, breathlessness and other morbidity frequently associated with anaemia. In the CRIT study only 13% of patients were transfused after ICU discharge with a median transfusion trigger of 8.3 g dl^{-1} (first, third quartile: 7.7, 9.0 g dl^{-1}), but the distribution of haemoglobin values among patients during this period is not reported.[15] A similar proportion of patients were transfused in the ABC study (12.7%) with mean transfusion triggers ranging from 8.3 to 8.7 g dl^{-1} dependent on the indication listed. The prevalence and severity of anaemia after ICU discharge was not specifically reported.[73] A single centre study in a UK teaching hospital followed a cohort of 283 patients managed with restrictive transfusion triggers in ICU who survived to discharge home from hospital.[81] In this study 11% of patients were transfused in the post-ICU period with a median transfusion trigger of 7.4 g dl^{-1} (first, third quartile: 68, 76 g dl^{-1}). Patients spent a median 13 days (first, third quartile: 6, 22; range 1–119 days) in hospital after ICU discharge. At the time of discharge home 77.4% of patients were anaemic, 32.5% had a haemoglobin concentration <10.0 g dl^{-1} and 11.3% <9.0 g dl^{-1}. A total of 48% of patients who spent >7 days in ICU had a haemoglobin concentration <10 g dl^{-1} when discharged home. Among patients discharged anaemic 82% had normochromic normocytic indices; 12% of patients had red cell hypochromasia, which could have indicated iron deficiency. There are no published studies on longer-term prevalence or recovery from anaemia or whether this is important for recovery.

In summary, there are currently few data concerning anaemia during the recovery phase of critical illness. The data available indicate that anaemia may persist for many weeks in some patients.

Aetiology of anaemia during critical illness

The aetiology of anaemia during critical illness is multifactorial in most patients (Table 4).

Haemodilution

Critically ill patients frequently develop intravascular hypovolaemia requiring fluid resuscitation. Current practice is often to administer crystalloid or colloid solutions during resuscitation and withhold red cell transfusion unless patients have severe haemorrhage. The standard clinical measure for anaemia is haemoglobin concentration or haematocrit, which is not a reliable estimate of red cell mass because it is sensitive to altered plasma volume (Fig. 1).

Table 4 Causes of anaemia during critical illness

Pre-existing chronic anaemia
Acquired anaemia
Haemodilution
Blood loss
Blood sampling
Haemorrhage
Reduced red cell survival
Reduced red cell production
Abnormal iron metabolism
Nutritional deficiencies
Inappropriate erythropoietin production
Abnormal red cell production

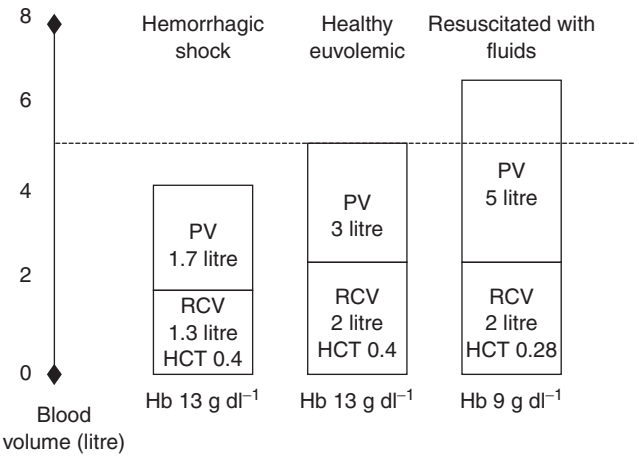

Fig 1 The relation between red cell volume, plasma volume and haemoglobin concentration during haemorrhage, healthy euvolaemia, and fluid resuscitation with clear fluids. PV, plasma volume; RCV, red cell volume; HCT, haematocrit; Hb, haemoglobin concentration.

The relative importance of haemodilution has not been established, in part because no studies have simultaneously measured red cell mass while changing plasma volume during resuscitation. It is currently difficult to perform these measurements in the clinical setting. It is likely that haemodilution accounts for a significant proportion of the decrease in haemoglobin concentration that occurs rapidly during the early stages of critical illness, particularly during fluid resuscitation.

Blood loss

Historically, blood loss has been considered a major cause of anaemia in intensive care patients. In practice, it is difficult to estimate total daily blood loss because accurate measurement from all sources is impractical. In one study, estimated total daily blood loss using a formula

based on haematocrit, blood volume estimates and transfused red cell volume suggested total blood loss of >100 ml day^{-1}.[74] Potential sources of blood loss are diagnostic blood sampling and haemorrhage from body sites.

Blood sampling

Phlebotomy contributes to the anaemia of critical illness. Early studies found that, on average, a critically ill patient lost 1–2 units of blood through blood sampling during their hospital stay.[34 67] Other studies estimated that phlebotomy could account for up to 30% of the total blood transfused in the ICU.[2 20] More recent data suggest that phlebotomy is still a significant source of blood loss. The ABC study found that the volume of blood lost through blood sampling was on average 41 ml per 24 h.[73] This, and other studies, shows that the number of samples and total blood volume sampled are larger among more severely ill patients and among patients receiving renal replacement therapy.[2 73 74] In the ABC study, the mean sampling volume was 10.3 ml and it follows that clinical care that includes frequent sampling will significantly increase diagnostic blood loss. Blood sampling volumes are highest during the first 24 h of ICU stay and decrease progressively among patients requiring longer periods in ICU.[73 74]

Haemorrhage

There are many potential sources of bleeding in critically ill patients. The contribution from gastrointestinal bleeding is probably overstated with modern resuscitation and management,[14 57] but may be relevant in high-risk patients including those receiving mechanical ventilation or with coagulopathy and renal failure.[13] Recent ICU-based transfusion studies suggest that between 20 and 55% of all transfusion events are associated with bleeding, but these analyses do not indicate the contribution of bleeding to anaemia.[24 58 73 76] In a recent multicentre study, 21% of ICU patients experienced at least one episode of significant bleeding during ICU stay, defined as loss of at least 300 ml of blood from any site during a 24 h period.[76] Of these admissions, 65% had one episode, 20% had two episodes and 15% had three or more episodes, and 18% of all ICU admissions received at least one red cell transfusion associated with haemorrhage during ICU stay. The mean number of red cell units transfused for each haemorrhage episode was 3.1, and haemorrhage-related transfusions accounted for 53% of all the red cell units given in ICU. The study did not document the source of bleeding and in only 24% of the transfusion episodes were $\geqslant$4 red cell units given. These data suggest that haemorrhage remains an important source of blood loss in a subgroup of intensive care patients, but is not the only explanation for the high prevalence of anaemia observed.

Reduced red cell survival

Complement activation, which occurs in critically ill patients with systemic inflammatory response syndrome or sepsis, could potentially cause premature RBC destruction, although no evidence of intravascular haemolysis has been found.[74] Changes in red cell deformability and membrane characteristics, which are discussed later in this article, could decrease red cell survival. Direct evidence suggesting that critical illness, and sepsis in particular, reduces red cell lifespan is lacking. However, there are experimental data showing that inflammatory mediators, such as TNF-α and IL-1, can decrease erythrocyte survival time in other settings.[64] Oxidative stress has recently been shown to induce premature apoptosis among red cells, despite their lack of nuclei.[44] Further work is needed to establish whether these mechanisms are clinically important in the critically ill.

