CLINICAL REVIEW

Managing anaemia in critically ill adults

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Cite this as: *BMJ* 2010;341:c4408
doi: 10.1136/bmj.c4408

Anaemia (haemoglobin <120 g/l for women, and <130 g/l for men) is common in acutely unwell patients. Maintaining sufficient oxygen transport to the tissues is fundamental to survival and recovery from acute illness, and in the United Kingdom 8-10% of the blood supply is used to treat patients in intensive care.[1] Red blood cells transport more than 97% of the oxygen content of blood—about 200 ml/l—and anaemia greatly reduces oxygen delivery, especially if patients also have cardiovascular and respiratory compromise.[2]

Transfusion of donor (allogeneic) red blood cells is the standard method for rapidly correcting anaemia in acutely unwell patients, but the risk-benefit balance of this intervention is a subject of continuing debate, controversy, and concern.[3] We highlight uncertainties in the management of anaemia in critically ill patients, especially in relation to the use of red cells, and summarise current evidence from observational studies and randomised trials. We focus on the management of anaemia in critically ill patients without active bleeding, such as those who are in adult medical and surgical intensive care units, high dependency units, and other acute units. We do not discuss the management of patients with major haemorrhage, for which recent evidence is available elsewhere.[w1-w3]

How common is anaemia in patients with critical illness?

Observational studies have shown that anaemia affects 60-80% of patients cared for in intensive care units, and 50-70% develop moderate to severe anaemia (haemoglobin concentration <90 g/l) during their stay.[4 5] Most patients have a normochromic, normocytic anaemia with high ferritin concentrations and low serum iron, transferrin, and transferrin saturation.[5 6] Only 10-15% of patients have a history of chronic anaemia before admission to intensive care, which highlights the importance of acute factors in its development.[7 8]

SUMMARY POINTS

Acute anaemia is common in critically ill patients

Several factors, including blood sampling and reduced red cell production associated with systemic inflammation, can contribute to anaemia

The risk-benefit profile for red cell transfusions to treat anaemia in non-bleeding critically ill adults is uncertain, but they may contribute to adverse patient outcomes in some situations

Best evidence suggests that using single unit red cell transfusions when haemoglobin is close to 70 g/l and aiming for a haemoglobin of 70-90 g/l is not harmful in most patients

Aiming for a haemoglobin nearer to 90-100 g/l might be better for patients with acute cardiac disease and the early stages of severe sepsis

SOURCES AND SELECTION CRITERIA

We searched randomised controlled trials and systematic reviews identified by the Systematic Reviews Initiative, NHS Blood and Transplant, Oxford (updated December 2009), which includes the Cochrane Library, Medline, Embase, and the SRI Systematic Review Handsearch Database. We supplemented this with searches of Medline and Embase using the terms "intensive care" or "critical care" and "blood transfusion" or "anaemia". We also reviewed recently published clinical guidelines and searched for current transfusion related trials on clinicaltrials.gov and the ISRCTN register.

Why do critically ill patients become anaemic?

Unless modified by blood transfusions, haemoglobin values typically decrease by about 5 g/l/day during critical illness,[9] and 20-50% of critically ill patients receive transfusions.[4 5] Box 1 lists the factors that contribute to anaemia during critical illness. In individual patients several factors usually contribute in varying degrees. When intravenous fluids are given plasma volume expands and the haemoglobin concentration decreases without a major change in red cell mass. This is important to consider when resuscitating a patient (fig 1). Blood sampling typically results in the loss of 30-60 ml

Box 1 | Factors contributing to anaemia during critical illness

Pre-existing chronic anaemia (about 10-15% of patients)
Renal impairment, liver disease
Pre-existing medical conditions
Recent surgery
Myelodysplasia

Acquired anaemia
Haemodilution
Blood loss
Blood sampling
Haemorrhage
Loss from extracorporeal circuits, such as haemofiltration circuits
Reduced red cell survival
Haemolysis
Damage by inflammatory processes
Reduced red cell production
Abnormal iron metabolism
Nutritional deficiencies
Inappropriately low erythropoietin production
Bone marrow hyporeactivity

