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Guideline

GUIDELINES FOR THE CLINICAL USE OF RED CELL TRANSFUSIONS

BACKGROUND

Red cell transfusions are required to increase the oxygen-carrying capacity of the blood by raising the haemoglobin concentration of patients with acute or chronic anaemia. However, there is no consensus on the precise indications for their use, despite numerous previous attempts in the form of guidelines and the agreements reached at Consensus Conferences.

There is evidence of very significant variation in the use of red cell transfusions, for example as provided by the Sanguis study, indicating that currently available guidelines have little impact on clinical practice (The Sanguis Study Group, 1994). This variation does not correlate with patient characteristics, appearing to be more dependent on the individual clinician ordering the transfusion, strongly suggesting that inappropriate use is widespread. Several recent events in relation to blood transfusion in the UK support the view that renewed efforts should be made to encourage better use of red cell transfusions including:

- renewed concerns about the safety of transfusion, in relation to both infectious and non-infectious complications of transfusion (Table I), as highlighted in the Serious Hazards of Transfusion (SHOT) initiative (Williamson *et al*, 1999), and the theoretical risk of transmission of variant Creutzfeldt–Jakob disease (vCJD) by blood transfusion (Murphy, 1999; Turner, 1999).
- new safety requirements, such as leucocyte depletion of blood components and nucleic acid testing, which are increasing the cost and complexity of the production of blood components.

The randomized controlled trials on which evidence-based guidelines for the transfusion of red cells should ideally be based have not been carried out. The purpose of this document is to set 'pragmatic' guidelines for the use of red cell transfusions. While recognizing that they are not wholly evidence based, it is hoped that they can be used to improve transfusion practice, as recommended by the UK Chief Medical Officer's *Better Blood Transfusion* initiative (NHS Executive, 1998), and provide a benchmark for clinical audit. There is evidence that the use of transfusion algorithms (Despotis *et al*, 1994) and prospective audit allied to educational programmes can be effective in modifying clinicians' behaviour in ordering transfusions (Toy, 1994). Clinical governance can be used to support this process and to hold clinicians accountable if they are unwilling to change their practice without providing a valid explanation for refusing to do so (Eisenstaedt, 1997). Meanwhile, it is hoped that randomized controlled trials will be carried out to provide the clinical outcome data for evidence-based transfusion practice in the future.

Alternative strategies for the management of anaemia are becoming more numerous, particularly in the peri-operative period and for patients with chronic anaemia. They include the use of autologous blood in its various forms (preoperative autologous donation, acute normovolaemic haemodilution and intraoperative cell salvage), pharmacological agents to reduce surgical bleeding and recombinant erythropoietin. In addition, a number of blood substitutes are likely to become available in the near future. The consideration of these alternative approaches is beyond the remit of this guideline.

WHAT PARAMETERS CAN BE USED TO INDICATE THE NEED FOR RED CELL TRANSFUSIONS?

Clinical findings

Symptoms such as fatigue and shortness of breath are subjective, but are still useful in determining the need for red cell transfusion in patients with chronic anaemia. Changes in respiratory rate and pulse may be difficult to interpret and may merely be an adaptive response to the anaemia rather than indicating impending adverse clinical effects. Mental function deteriorates with cerebral hypoxia, but the effect is probably too subtle to be clinically useful. Myocardial ischaemia is not always associated with changes on the electrocardiogram (ECG) or echocardiography, and does not necessarily lead to serious outcomes such as myocardial infarction or death.

There are few trials in this area, but a recent study used physical activity as a measure of the adequacy of post-operative haemoglobin concentration. No difference was found between patients who received transfusions to maintain the haemoglobin concentration above 10 g/dl and patients who received transfusions when they were symptomatic or when their haemoglobin concentration fell below 8 g/dl (Carson *et al*, 1998).

Acute anaemia. Acute anaemia is usually caused by blood loss, where the effects of anaemia should be separated from those of hypovolaemia. Clinical experience has shown that losses of up to 30–40% can be treated with crystalloids

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Table I. Some risks of blood transfusion.*

Risk factor	Estimated risk per unit	No. of deaths per million units	Reference
Infection			
Viral†			
Hepatitis A	1/1 000 000	0	Dodd (1994)
Hepatitis B	1/50 000–1/170 000	0–0·14	Regan *et al* (2000)
Hepatitis C	1/200 000	< 0·5	Regan *et al* (2000)
HIV	< 1/2 000 000	< 0·5	Regan *et al* (2000)
HTLV types I and II	1/19 000 to < 1/80 000	0	Brennan *et al* (1993); Flanagan *et al* (1995)
Parvovirus B19	1/10 000	0	Dodd (1994)
Bacterial contamination			
Red cells	1/500 000	0·1–0·25	Sazama (1990); Dodd (1994)
Platelets	1/12 000	21	Dodd (1994)
Immune			
Acute haemolytic reactions	1/250 000–1/1 000 000	0·67	Sazama (1990); Linden *et al* (1997)
Delayed haemolytic reactions	1/1000	0·4	Ness *et al* (1990); Sazama (1990); Shulman (1990); Linden *et al* (1997)
Transfusion-related acute lung injury (TRALI)‡	–	–	Popovsky & Moore (1985); Linden *et al* (1997)
Transfusion-associated graft-versus-host disease (TA-GvHD)‡	–	–	Anderson *et al* (1991)

*Adapted from Goodnough *et al* (1999).