Reduced red cell production

Several studies have demonstrated inappropriately low reticulocyte counts in anaemic, critically ill patients.[16 72 74] This suggests that critically ill patients do not have a normal erythropoietic response to anaemia. Healthy blood donors or patients treated for iron deficiency rapidly release reticulocytes into the circulation in response to anaemia. Bone marrow suppression appears to be associated with the presence or persistence of an inflammatory state. Several mechanisms may be involved, many of which are implicated in the anaemia of chronic disease. Corwin coined the term 'acute anaemia of chronic disease' to describe the abnormal erythropoiesis that occurs during critical illness.[18] This term is useful because there appear to be many similarities between erythropoiesis during acute and chronic inflammatory conditions, including cancer. A number of factors, which normally regulate or limit red cell production, could contribute to reduced red cell production during critical illness.

Iron metabolism

Acute inflammation is thought to decrease the iron available for erythropoiesis. The interpretation of iron indices in inflammatory states is difficult because serum ferritin is increased and serum transferrin is decreased as part of the acute phase response.[8] ICU patients typically have low values for serum iron, total iron binding capacity and serum iron/total iron binding capacity ratio, but the serum ferritin concentration is normal or more usually elevated.[62 72 74] These biochemical changes, which are similar in both acute and chronic inflammatory conditions, indicate a change in iron homeostasis. During inflammation, iron is transferred into macrophages, where it is incorporated into the ferritin.[84] Consequently, the anaemia of inflammatory disease is characterized by low serum iron concentrations despite increased storage iron. The iron transport protein transferrin may be at the lower limit or below normal, and transferrin saturation is frequently below the reference range. The net effect of these changes is a low bioavailability of free iron for erythropoiesis.[36 64] *Functional iron deficiency* is a term used to describe the inability to incorporate iron into haemoglobin for normal red cell production, often despite adequate body stores of iron.[25] This can be detected by measuring reduced reticulocyte haemoglobin

concentration (CHR) or increased per cent hypochromic red cells in peripheral blood using specialized flow cytometry-based analysers. The CHR is thought to indicate recent functional iron deficiency by measuring iron concentration in recently produced reticulocytes, whereas per cent hypochromic red cells is thought to reflect status over the lifespan of all circulating cells (3–4 months).[25] Using per cent hypochromic red cells, Bellamy and colleagues found that 35% of patients have red cell indices consistent with functional iron deficiency at ICU admission.[7 54] Patients demonstrating this feature had longer stays in intensive care compared with patients without functional iron deficiency. They suggested that this might be a marker of nutritional status or general health, but it could also indicate an acute, incompletely understood, response to acute inflammatory processes. It is also uncertain whether changes in red cell shape, which have been demonstrated during inflammation and sepsis,[55] alter these automated parameters.

Soluble transferrin receptor (sTFR) concentrations reflect receptors shed into the circulation from the surface of red cell precursors and can be measured using commercially available assays. Increased circulating concentrations are thought to indicate active erythropoiesis and are also a marker of iron deficiency.[25] Circulating sTFR concentrations are normal in anaemic critically ill patients.[38 72] This is against a high prevalence of significant true iron deficiency during critical illness. However, normal levels could also be attributable to marrow hypo-reactivity and inappropriately low rates of new red cell production in response to anaemia.

In the anaemia of chronic disease pro-inflammatory cytokines induce the production of hepcidin, a regulatory hormone that inhibits intestinal absorption of iron.[1] An excellent review of current understanding of this and other biological mechanisms for anaemia in chronic disease has been published recently.[84] The importance of this mechanism in acute critical illness is uncertain. There are no large studies that examined the effect of iron therapy alone on anaemia during critical illness, but in one small study daily i.v. iron disaccharide therapy alone for 14 days did not increase reticulocyte counts or have any beneficial effect compared with the control group.[72] Theoretical arguments against iron therapy during severe illness have been made with the suggestion that iron accumulation in immune cells could impair host defences. The clinical significance of this hypothesis is uncertain. Oral iron therapy is unlikely to be efficacious in the critically ill and could contribute to constipation or other gastrointestinal complications. The risk to benefit profile of i.v. iron is currently unknown.

In summary, changes in iron metabolism occur during critical illness that resemble the pattern observed in patients with the anaemia of chronic inflammatory diseases (Table 5). Although total body iron is probably normal it is less available for normal red cell production. The interpretation of iron indices is difficult during critical illness because inflammation induces changes to the normal biochemical markers.

Table 5 Biochemical characteristics of anaemia in critically ill patients

	Change	Comment
Serum iron	↓	Similar to anaemia of chronic disease
Total iron binding capacity	↓	
Serum iron/total iron binding capacity ratio	↓	
Ferritin	↑	'Positive' acute phase protein
Transferrin	↓	'Negative' acute phase protein
Transferrin saturation	↓	
Soluble transferrin receptor concentration	N	Increase thought to indicate iron deficiency or new erythropoiesis
Per cent hypochromic red cells	N/↑	Indicative of functional iron deficiency
Vitamin B12 and folate	N	
Erythropoietin concentration	N/slight ↑	Inappropriately low for degree of anaemia, may be transiently increased in acute renal failure

B12 and folate metabolism

There are few studies evaluating the prevalence of vitamin B12 or folate deficiency in intensive care patients either on admission or during prolonged illness. Rodriguez and colleagues[62] found evidence of deficiency in only 2% of ICU patients. The relation between these and other nutritional deficiencies and anaemia are unknown. Based on available evidence, these vitamins do not limit red cell production in anaemic, critically ill patients.

Inappropriately low circulating erythropoietin concentrations

The normal response to anaemia is to increase erythropoietin release from the kidneys. Appropriate values for circulating erythropoietin concentration have been established in otherwise healthy patients with various degrees of anaemia[5] and in various types of medical anaemia. Studies of endogenous erythropoietin concentrations in critically ill patients have consistently shown inappropriately low erythropoietin concentrations for the degree of anaemia.[22 43 63 72 74] An exception to this may be patients during the initial phase of acute renal failure complicating critical illness, during which a transient, marked elevation of circulating erythropoietin concentration occurs.[22] After 48 h, circulating concentrations among critically ill patients with and without acute renal failure are similar, suggesting a response to acute renal tubular injury.[22] The blunted erythropoietin response during critical illness could result from inhibition of the erythropoietin gene by inflammatory cytokines.[18 39]

In summary, critical illness is associated with inappropriately low circulating levels of erythropoietin compared with 'non-inflammatory' causes of anaemia. As a result, red cell precursors may lack appropriate stimulation.