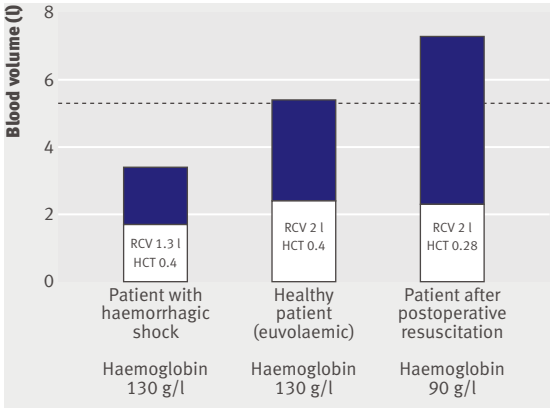

Fig 1 | The relation between red cell volume (RCV), plasma volume (PV), haemoglobin concentration, and haematocrit (HCT) during haemorrhage, healthy euvolaemia, and fluid resuscitation with clear fluids indicating the important effect of changes to plasma volume on the haemoglobin concentration

of blood each day,[7] and loss from artificial circuits, such as haemofiltration circuits, or occult loss may increase daily losses.[10] Several high quality observational studies have shown impaired erythropoiesis during critical illness. The healthy response to acute blood loss, the reticulocyte response, is usually absent,[11] probably because of the failure of the kidneys to increase erythropoietin production and a hyporeactive bone marrow.[10 w4 w5] These biochemical characteristics are almost identical to the anaemia of chronic disease, which suggests that they result from systemic inflammation.[5 11 12] Absolute iron deficiency is rare, but many patients have a functional iron deficiency from redistribution of iron into macrophages and reticuloendothelial cells, which may limit availability of iron for red cell production. Inflammation makes iron studies difficult to interpret. Reduced red cell survival is likely in critically ill patients, especially those with sepsis, because red cells become less deformable as a result of oxidative damage and cell membrane changes.[13]

Table 1 | Risks associated with blood transfusions

Risk	Mechanism and prevalence[2 3]
Transfusion process errors resulting in the wrong blood being transfused	Errors in the process and administration of transfusion are still the most common cases reported to the UK national haemovigilance scheme (www.shotuk.org)
Transfusion reactions	Acute transfusion reactions may occur because of haemolytic reactions or anaphylaxis
Transfusion transmitted infections (eg, hepatitis B, hepatitis C, HIV, variant Creutzfeldt-Jakob disease (vCJD)	Transfusion transmitted bacterial infections are more common than viral risks, which are now very low in developed countries. The exact risk of vCJD transmission is unclear
Transfusion associated circulatory overload	Standardised reporting has been inconsistent and the true prevalence is unknown
Transfusion associated lung injury	Acute lung injury related to transfusion still occurs, although many transfusion services have taken measures to reduce this risk, such as use of male only plasma (antileucocyte antibodies, found mostly in parous women, are thought to be responsible for most cases of transfusion associated lung injury)
Transfusion associated immunomodulation	Studies have suggested that such risks exist (for example, increased overall rates of infection), but the size of this effect is unclear
Increased incidence of hospital acquired infections	This may occur as a consequence of several of the mechanisms described above

Are there risks associated with blood transfusions?

Observational studies have found it difficult to measure clinical benefit from red cell transfusion in patients with acute severe illness and have often found higher complication rates in transfused patients than in otherwise similar patients who received fewer or no transfusions.[2 4] These studies found associations between receiving red cells and a range of adverse outcomes including higher rates of hospital acquired infections, organ dysfunction, longer stays in the intensive care unit and hospital, and increased mortality.[14] However, observational studies are open to confounding bias because patients who are more severely ill are more likely to die and also more likely to be transfused, so the association between transfusion and mortality may not be causal.[6]

Several small randomised trials have explored the relation between red cell transfusion and complications, but most were inconclusive. The largest randomised trial to compare different haemoglobin transfusion "triggers" (the Transfusion Requirements In Critical Care, TRICC trial, described below) found that using red cells more restrictively was at least as effective as a more liberal approach.[15] It found a trend towards lower mortality in patients managed with a restrictive approach, especially if they were younger or less severely unwell, and patients in the liberally transfused group had higher rates of organ dysfunction and cardiac complications.