†HIV, human immunodeficiency virus; HTLV, human T-cell lymphotropic virus.

‡Data from the Serious Hazards of Transfusion (SHOT) scheme (1996–99) would suggest that the incidence of TRALI is in the range of 1 in 50 000–1 in 200 000, and TA-GVHD between 1 in 500 000 and 1 in 1000 000 units transfused.

Table II. Classification of hypovolaemic shock according to blood loss (Baskett, 1990).

	Class I	Class II	Class III	Class IV
Blood loss				
Percentage	< 15	15–30	30–40	> 40
Volume (ml)	750	800–1500	1500–2000	> 2000
Blood pressure				
Systolic	Unchanged	Normal	Reduced	Very low
Diastolic	Unchanged	Raised	Reduced	Very low unrecordable
Pulse (beats/min)	Slight tachycardia	100–120	120 (Thready)	> 120 (Very thready)
Capillary refill	Normal	Slow (> 2s)	Slow (> 2s)	Undetectable
Respiratory rate	Normal	Normal	Tachypnoea (> 20/min)	Tachypnoea (> 20/min)
Urinary flow rate (ml/h)	> 30	20–30	10–20	0–10
Extremities	Colour normal	Pale	Pale	Pale and cold
Complexion	Normal	Pale	Pale	Ashen
Mental state	Alert	Anxious or aggressive	Anxious, aggressive, or drowsy	Drowsy, confused, or unconscious

alone in young healthy patients. Acute isovolaemic anaemia to a haemoglobin concentration of around 5 g/dl in a study of volunteers and patients produced no evidence of inadequate oxygenation (Weiskopf *et al*, 1998). Recent studies have shown that a threshold for red cell transfusion of 8 g/dl was as safe as one of 9 g/dl in patients undergoing coronary artery bypass surgery (Bracey et al, 1999), and a threshold of 7 g/dl was as safe and possibly superior to a threshold of 10 g/dl in critically ill patients (Hebert *et al*, 1999).

Reliable measures of oxygen delivery to critical organs are not available. Even with invasive haemodynamic monitoring in critically ill patients, there is difficulty in knowing which measurements, such as cardiac output and oxygen consumption, should be used for monitoring haemodynamic therapy.

Estimation of actual and likely further blood loss is an important consideration in the decision to administer a red cell transfusion in the treatment of acute blood loss.

Chronic anaemia. The symptoms of chronic anaemia depend on the patient's age, level of activity, and coexisting medical problems such as cardiovascular and respiratory disease.

The haemoglobin concentration

The benefit of red cell transfusion is usually considered in terms of increasing the oxygen-carrying capacity of the blood, but a more relevant consideration is the avoidance of tissue hypoxia. Adequacy of tissue oxygenation is determined by the balance between oxygen consumption and oxygen delivery. Many factors influence oxygen consumption, including exercise, body temperature, sympathetic and metabolic activity, heart rate and the effect of drugs including anaesthetic agents. Oxygen delivery is the product of the oxygen content of the blood and the cardiac output. When the haemoglobin concentration falls, there is a compensatory increase in the cardiac output. This, together with other factors such as reduced blood viscosity and peripheral vasodilatation, act to maintain adequate oxygen delivery to the tissues.

Clinicians may underestimate the effectiveness of such adaptive mechanisms, perhaps explaining the tendency towards over-reliance on measurement of the haemoglobin concentration and excessive use of red cell transfusions. Chronic anaemia is even better tolerated than acute anaemia because of better oxygen delivery associated with an increase in 2,3 DPG and a shift in the oxygen dissociation curve. The reserve of oxygen-carrying capacity is such that cardiac output at rest does not usually increase until the haemoglobin concentration falls below 7 g/dl.