Abnormal red blood cell maturation

Inflammatory cytokines such as tumour necrosis factor α, interleukin-1 and interleukin-6 have been shown to directly inhibit red cell formation.[19 40 64] Elevated concentrations of these cytokines are frequently present in the circulation of

critically ill patients, particularly those with inflammation, sepsis or both. In addition, other circulating factors such as interferon γ have been shown to induce apoptosis of erythroid precursors in experimental studies and could be important during critical illness. These factors, together with a relative deficiency of circulating erythropoietin and decreased iron availability, may explain the poor erythroid response that occurs in response to anaemia. Reticulocyte counts are usually not increased in anaemic critically ill patients unless stimulated by pharmacologic doses of erythropoietin, which also suggests a bone marrow hyporeactivity.[62 72] A recent study, published only in abstract form, in 10 anaemic critically ill patients with sepsis examined bone marrow samples and separated out bone marrow progenitors.[12] These authors reported that erythroid precursors had functional erythropoietin receptors, but found increased apoptosis of this cell line in septic patients compared with controls. Serum from septic patients decreased colony formation of erythroid cells compared with controls, but, interestingly, addition of erythropoietin was reported to partially reverse this effect.

In summary, inflammation inhibits normal erythrogenesis and is a likely contributor to the anaemia of critical illness in a similar way to the mechanisms recently described in chronic inflammatory conditions (Fig. 2).[84] It is currently uncertain how long inappropriate erythrogenesis lasts or what are the main factors that influence recovery among survivors.

Summary of factors contributing to anaemia during critical illness

Blood loss contributes to anaemia but is rarely the only explanation for anaemia. During resuscitation with colloid and crystalloid solutions haemodilution contributes to a decreased haemoglobin concentration, but potentially without altering red cell mass. A major factor resulting in the development and persistence of anaemia is reduced new red blood cell production. This appears to result from a combination of inappropriately low circulating erythropoietin and hypo-reactive bone marrow.

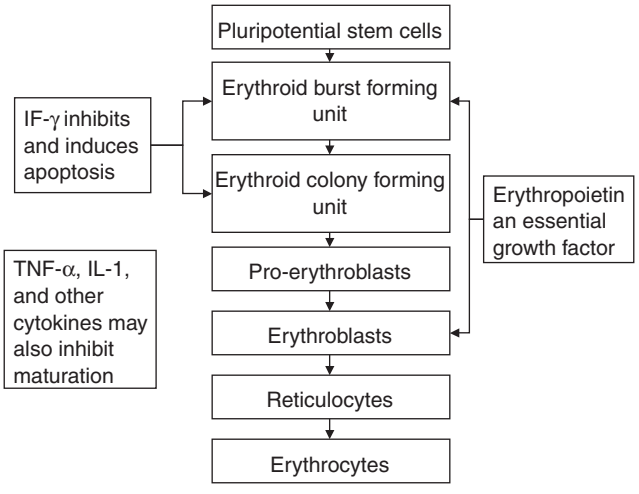

Fig 2 Schematic diagram showing stages in red blood cell maturation from pluripotential stem cells and the sites of action of potential inhibitors during critical illness.

Red cell function during critical illness

For effective oxygen transport to tissues, red cells need to transit capillaries and release oxygen from haemoglobin. It is known that endothelial cell activation occurs during sepsis and inflammation and that disturbances to normal microvascular perfusion occur. Normal red blood cells have a greater diameter (8 μm) than capillaries and therefore need to deform to pass through them. The haemocrit within capillaries is substantially lower than in arterial or venous blood (8%) as a result of the process of plasma skimming. Recent data suggest that changes to red cell deformability and metabolism occur during critical illness, which could influence oxygen transport (Table 6). A detailed review of red blood cell rheology and how this may be altered specifically in sepsis has been published recently.[56]

Red cell deformability

Normal red cells deform through processes that involve the entire cell. The cell surface is rich in sialic acid residues giving the cell surface a negative charge. Sialic acid residues are attached to transmembrane glycophorin molecules. These glycophorin molecules, together with other proteins such as the Band 3 protein, interact with intracellular proteins including actin and spectrin. This complex structure maintains red cell shape and deformability. These processes are energy dependent and are also thought to be influenced by nitric oxide, intracellular calcium and intracellular 2,3 diphosphoglycerate (2,3 DPG) concentrations.[56]

Red cell deformability has been measured using a number of experimental techniques, mostly based on filterability or cell shape changes during application of deforming forces. Decreased red cell deformability has been demonstrated using such techniques during sepsis,[3 4] burns,[6] ischaemia-reperfusion injury,[41] and haemorrhagic[86] and cardiogenic shock.[42] It has been widely postulated that oxidant injury to red cell membranes may account for these changes. In a recent study, Piagnerelli and colleagues[55] studied healthy volunteers, septic and non-septic critically ill patients. The authors measured circulating red cell membrane glyco-

Table 6 Summary of physiological changes that have been described in red blood cells during critical illness

Changes to red cell structure
Decrease in cell membrane sialic acid residues and glycophorin content
More spherical shape
Decrease in cell deformability
Changes to intracellular 2,3 diphosphoglycerate concentration
Decreased concentration during acidosis
Increased concentration during alkalosis

phorin and surface sialic acid content, cell deformability using a flow cytometry technique, and change in cell shape in response to suspension in hypo-osmolar solution. Using these techniques, the authors found that glycophorin and sialic acid content were decreased in critically ill patients, most notably in septic patients. The cells were more spherical in critically ill patients, which correlated with the decrease in sialic acid content. Cells in septic, critically ill patients showed the least changes in response to hypo-osmolar solutions, most likely because they had already undergone an increase in sphericity. It is clear from these findings that critical illness induces changes in circulating red blood cell composition and shape, but it is uncertain whether these have clinically important effects.

Oxygen unloading

The haemoglobin oxygen dissociation curve is altered by pH, Pa_{CO_2} temperature and the red cell concentration of 2,3 DPG. Acidosis, hypercapnia, fever and an increase in intracellular 2,3 DPG concentration all cause right-shift of the haemoglobin oxygen dissociation curve. This results in increased oxygen unloading for a particular Pa_{O_2}, which favours oxygen release to ischaemic or highly metabolically active tissues (Fig. 3).

Two recent studies have investigated red cell 2,3 DPG concentration and the position of the oxygen dissociation curve (assessed by calculating p50 values) in patients in ICUs. Morgan and colleagues[51] found a small decrease in red cell 2,3 DPG and calculated p50 in 20 male ICU patients. There was a weak inverse correlation between 2,3 DPG concentration and the haemoglobin concentration. In a larger series of 111 mixed general ICU patients studied during the first 24 h in the ICU, Saleh and colleagues found no overall difference between critically ill patients and healthy volunteers.[21] The p50 values were similar overall to published normal values, although the range of both 2,3 DPG and p50 values observed was wider for critically ill patients than in healthy individuals. In this study no increase in 2,3 DPG was found in anaemic patients.