Table 1 lists known risks associated with red cell transfusion.[2 3] The contribution of blood transfusions to complications such as hospital acquired infections and organ failure is difficult to quantify, partly because these complications are common in critically ill patients, and because red cell products vary across different studies and blood services.[16] Red cells can be stored in different types of solution, subjected to different processing steps (for example, the timing and process of removing white blood cells), and stored for varying durations before transfusion. All these factors could alter the risk-benefit profile, but at present the mechanisms and relative clinical importance are poorly understood.[2 17]

Maintaining adequate supplies of donor blood is increasingly challenging and expensive for blood transfusion services as more potential donors are excluded and more testing and processing occurs.[16] Demand for blood is likely to increase as the population ages.[18 w6] Using blood transfusion safely and appropriately is therefore a priority for health systems for economic reasons and to maximise benefit to the patient. Quality improvement reports have shown that some interventions can decrease iatrogenic blood loss in patients and reduce the incidence and severity of anaemia in critically ill patients (box 2).[19]

Box 2 | Measures to reduce anaemia

- Minimise iatrogenic blood loss from extracorporeal circuits
- Avoid unnecessary blood tests and sampling
- Use blood conservation devices to return the "deadspace" sample to the patient when sampling from indwelling arterial or venous catheters[19]
- Use paediatric blood sampling tubes

Table 2 | Useful clinical symptoms, signs, and tests when deciding if red cell transfusion is needed

Clinical symptom, sign, or test	Considerations
Most useful	
Lactic acidosis	This is a useful indicator of inadequate oxygen delivery, especially early in critical illness (during the "resuscitation phase"). It commonly results from hypoxia or inadequate cardiac output rather than anaemia, so careful cardiorespiratory assessment is needed. Lactic acidosis can also result from poisoning and other conditions causing critical illness
Low central venous oxygen saturations (from a central venous catheter)	These measures are invasive, but low saturations (less than 70%) imply that the body is extracting more oxygen from arterial blood than normal. This may mean oxygen delivery is insufficient to meet demand. As for lactic acidosis, correct hypoxia and ensure that cardiac output is optimised before blood transfusion unless haemoglobin concentrations are ‹70-80 g/l or the patient is bleeding
Haemoglobin value	This is the most commonly used transfusion "trigger." The best evidence to guide the appropriate value comes from the "TRICC" trial (see box 2)
Less useful	
Fatigue and breathlessness	Although common in patients with chronic anaemia, these symptoms can be caused by the disease causing critical illness. Patients may also be unable to provide a history
Pallor	Pallor does not reliably predict the haemoglobin concentration and can also result from hypovolaemia and excessive adrenergic activity (eg, anxiety)
High heart rate	Many other factors, such as pain, anxiety, dehydration, hypovolaemia, and adrenergic drugs, can increase heart rate in critically ill patients

Box 3 | Summary of key findings of the TRICC trial

PICO details

Population

Non-bleeding critically ill patients whose haemoglobin value was 90 g/l or less during the first three days in the intensive care unit

Intervention and comparator

The trial compared a restrictive strategy (haemoglobin transfusion trigger ‹70 g/l; target value 70-90 g/l) with a liberal strategy (haemoglobin trigger 100 g/l; target value 100-120 g/l) for managing anaemia with blood transfusions during the intensive care unit stay

Outcomes

The restrictive group received 54% fewer units of blood and 33% received no blood transfusions in the intensive care unit, whereas all of the liberal group were transfused

The restrictive group showed a non-significant trend towards lower mortality (18.7% *v* 23.3%; P=0.11)

The restrictive group had lower rates of cardiac complications (13.2% *v* 21.0%) and new organ failures (difference in multiple organ dysfunction score of 1 between the groups)

The liberal group showed a trend towards higher rates of acute respiratory distress syndrome (11.4% *v* 7.7%)

Predefined subgroup analyses

Younger patients (‹55 years) and patients with lower illness severity during the first 24 hours in the intensive care unit (APACHE II score ‹20) had significantly better outcomes when they were in the restrictive group (these patients were more anaemic and received fewer blood transfusions)

Subgroup analyses that were not predefined (post hoc analyses)