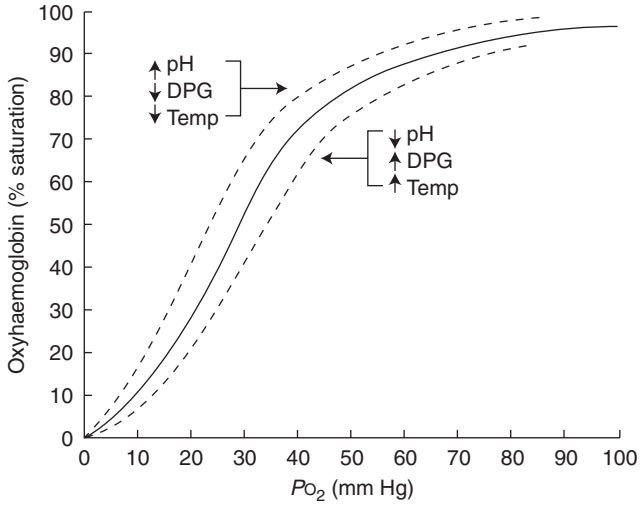

Fig 3 The haemoglobin oxygen dissociation curve and factors that cause left- and right-shift.

Both studies found that 2,3 DPG concentrations were lower in acidaemic patients, and a multivariate regression analysis performed by Saleh and colleagues found that plasma pH was the factor strongly associated independently with red cell 2,3 DPG concentration. The authors speculated that this observation may be explained by a decreased activity of 2,3 DPG generating enzymes within red cells under acidotic conditions, which has been shown *in vitro*.[37] As acidosis favours oxygen unloading, and decreased 2,3 DPG impairs unloading, the true position of the dissociation curve under these conditions is uncertain. It is possible that these effects cancel, as was suggested by the normal p50 calculated for most patients. It is not known whether these changes have clinically relevant adverse effects on oxygen unloading. However, no association between lower 2,3 DPG concentration and ICU mortality was observed.[21]

Management of anaemia

Reduction of red cell loss

There are no studies of strategies to decrease blood sampling rates or volumes to reduce the prevalence or severity of anaemia in critically ill patients or red cell transfusion requirements. However, it has been shown that simple interventions can decrease sampling volumes in intensive care.[53 67] Paradoxically, implementing evidence-based ICU care, such as tight glycaemic control, could increase blood sampling rates.

Transfusion triggers

The established method for managing anaemia in the ICU is allogeneic red cell transfusion. The key question in deciding how to use red cell transfusion in the ICU is identifying the most appropriate transfusion trigger and the target haemoglobin range for each patient. Several concepts are useful in deciding when to treat anaemia using allogeneic red cell transfusion.

Critical haemoglobin concentration

The 'critical haemoglobin concentration' is usually defined as the concentration below which oxygen consumption is supply-dependent assuming normovolaemia is maintained.[49 68] This is unlikely to be a fixed value, but varies between organs and is dependent on the metabolic activity of the tissue and oxygen extraction capabilities. Studies in dogs, pigs and baboons[60 71] have demonstrated this critical Hb concentration in animal models to be around 4 g dl^{-1}.

A classic series of studies of acute normovolaemic haemodilution in healthy volunteers and surgical patients have attempted to define critical haemoglobin concentration in humans.[45 82 83] The first published studies focused on

the cardiovascular and metabolic response to acute normovolaemic haemodilution.[83] Aliquots of blood (450–900 ml) were removed to reduce the individual's haemoglobin concentration to 5 g dl^{-1}. Normovolaemia was maintained by infusing 5% human albumin, autologous plasma or both using central venous pressure guidance. At a haemoglobin concentration of 5 g dl^{-1}, heart rate, stroke volume and cardiac output were increased, and oxygen delivery was reduced. There was no evidence of inadequate oxygenation using global indices and the calculated oxygen consumption increased slightly from a mean of 3.07 to 3.42 ml kg^{-1} min^{-1}. Plasma lactate concentration did not change. Subsequent studies did find some evidence suggestive of organ-specific hypoxia. Continuous ECG ST-segment analysis revealed that 3 of 55 healthy subjects developed transient, reversible ST-segment depression at haemoglobin concentrations of 5–7 g dl^{-1},[45] although the subjects were asymptomatic and in two the changes may have been related to high heart rates. A later study focusing on cognitive function during acute normovolaemic haemodilution also found that acute reduction of the haemoglobin concentration to $\leqslant$6 g dl^{-1} produced subtle, reversible increases in reaction time and impaired immediate and delayed memory, which were not detectable at a haemoglobin concentration of 7 g dl^{-1}.[82]

There is considerable clinical evidence from Jehovah's Witness patients that suggests that acute anaemia is well tolerated under many circumstances. Many reports of clinical experiences with Jehovah's Witnesses suggest that mortality is only increased at very low haemoglobin concentrations (<5 g dl^{-1}) and that survival is possible at extremely low oxygen-carrying capacity (haemoglobin concentration as low as 1.4 g dl^{-1}).[9 33]

In summary, these data suggest that the critical haemoglobin concentration below which true anaemic hypoxia occurs is <4–5 g dl^{-1} in most healthy individuals assuming hypovolaemia is not present. This value may clearly be altered by patient factors related to chronic and acute disease in intensive care.

Acceptable haemoglobin concentration during critical illness

An acceptable haemoglobin concentration is the degree of anaemia that is the best balance between the risks of red cell transfusion and the risks of low haemoglobin concentration. There are two broad groups of evidence concerning the acceptable haemoglobin concentration for critically ill patients. The first is the TRICC trial[29] and other large cohort studies that have examined transfusion practice in critically ill groups of patients. The second group includes studies that examined the effect of transfusions on indices of tissue hypoxia in critically ill patients. These studies have been considered in detail in a recent review[49] and are summarized briefly here.

The TRICC trial and other recent large epidemiological studies: This study showed that a restrictive transfusion strategy is at least as effective as and possibly superior to a liberal transfusion strategy in critically ill patients and provides compelling evidence that a haemoglobin concentration in the 7–9 g dl^{-1} range, using a trigger of 7 g dl^{-1}, is well tolerated by most critically ill patients and has no overall adverse effect on mortality.[29] Among patients aged <55 yr, and among the subgroup with admission APACHE II score <20, there was a statistically significantly better 30 day mortality among patients in the restrictive group. The study was not powered for subgroup analyses, but when these were carried out there was no statistically or clinically important difference in ventilation times[26] or in mortality for patients with cardiovascular disease.[32] Outcomes were also similar for the 203 patients admitted with trauma.[48]

Effect of blood transfusions on indices of tissue hypoxia during critical illness: Most epidemiological studies in intensive care have primarily classified reasons for red blood cell transfusion into haemorrhage or various other categories. The other categories have usually indicated the intention of the clinician to increase the haemoglobin concentration in the absence of clinical bleeding. Categories include descriptive terms such as 'diminished/reduced physiological reserve', 'altered tissue perfusion', 'tissue hypoxia' and 'coronary disease'.[11 15 24 73] These all indicate a clinical concern that the patient either has or is at risk for tissue hypoxia or organ-specific ischaemia. In these studies such indications usually account for 40–80% of the transfusion episodes.[11 15 24 58 73]

Many studies have assessed the effect of blood transfusions on indices of tissue hypoxia during critical illness. Interpretation of these studies requires consideration of factors that include (i) the baseline haemoglobin concentration, (ii) the index of tissue hypoxia studied and the change considered significant, (iii) the method used to measure the index of tissue hypoxia, its accuracy and confounding factors (this is particularly true for global oxygen consumption measurement and for gastric tonometry indices) and (iv) the nature of the blood product used (age of red cells and leucodepletion status).

The published studies have been reviewed recently.[35 47 49] Commonly used indices of tissue hypoxaemia on a 'whole body' level are the oxygen consumption (VO_2), plasma or whole blood lactate concentration, mixed venous oxygen saturation (Sv_{O_2}) and mixed venous oxygen partial pressure (Pv_{O_2}). Regional indices include gastric tonometry derived indices (pHi and 'P_{CO_2}' 'gap'). For the most methodologically robust studies, there is little evidence that red blood cell transfusion consistently improves clinical indices of tissue hypoxia in the critically ill assuming baseline haemoglobin concentrations of >8 g dl^{-1}. Even transfusion with very fresh red cells (storage age $\leqslant$5 days) did not improve clinical indices of tissue hypoxia in euvolaemic critically ill patients.[78] These data show that although clinicians frequently transfuse because they are concerned about inadequate oxygen delivery to tissues, this does not usually

result in measurable improvements using currently available indices of tissue hypoxia. These data support the TRICC study findings that a haemoglobin of 7–9 g dl^{-1} is safe for most critically ill patients.

Possible exceptions to the restrictive strategy used in the TRICC trial

The patient with chronic ischaemic heart disease

The only published subgroup analysis for the TRICC trial in which the survival lines were reversed in favour of a liberal strategy, but with non-significant outcome difference, was for patients with ischaemic heart disease at study entry.[32] The evidence for the safest transfusion trigger for patients with ischaemic heart disease is inadequate and of particular concern to many clinicians.[80] This subject has been recently reviewed in detail.[33 79] Retrospective cohort studies have found associations between anaemia and excess mortality among patients with non-acute coronary disease compared with patients without coronary disease at haemoglobin concentrations <9–10 g dl^{-1}.[10 31] However, in the TRICC trial the numbers of adverse cardiac events was actually fewer in the restrictive group.[29] Specifically, the number of myocardial infarctions was smaller among the patients managed with restrictive transfusion triggers, who were more anaemic during their critical illness.

Most experts suggest that critically ill patients with chronic ischaemic heart disease can be managed with a transfusion trigger of 7–8 g dl^{-1}, and a target haemoglobin of 7–9 g dl^{-1}, unless there is evidence of myocardial ischaemia.

The patient with an acute coronary syndrome

The evidence is also contradictory for patients with acute coronary syndromes. Wu and colleagues[85] retrospectively examined data for 78 974 patients aged >65 years admitted with an acute myocardial infarction. They categorized patients by their admission haematocrit value and observed an association between anaemia at admission and higher 30 day mortality. Of the cohort, 4.7% of patients received a blood transfusion. Patients had a lower 30 day mortality if their admission haematocrit value was <33% and they had received a transfusion. More recently, Rao and colleagues[59] examined detailed prospectively collected data for 24 112 patients who were enrolled in three international randomized trials in patients with acute coronary syndromes. Of these patients 2401 (10%) received at least one transfusion during hospitalization. Using complex statistical approaches, which included adjustments for co-morbidities and time from admission, the authors found an increased risk for 30 day mortality among patients who received a transfusion. When the authors explored the importance of the lowest haemoglobin value in the patients, there was no demonstrable benefit from transfusion on mortality probability in their statistical model at haematocrit values of 20–25% and at values above 30% transfusion was associated with higher probability for death. These data are confusing and illustrate the limitations of cohort studies for addressing questions concerning anaemia, blood transfusions and outcomes in clinical conditions for which many factors influence mortality.

There is an urgent need for prospective randomized trials of transfusion strategy for patents with ischaemic heart disease, particularly as up to 28% of general intensive care populations may have cardiac disease at admission.[80]

Most experts appraising the available evidence suggest that transfusion (of single red cell units) should be considered at haemoglobin values of <8 g dl^{-1} with the aim of achieving values of 9 g dl^{-1} for most patients with severe or acute ischaemic heart disease.[28]

Early severe sepsis

Goal-directed therapy during early severe sepsis improved mortality in a well-performed single centre randomized trial.[61] The intervention algorithm used central venous oxygen saturation <70% as a trigger for interventions to increase global oxygen delivery. Part of this algorithm was blood transfusion to maintain a haematocrit ⩾30% (haemoglobin ⩾10 g dl^{-1}), but it is unclear how important this component was to improving mortality. The patients in the goal-directed therapy group received significantly more blood transfusions and had a higher haemoglobin concentration. Until further studies are performed, a target haemoglobin concentration of 10 g dl^{-1} (haematocrit 30%) should be considered for patients during the early phase of severe sepsis if the central venous oxygen saturation is <70%. It is unclear how long a higher transfusion trigger should be used for these patients. The treatment algorithm was continued for 6 h in the randomized trial.

Risks from allogeneic blood transfusion

It is clear from the above description that for most clinical situations the transfusion trigger for an individual patient relies on clinical judgement between values of 7 and 9 g dl^{-1}. The decision to transfuse should therefore be made with the risk profile, and benefits, in mind. Current risks from red cell transfusion have been described in a recent review.[47] The importance of leucodepletion is considered here because it has particular relevance to critical illness and the interpretation of the TRICC and recent epidemiological studies.

During the TRICC trial, red blood cells were not routinely leucodepleted in Canada. In most of Europe, Canada and parts of the US all red cells are now leucodepleted prior to storage. Most published studies of anaemia in critically ill patients used exclusively or partly non-leucodepleted blood products, which could have had an independent adverse effect on outcomes in the study. Meta-analyses of published studies of leucodepletion have conflicting results and it remains uncertain what effect this has on mortality or other relevant outcomes such as infection.[69 70] A recent

before and after study performed in Canada around the introduction of universal leucodepletion found a small decrease in hospital mortality (<1%) among transfused surgical and intensive care patients, which just reached statistical significance and equated to a number needed to treat of about 100.[27] There was no reduction in serious infections, although the incidence of fever decreased, as would be expected after leucoreduction. This uncertainty relating to the clinical importance of transfused leucocytes in blood means that it is currently unknown whether the results of published studies would be different with leucodepleted red cells.