There was a trend for patients with known ischaemic heart disease to have better outcomes in the liberal group

No differences in outcomes were seen in the subgroup of patients who were mechanically ventilated[w17]

Uncertainties about the generalisability of the findings

The blood used was not leucodepleted. Transfused leucocytes may have adverse effects in critically ill patients and most countries now routinely leucodeplete blood before storage[w18]

The storage age of the blood was unknown. Longer storage times might affect patient outcomes, especially if the blood was not leucodepleted[17]

The study could not prove that the restrictive approach was safe for all patient subgroups, especially those with heart disease and sicker older patients

Improvements in critical care and blood processing over the past decade might mean the findings would be different if the trial were repeated now

When should a patient receive a blood transfusion?

Physiological reserve

Oxygen delivery to tissues is typically 1000 ml per minute in healthy people, but only 250 ml per minute is used, so there is a large "safety margin." In controlled experimental conditions, young healthy adults can compensate for haemoglobin concentrations of 40-50 g/l if the circulating blood volume is maintained with fluids.[20 w7 w8] Older acutely unwell people are less likely to tolerate this level of anaemia, especially if they have coexisting disease.

Many studies, varying widely in quality, have examined the effect of red cell administration on various physiological measures of oxygen supply in critically ill patients.[4] Typically the haemoglobin concentration was increased from 70-90 g/l to more than 100 g/l, and most studies failed to show clinically important changes to the selected end points. This probably means that transfusion is not needed for most patients at these haemoglobin concentrations, but it could also be an indication of the insensitivity of available measures of oxygenation. Table 2 shows physiological and biochemical measures that can help guide blood transfusion decisions, although they lack specificity as diagnostic tests and transfusion triggers. A high or rising lactate concentration and a low or falling central venous haemoglobin oxygen saturation (measured from a central venous catheter) are clinically useful triggers that signal the need to increase oxygen delivery. When faced with evidence of poor oxygenation, clinicians must decide whether to increase the cardiac output (with fluids or inotropic drugs, or both) or improve the oxygen carrying capacity of blood (with red cells). The lack of reliable clinical or laboratory tests to indicate when transfusion is needed means that clinicians rely heavily on the haemoglobin concentration as the primary trigger for transfusion. The problem is that the correct trigger haemoglobin is usually unknown for an individual patient and might vary depending on their clinical condition.

What haemoglobin concentration should trigger blood transfusion in critically ill patients?

The best evidence on what haemoglobin concentration should trigger transfusions in critically ill patients comes from a well performed non-blinded multicentre Canadian trial published in 1999 (the TRICC trial; summarised in box 3),[15] which is widely considered the most important trial in transfusion medicine. Patients with a haemoglobin 90 g/l or less were randomised to either a relatively high haemoglobin transfusion trigger of less than 100 g/l with a target of 100-120 g/l (the "liberal" group) or a lower haemoglobin transfusion trigger of less than 70 g/l with a target of 70-90 g/l ("restrictive" group). The findings strongly support using red cells only to maintain a haemoglobin concentration of 70-90 g/l, especially in younger or less severely ill patients. The generalisability of these findings are unclear, however, and this might explain why clinical practice still varies. This trial has never been replicated in adult critical care, and a recent Cochrane systematic review noted the need for further trials.[21]

We recommend using a haemoglobin transfusion trigger close to 70 g/l as the default position but to modify this using clinical judgment in individual patients. We

ONGOING RESEARCH

- A large multicentre trial in critically ill patients is comparing the effect of fresh red cells (stored for fewer than eight days) with red cells of standard age (typically 18-21 days' storage) on mortality and other outcomes (ABLE study; ISRCTN44878718)
- A multicentre trial in patients who have undergone cardiac surgery is comparing the effect of transfusing red cells stored for up to 10 days with red cells stored for 21 days or more on mortality and other important clinical outcomes (RECESS study; NCT00991341)
- Trials in the US (ProCESS trial), Australia (ARISE), and the UK (ProMISe) are all evaluating goal directed early "bundles" of care for severe sepsis with current standard care
- Several research trials and programmes are re-evaluating the effect of different transfusion triggers on patient outcomes—for example, in cardiac surgery (TiTRE2 trial; ISRCTN70923932), hip fracture surgery (FOCUS trial; NCT00071032), and intensive care (RELIEVE trial; NCT 00944112)

consider a single unit transfusion followed by reassessment of the haemoglobin value before further transfusion to be best practice unless the patient is actively bleeding or has a haemoglobin concentration substantially lower than 70 g/l.