Erythropoietin therapy

The poor endogenous erythropoietin response to anaemia found in critically ill patients makes exogenous administration a potential treatment. In critically ill patients with multiple organ failure, recombinant human erythropoietin therapy (rHuEPO) can stimulate erythropoiesis. A prospective trial randomized 160 critically ill patients to receive rHuEPO or placebo.[17] rHuEPO was given in a dose of 300 $\mu g\ kg^{-1}$ daily for 5 days and then on alternate days for a minimum of 2 weeks, or until ICU discharge, and a maximum of 6 weeks. The rHuEPO group was transfused with a total of 166 units of red cells compared with 305 units transfused to the placebo group. Despite receiving fewer red cell transfusions, patients in the rHuEPO group had a significantly greater increase in haematocrit. The same investigators published a larger multicentre trial in which 1302 critically ill patients, who remained in the ICU for at least 2 days, were randomized to receive rHuEPO or placebo.[16] rHuEPO was given in a dose of 40 000 units once a week for up to 4 weeks, together with oral iron therapy. The percentage of patients who received any red cell transfusion during the 28 day study period was significantly lower in the rHuEPO group than in the placebo group (50.5% *vs* 60.4%, $P<0.001$). This was despite similar transfusion triggers for the two groups (mean haemoglobin transfusion threshold 8.5 $g\ dl^{-1}$ in each group). Overall, the erythropoietin group received 19% less red cell units during the 28 day study period and the red cell transfusion rate per day alive was lower in the intervention group [ratio between the groups 0.81 (95% CI 0.79–0.83)]. Despite this the increase in haemoglobin concentration from baseline was greater in the erythropoietin group (1.32 *vs* 0.94 $g\ dl^{-1}$) over the study period. Mortality was similar between the groups (14% *vs* 15%). The reduction in the total number of red cell units transfused and the increase in haemoglobin concentration were more modest in this study than the earlier trial. These differences may be accounted for by the shorter follow-up period and the smaller total dose of rHuEPO used in the second trial.

There is little doubt that rHuEPO is effective as a blood-sparing therapy in critically ill patients, but it is an expensive therapy and a key question is whether it is cost effective. Central to this evaluation is the balance between the value of avoiding transfusion and the possible risks of receiving erythropoietin, neither of which are fully understood. In order to assess this balance, high quality data concerning the attributable risks of both blood transfusions and erythropoietin therapy are needed in critically ill patients. Other than viral infection and transfusion errors, most data concerning transfusion risks, such as pneumonia or other infection, were generated from cohort studies of patients receiving non-leucodepleted blood and could be misleading. Two published evaluations of erythropoietin cost-effectiveness in the critically ill have contradictory conclusions. MacLaren and Sullivan[46] concluded that it was cost effective against accepted parameters, but only if assumptions that allogeneic blood transfusions cause bacterial infections (common events in this population) were true. In contrast, Shermock and colleagues[66] mainly considered viral infection, transfusion errors and Transfusion Associated Lung Injury (rare events in this population) and found no evidence of cost-effectiveness.

Further work is needed to establish which patients are most suitable for rHuEPO therapy, at what point in their critical illness, and for how long. Based on the epidemiology of ICU anaemia discussed earlier, the haemoglobin concentration at ICU admission, or the development of renal failure and thrombocytopenia, could potentially be used as indications for rHuEPO. Further studies are needed to assess the impact of rHuEPO in specific patient subgroups such as these. At present rHuEPO is not licensed for use in critical illness.

Conclusions and unanswered questions

Anaemia is one of the commonest complications of critical illness. It results from many factors including haemodilution, blood sampling, haemorrhage, bone marrow suppression and an inadequate erythropoietin response. Circulating red blood cells undergo changes in structure and function during critical illness that alter their shape, deformability and intracellular 2,3 DPG concentrations. Despite these factors anaemia is well tolerated by critically ill patients and a haemoglobin of 7–9 $g\ dl^{-1}$ does not adversely affect outcome in comparison with maintaining a value >10 $g\ dl^{-1}$. The effectiveness of red blood cell transfusions in patients with a haemoglobin concentration >7–8 $g\ dl^{-1}$ has not been proved either for outcome or for improving tissue hypoxia. Transfusing stored allogeneic red cells could be harmful under some circumstances. The reasons for this are not clear, but more work is needed to determine whether the red cell storage lesion, the storage age of red cells or both are clinically important.[50 75]

It is uncertain whether specific subgroups of critically ill patients benefit from higher haemoglobin concentrations. Specifically, during early sepsis, a targeted high oxygen delivery improves outcome, but it is unclear how important the haemoglobin concentration, red cell transfusions or

both are as components of this treatment or how long more liberal use of blood transfusions is necessary.[61] The optimum haemoglobin concentration for patients with ischaemic heart disease is uncertain and the conflicting data in acute coronary syndromes illustrate the urgent need for an adequately powered randomized trial. There are very few data for patients with chronic respiratory disease, cerebrovascular disease or neurotrauma in whom anaemia may be tolerated less well.

After the acute phase of critical illness, anaemia is common and may persist for many weeks in some patients. It is not known whether anaemia delays recovery during this period or whether interventions to treat it improve patient outcomes such as fatigue, functional status and perceived quality of life. There is an urgent need for more randomized trials of the management of anaemia during various types of critical illness. These studies are increasingly pertinent as the cost of producing blood products escalates and the potential donor pool is declining.

References

1 Andrews NC. Anemia of inflammation: the cytokine-hepcidin link. *J Clin Invest* 2004; **113**: 1251–3

2 Andrews T, Waterman H, Hillier V. Blood gas analysis: a study of blood loss in intensive care. *J Adv Nurs* 1999; **30**: 851–7

3 Baskurt OK, Gelmont D, Meiselman HJ. Red blood cell deformability in sepsis. *Am J Respir Crit Care Med* 1998; **157**: 421–7

4 Baskurt OK, Meiselman HJ. Blood rheology and hemodynamics. *Semin Thromb Hemost* 2003; **29**: 435–50

5 Beguin Y, Clemons GK, Pootrakul P, Fillet G. Quantitative assessment of erythropoiesis and functional classification of anemia based on measurements of serum transferrin receptor and erythropoietin. *Blood* 1993; **81**: 1067–76

6 Bekyarova G, Yankova T, Kozarev I, Yankov D. Reduced erythrocyte deformability related to activated lipid peroxidation during the early postburn period. *Burns* 1996; **22**: 291–4

7 Bellamy MC, Gedney JA. Unrecognised iron deficiency in critical illness. *Lancet* 1998; **352**: 1903

8 Biesma DH, Van de Wiel A, Beguin Y, Kraaijenhagen RJ, Marx JJ. Post-operative erythropoiesis is limited by the inflammatory effect of surgery on iron metabolism. *Eur J Clin Invest* 1995; **25**: 383–9

9 Brimacombe J, Skippen P, Talbutt P. Acute anaemia to a haemoglobin of 14 $g.l^{-1}$ with survival. *Anaesth Intensive Care* 1991; **19**: 581–3

10 Carson JL, Duff A, Poses RM, *et al*. Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. *Lancet* 1996; **348**: 1055–60

11 Chohan SS, McArdle F, McClelland DB, Mackenzie SJ, Walsh TS. Red cell transfusion practice following the transfusion requirements in critical care (TRICC) study: prospective observational cohort study in a large UK intensive care unit. *Vox Sang* 2003; **84**: 211–18

12 Claessens Y, Chiche J, Pene F, Dhainaut J, Mira J, Cariou A. Erythropoietin reverses septic shock-induced apoptosis of erythroid progenitors. *Intensive Care Med* 2003; S66

13 Cook D, Heyland D, Griffith L, Cook R, Marshall J, Pagliarello J. Risk factors for clinically important upper gastrointestinal bleeding in patients requiring mechanical ventilation. Canadian Critical Care Trials Group. *Crit Care Med* 1999; **27**: 2812–17

14 Cook DJ, Griffith LE, Walter SD, *et al*. The attributable mortality and length of intensive care unit stay of clinically important gastrointestinal bleeding in critically ill patients. *Crit Care* 2001; **5**: 368–75

15 Corwin HL, Gettinger A, Pearl RG, *et al*. The CRIT Study: Anemia and blood transfusion in the critically ill—current clinical practice in the United States. *Crit Care Med* 2004; **32**: 39–52

16 Corwin HL, Gettinger A, Pearl RG, *et al*. Efficacy of recombinant human erythropoietin in critically ill patients: a randomized controlled trial. *JAMA* 2002; **288**: 2827–35

17 Corwin HL, Gettinger A, Rodriguez RM, *et al*. Efficacy of recombinant human erythropoietin in the critically ill patient: a randomized, double-blind, placebo-controlled trial. *Crit Care Med* 1999; **27**: 2346–50

18 Corwin HL, Krantz SB. Anemia of the critically ill: 'acute' anemia of chronic disease. *Crit Care Med* 2000; **28**: 3098–9

19 Danielson B. R-HuEPO hyporesponsiveness—who and why? *Nephrol Dial Transplant* 1995; **10** (Suppl 2): 69–73

20 Eckardt KU. Anemia in critical illness. *Wien Klin Wochenschr* 2001; **113**: 84–9

21 El Din S Ibrahim, McLellan SA, Walsh TS. Red blood cell 2,3-diphosphoglycerate concentration and in vivo P50 during early critical illness. *Crit Care Med* 2005; **33**: 2247–52

22 Elliot JM, Virankabutra T, Jones S, *et al*. Erythropoietin mimics the acute phase response in critical illness. *Crit Care* 2003; **7**: R35–40

23 Emmanuel JE, McClelland B, Page R, editors. *The Clinical Use of Blood in Medicine, Obstetrics, Paediatrics, Surgery Anaesthesia, Trauma & Burns*. World Health Organisation, 1997; 337.

24 French CJ, Bellomo R, Finfer SR, Lipman J, Chapman M, Boyce NW. Appropriateness of red blood cell transfusion in Australasian intensive care practice. *Med J Aust* 2002; **177**: 548–51

25 Goodnough LT, Skikne B, Brugnara C. Erythropoietin, iron, and erythropoiesis. *Blood* 2000; **96**: 823–33

26 Hebert PC, Blajchman MA, Cook DJ, *et al*. Do blood transfusions improve outcomes related to mechanical ventilation? *Chest* 2001; **119**: 1850–7

27 Hebert PC, Fergusson D, Blajchman, *et al*. Clinical outcomes following institution of the Canadian universal leukoreduction program for red blood cell transfusions. *JAMA* 2003; **289**: 1941–9

28 Hebert PC, Fergusson DA. Do transfusions get to the heart of the matter? *JAMA* 2004; **292**: 1610–12

29 Hebert PC, Wells G, Blajchman MA, *et al*. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med* 1999; **340**: 409–17

30 Hebert PC, Wells G, Martin C, *et al*. Canadian survey of transfusion practices in critically ill patients. Transfusion Requirements in Critical Care Investigators and the Canadian Critical Care Trials Group. *Crit Care Med* 1998; **26**: 482–7

31 Hebert PC, Wells G, Tweeddale, *et al*. Does transfusion practice affect mortality in critically ill patients? Transfusion Requirements in Critical Care (TRICC) Investigators and the Canadian Critical Care Trials Group. *Am J Respir Crit Care Med* 1997; **155**: 1618–23

32 Hebert PC, Yetisir E, Martin C, *et al*. Is a low transfusion threshold safe in critically ill patients with cardiovascular diseases? *Crit Care Med* 2001; **29**: 227–34

33 Hebert PC. The anemic patient in the intensive care unit: how much does the heart tolerate? *Curr Opin Crit Care* 2000; **6**: 372–80

34 Henry ML, Garner WL, Fabri PJ. Iatrogenic anemia. *Am J Surg* 1986; **151**: 362–3

35 Ho J, Sibbald WJ, Chin-Yee IH. Effects of storage on efficacy of red cell transfusion: when is it not safe? *Crit Care Med* 2003; **31**: S687–97

36 Hobisch-Hagen P, Wiedermann F, Mayr A, *et al*. Blunted erythropoietic response to anemia in multiply traumatized patients. *Crit Care Med* 2001; **29**: 743–7

37 Hogman CF, Knutson F, Loof H, Payrat JM. Improved maintenance of 2,3 DPG and ATP in RBCs stored in a modified additive solution. *Transfusion* 2002; **42**: 824–9

38 Hutchinson C, Walsh TS, Black J, Ross JA. Soluble transferrin receptor assay as a marker of anaemia in critically ill patients. *Br J Anaesth* 2003; **90**: 544P

39 Jelkmann W, Pagel H, Wolff M, Fandrey J. Monokines inhibiting erythropoietin production in human hepatoma cultures and in isolated perfused rat kidneys. *Life Sci* 1992; **50**: 301–8

40 Jongen-Lavrencic M, Peeters HR, Rozemuller H, *et al*. IL-6-induced anaemia in rats: possible pathogenetic implications for anemia observed in chronic inflammations. *Clin Exp Immunol* 1996; **103**: 328–34

41 Kayar E, Mat F, Meiselman HJ, Baskurt OK. Red blood cell rheological alterations in a rat model of ischemia-reperfusion injury. *Biorheology* 2001; **38**: 405–14

42 Kirschenbaum LA, Astiz ME, Rackow EC, Saha DC, Lin R. Microvascular response in patients with cardiogenic shock. *Crit Care Med* 2000; **28**: 1290–4

43 Krafte-Jacobs B, Levetown ML, Bray GL, Ruttimann UE, Pollack MM. Erythropoietin response to critical illness. *Crit Care Med* 1994; **22**: 821–6

44 Lang KS, Duranton C, Poehlmann H, *et al*. Cation channels trigger apoptotic death of erythrocytes. *Cell Death Differ* 2003; **10**: 249–56

45 Leung JM, Weiskopf RB, Feiner J, *et al*. Electrocardiographic ST-segment changes during acute, severe isovolemic hemodilution in humans. *Anesthesiology* 2000; **93**: 1004–10

46 MacLaren R, Sullivan PW. Cost-effectiveness of recombinant human erythropoietin for reducing red blood cells transfusions in critically ill patients. *Value Health* 2005; **8**: 105–16

47 Madjdpour C, Spahn DR. Allogeneic red blood cell transfusions: efficacy, risks, alternatives and indications. *Br J Anaesth* 2005; **95**: 33–42

48 McIntyre L, Hebert PC, Wells G, *et al*. Is a restrictive transfusion strategy safe for resuscitated and critically ill trauma patients? *J Trauma* 2004; **57**: 563–8

49 McLellan SA, McClelland DB, Walsh TS. Anaemia and red blood cell transfusion in the critically ill patient. *Blood Rev* 2003; **17**: 195–208