Some evidence exists to support using a higher transfusion trigger than 70 g/l in the following clinical scenarios.

Patients with chronic ischaemic heart disease

Coronary blood flow occurs mainly during diastole. The heart muscle has a high metabolic rate and normally extracts 60-70% of available oxygen to meet its needs. If coronary stenoses limit blood flow it is logical to suppose that anaemia will increase the risk of myocardial ischaemia, especially if tachycardia and shock limit perfusion further. Several large cohort studies found that in patients with chronic ischaemic heart disease haemoglobin concentrations less than 90 g/l were associated with higher mortality during surgery and critical illness.[22 w9 w10] No high quality randomised trials have confirmed this association. A subgroup analysis of patients in the TRICC trial who had pre-existing ischaemic heart disease found a non-significant trend towards lower mortality for the liberally transfused group.[23] However, in the entire study cohort the rates of new cardiac complications were lower in the restrictive group.[15] A lack of high quality evidence means that clinicians have to make decisions on the basis of the severity of coronary artery disease in the individual patient, on whether electrocardiography shows evidence of ischaemia, and on whether coronary blood flow is likely to be adequate.

Patients with acute coronary syndrome

Several cohort studies have found associations between anaemia and higher mortality after acute coronary syndrome,[22 w11-w13] but no evidence is available from randomised controlled trials to suggest what haemoglobin value should be targeted. The most recent highest quality cohort studies do not show benefit from transfusion when the haemoglobin concentration is more than 80 g/l, but the overall quality of evidence is low and controlled trials are needed, especially because bleeding and anaemia are both common in patients who are treated for acute coronary syndrome.[24]

We agree with current recommendations to keep the haemoglobin concentration no lower than 80-90 g/l in patients with an acute coronary syndrome, although the supporting evidence is weak and based largely on physiological reasoning.[4 22]

Patients with early sepsis

Patients with sepsis are at risk of inadequate oxygen delivery to the tissues, particularly during the first six to 12 hours after onset. After this time, abnormalities in the utilisation of cellular oxygen probably become more important than oxygen supply. One single centre, non-blinded, randomised controlled trial used oxygen saturation of less than 70% in central venous blood (measured via a central venous catheter) as a trigger for a resuscitation protocol that included giving red cells to keep the haemoglobin concentration more than 90-100 g/l.[25] Fifty per cent more patients in the intervention group received blood during the first six hours of care compared with controls, but patients also received more fluids and inotropic drugs. The intervention improved hospital survival from 30.5% to 46.5%, but the relative importance of blood transfusion was uncertain. Until additional evidence emerges it is reasonable to consider transfusing patients with early sepsis to haemoglobin values of 90-100 g/l in addition to resuscitation with fluids and adrenergic drugs, but only if there is clear evidence that oxygen supply may be inadequate (oxygen saturation of <70% in central venous blood, or severe or worsening lactic acidosis). Once patients are haemodynamically stable, a haemoglobin of 70-90 g/l is probably adequate.