50 McLellan SA, Walsh TS, McClellan DB. Should we demand fresh red blood cells for perioperative and critically ill patients? *Br J Anaesth* 2002; **89**: 537–40

51 Morgan TJ, Koch D, Morris D, Clague A, Purdie DM. Reduced red cell 2,3-diphosphoglycerate concentrations in critical illness without decreased *in vivo* P50. *Anaesth Intensive Care* 2001; **29**: 479–83

52 Nguyen BV, Bota DP, Melot C, Vincent JL. Time course of hemoglobin concentrations in nonbleeding intensive care unit patients. *Crit Care Med* 2003; **31**: 406–10

53 O'Hare D, Chilvers RJ. Arterial blood sampling practices in intensive care units in England and Wales. *Anaesthesia* 2001; **56**: 568–71

54 Patteril MV, Davey-Quinn AP, Gedney JA, Murdoch SD, Bellamy MC. Functional iron deficiency, infection and systemic inflammatory response syndrome in critical illness. *Anaesth Intensive Care* 2001; **29**: 473–8

55 Piagnerelli M, Boudjeltia KZ, Brohee D, *et al*. Alterations of red blood cell shape and sialic acid membrane content in septic patients. *Crit Care Med* 2003; **31**: 2156–62

56 Piagnerelli M, Boudjeltia KZ, Vanhaeverbeek M, Vincent JL. Red blood cell rheology in sepsis. *Intensive Care Med* 2003; **29**: 1052–61

57 Pimentel M, Roberts DE, Bernstein CN, Hoppensack M, Duerksen DR. Clinically significant gastrointestinal bleeding in critically ill patients in an era of prophylaxis. *Am J Gastroenterol* 2000; **95**: 2801–6

58 Rao MP, Boralessa H, Morgan C, *et al*. Blood component use in critically ill patients. *Anaesthesia* 2002; **57**: 530–4

59 Rao SV, Jollis JG, Harrington RA, *et al*. Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. *JAMA* 2004; **292**: 1555–62

60 Rasanen J. Supply-dependent oxygen consumption and mixed venous oxyhemoglobin saturation during isovolemic hemodilution in pigs. *Chest* 1992; **101**: 1121–4

61 Rivers E, Nguyen B, Havstad S, *et al*. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; **345**: 1368–77

62 Rodriguez RM, Corwin HL, Gettinger A, Corwin MJ, Gubler D, Pearl RG. Nutritional deficiencies and blunted erythropoietin response as causes of the anemia of critical illness. *J Crit Care* 2001; **16**: 36–41

63 Rogiers P, Zhang H, Leeman M, *et al*. Erythropoietin response is blunted in critically ill patients. *Intensive Care Med* 1997; **23**: 159–62

64 Scharte M, Fink MP. Red blood cell physiology in critical illness. *Crit Care Med* 2003; **31**: S651–7

65 Shapiro MJ, Gettinger A, Corwin HL, *et al*. Anemia and blood transfusion in trauma patients admitted to the intensive care unit. *J Trauma* 2003; **55**: 269–73

66 Shermock KM, Horn E, Lipsett PA, Pronovost PJ, Dorman T. Number needed to treat and cost of recombinant human erythropoietin to avoid one transfusion-related adverse event in critically ill patients. *Crit Care Med* 2005; **33**: 497–503

67 Smoller BR, Kruskall MS, Horowitz GL. Reducing adult phlebotomy blood loss with the use of pediatric-sized blood collection tubes. *Am J Clin Pathol* 1989; **91**: 701–3

68 Spahn DR, Casutt M. Eliminating blood transfusions: new aspects and perspectives. *Anesthesiology* 2000; **93**: 242–55

69 Vamvakas EC. Meta-analysis of randomized controlled trials comparing the risk of postoperative infection between recipients of allogeneic and autologous blood transfusion. *Vox Sang* 2002; **83**: 339–46

70 Vamvakas EC. WBC-containing allogeneic blood transfusion and mortality: a meta-analysis of randomized controlled trials. *Transfusion* 2003; **43**: 963–73

71 van der Linden P, Schmartz D, De Groote F, *et al*. Critical haemoglobin concentration in anaesthetized dogs: comparison of two plasma substitutes. *Br J Anaesth* 1998; **81**: 556–62

72 van Iperen CE, Gaillard CA, Kraaijenhagen RJ, Braam BG, Marx JJ, van de Wiel A. Response of erythropoiesis and iron metabolism to recombinant human erythropoietin in intensive care unit patients. *Crit Care Med* 2000; **28**: 2773–8

73 Vincent JL, Baron JF, Reinhart K, *et al*. Anemia and blood transfusion in critically ill patients. *JAMA* 2002; **288**: 1499–507

74 von Ahsen N, Muller C, Serke S, Frei U, Eckardt KU. Important role of nondiagnostic blood loss and blunted erythropoietic response in the anemia of medical intensive care patients. *Crit Care Med* 1999; **27**: 2630–9

75 Walsh TS. Is stored blood good enough for critically ill patients?. *Crit Care Med* 2005; **33**: 238–9

76 Walsh TS, Garrioch M, Maciver C, *et al*. Red cell requirements for intensive care units adhering to evidence-based transfusion guidelines. *Transfusion* 2004; **44**: 1405–11

77 Walsh TS, Lee RJ, Maciver C, *et al*. Anaemia during and at discharge from intensive care: the impact of restrictive blood transfusion practice. *Intensive Care Med* 2005; **32**: 100–9

78 Walsh TS, McArdle F, McLellan SA, *et al*. Does the storage time of transfused red blood cells influence regional or global indexes of tissue oxygenation in anemic critically ill patients? *Crit Care Med* 2004; **32**: 364–71

79 Walsh TS, McClelland DB. When should we transfuse critically ill and perioperative patients with known coronary artery disease? *Br J Anaesth* 2003; **90**: 719–22

80 Walsh TS, McClelland DB, Lee RJ, *et al*. Prevalence of ischaemic heart disease at admission to intensive care and its influence on red cell transfusion thresholds: multicentre Scottish Study. *Br J Anaesth* 2005; **94**: 445–52

81 Walsh TS, Saleh E, Lee RJ, McClellan DBL. The prevalence and characteristics of anaemia at discharge home after intensive care. *Intensive Care Med* 2006; in press

82 Weiskopf RB, Kramer JH, Viele M, *et al*. Acute severe isovolemic anemia impairs cognitive function and memory in humans. *Anesthesiology* 2000; **92**: 1646–52

83 Weiskopf RB, Viele MK, Feiner J, *et al*. Human cardiovascular and metabolic response to acute, severe isovolemic anemia. *JAMA* 1998; **279**: 217–21

84 Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med* 2005; **352**: 1011–23

85 Wu WC, Rathore SS, Wang Y, Radford MJ, Krumholz HM. Blood transfusion in elderly patients with acute myocardial infarction. *N Engl J Med* 2001; **345**: 1230–6

86 Zaets SB, Berezina TL, Morgan C, *et al*. Effect of trauma-hemorrhagic shock on red blood cell deformability and shape. *Shock* 2003; **19**: 268–73