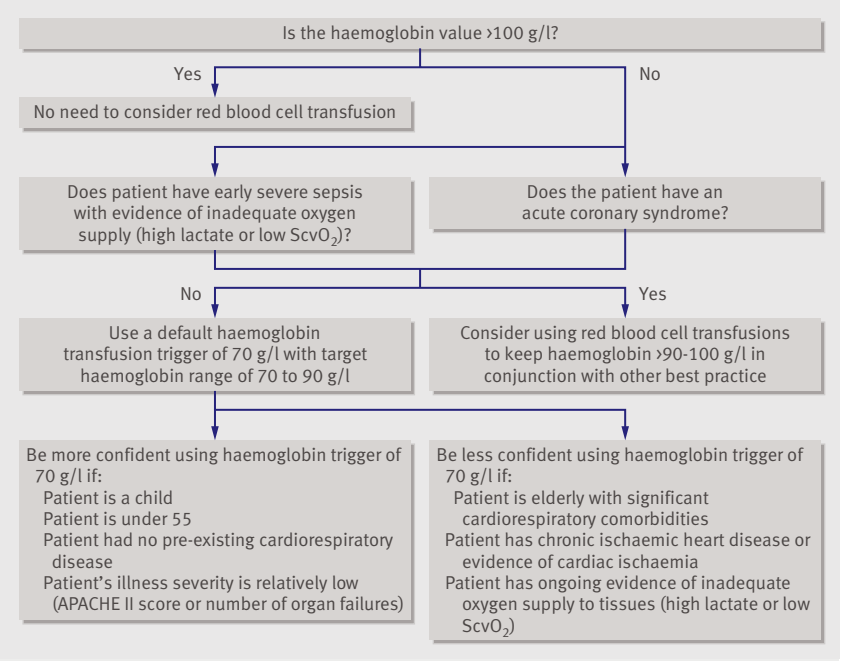

Fig 2 | **Suggested approach to making transfusion decisions in critically ill patients with no evidence that haemorrhage is causing cardiovascular instability. $ScvO_2$=oxygen saturation of less than 70% in central venous blood**

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- Management of alopecia areata (*BMJ* 2010;341:c3671)

ADDITIONAL EDUCATIONAL RESOURCES

Resources for healthcare professionals

NHS Scotland (www.learnbloodtransfusion.org.uk/)—An interactive eLearning resource relating to safe transfusion practice, which is ideal for training of healthcare staff who prescribe or administer blood products

Scottish Intercollegiate Guidelines Network. Perioperative blood transfusion for elective surgery. Guideline no 54. 2001. www.sign.ac.uk/guidelines/fulltext/54/index.html

Resource for patients

NHS Choices (www.nhs.uk/Conditions/Blood-transfusion/Pages/Introduction.aspx)—UK based website providing information in lay terms on blood transfusions, when they are needed, and what questions to ask healthcare professionals when they recommend a blood transfusion

National Heart Lung and Blood Institute. (www.nhlbi.nih.gov/health/dci/Diseases/bt/bt_whatis.html)—US based website providing a wide range of information about blood transfusions using lay terminology

TIPS FOR NON-SPECIALISTS

- Before giving a blood transfusion consider the potential risks and benefits for the individual patient
- Most critically ill patients can safely tolerate a haemoglobin concentration of 70-90 g/l
- If the patient is not bleeding a haemoglobin value of 70-80 g/l is a safe transfusion trigger, with a target value of 70-90 g/l
- In patients who are not bleeding transfuse a single unit of red cells and re-measure the haemoglobin concentration before considering more

Acute neurological disease

The quality of evidence to guide transfusion in patients with intracerebral haemorrhage, thrombotic stroke, subarachnoid haemorrhage, and traumatic brain injury is low and no randomised trials exist.[4 26] Anaemia and the need for blood transfusion are associated with greater disability and mortality in these patients, but clinicians must judge on a case by case basis whether blood transfusion is necessary. Using direct measures of brain oxygenation may help.[w14]

Figure 2 presents an approach to making decisions about transfusion in critically ill adults.

What alternatives to blood transfusions are available to treat anaemia?

Several large well conducted randomised trials have evaluated the effect of using recombinant human erythropoietin, which is not currently licensed for use in this setting, to treat anaemia in people with critical illness.[27 w15 w16] The dose and frequency of treatment, the use of supplemental iron, and the haemoglobin transfusion triggers used differed between trials. This treatment resulted only in a modest reduction in the use of red cells in early smaller trials, and in the largest most recent trial transfusion was not significantly reduced.[27] Although thrombotic events increased, which is a concern, overall mortality decreased, especially in patients with trauma, so this treatment may have other beneficial effects.[27]

Contributors: TSW wrote the first draft of the manuscript and finalised all revisions. DW and SJS made revisions and suggestions to the drafts. All authors searched the literature. TSW is guarantor.
Competing interests: None declared.
Provenance and peer review: Commissioned; externally peer reviewed.

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