For many years, it was traditional to use a trigger of a haemoglobin concentration of 10 g/dl for peri-operative red cell transfusion and for transfusions to medical patients. However, there is evidence that renal transplant patients and Jehovah's Witnesses undergo surgery successfully with lower haemoglobin concentrations (Carson *et al*, 1988; Stehling & Simon, 1994). In the study of Jehovah's Witnesses, no patient with a preoperative haemoglobin concentration of > 8 g/dl and with blood loss < 500 ml died, although there was very limited information on morbidity, including post-operative recovery (Carson *et al*, 1988). A review of 61 untransfused Jehovah's Witnesses with haemoglobin concentrations < 8 g/dl found that

mortality only occurred with haemoglobin concentrations less than 5 g/dl (Viele & Weiskopf, 1994). Furthermore, acute isovolaemic anaemia to a haemoglobin concentration of around 5 g/dl in volunteers and patients produced no evidence of inadequate oxygenation (Weiskopf *et al*, 1998). Finally, a recent review of the literature on red cell transfusion found insufficient evidence to justify the use of a single haemoglobin concentration as a threshold for the transfusion of patients with acute or chronic anaemia (Hebert *et al*, 1997).

Numerous guidelines for the use of red cell transfusions have been produced. Up to 15 were quoted in one paper (Weiskopf, 1998) with various suggestions for the threshold for transfusion. There was a tendency for a lowering of the haemoglobin concentration used as the threshold for transfusion. However, it has been suggested that this trend may have gone too far and that many patients are undertransfused (Valeri *et al*, 1998). Although it is difficult to know to what extent this view is correct, there should be support for audit of transfusion practice for both under- and overtransfusion (Lenfant, 1992), and concern about undertransfusion should be considered when drawing up guidelines for the use of red cell transfusions.

Conclusions

There are no reliable parameters to guide the need for red cell transfusion. The decision to transfuse red cells is a complex one and depends on factors such as the cause of the anaemia, its severity and chronicity, the patient's ability to compensate for anaemia, the likelihood of further blood loss and the need to provide some reserve before the onset of tissue hypoxia. The risks of transfusion also need to be balanced against the perceived benefits. Although guidelines for red cell transfusion often specify a given concentration of haemoglobin in order to be pragmatic, consideration of the patient's clinical condition is an essential part of the decision to transfuse red cells or not and is a matter for clinical judgement.

RED CELL COMPONENTS

There are few clinical data on the advantages and disadvantages of different types of red cell components in the management of acute and chronic anaemia. This guideline assumes the use of red cells suspended in optimal additive solution, the standard red cell preparation available from the UK Blood Services.

The question of the use of whole blood, particularly in the treatment of acute blood loss, is often raised. There are no data to suggest that the use of whole blood, even 'fresh' whole blood, is associated with a better outcome than stored blood in acute blood loss.

RECOMMENDATIONS

These are adapted from a number of existing guidelines (American College of Physicians, 1992; American Society of Anesthiologists Task Force on Blood Component Therapy, 1996; Consensus Conference on Red Cell Transfusion, Royal College of Physicians Edinburgh, 1994) and a recent systematic review of published recommendations and guidelines for the transfusion of red cells (Calder *et al*, 1997). They are primarily intended to guide transfusion practice for adults. A separate guideline on neonatal and paediatric transfusion is being prepared by the British Committee for Standards in Haematology.

General principles

- Clinicians prescribing red cell transfusions should be aware of the appropriate indications and the risks and benefits of transfusion.
- Patients should be given information about the risks and benefits of red cell transfusion in advance of transfusion whenever possible, together with possible alternatives including autologous transfusion. Patients have the right to refuse transfusion, but written informed consent is not presently required.
- The cause of anaemia should be established, and treatment with red cell transfusions should not be given where effective alternatives exist, e.g. treatment of iron deficiency, megaloblastic and autoimmune haemolytic anaemia unless the anaemia is life-threatening.
- There is no universal 'trigger' for red cell transfusions, i.e. a given concentration of haemoglobin at which transfusion of red cells is appropriate for all patients. Clinical judgement plays a vital role in the decision to transfuse red cells or not.
- In acute blood loss, crystalloids or synthetic colloids, not blood, should be used for initial rapid acute volume replacement. The effects of anaemia need to be considered separately from those of hypovolaemia. It is accepted that, in patients with acute massive blood loss, i.e. $> 50\%$ of circulating blood volume (Fearn & Mortimer, 2000), empirical decisions about the immediate use of red cell transfusion have to be taken. However, it is important to define patients' needs for blood components and fluid replacement as specifically as possible to ensure that blood is prescribed rationally (Stainsby *et al*, 2000).
- Local arrangements should be in place to provide compatible blood urgently for patients with major bleeding (BCSH, 1996), including the emergency use of O RhD-negative blood.
- The reason for administration of red cell transfusions should be documented in patients' medical records.

Indications for the use of red cell transfusions

(1) Acute blood loss. Patients with acute massive blood loss should ideally be managed by experienced clinicians in a suitable setting, such as Accident and Emergency resuscitation rooms, high-dependency or intensive care units. A blood sample should be sent to the hospital blood bank for compatibility testing and for urgent provision of blood according to hospital policy.

It may be difficult to assess the amount of blood loss, but consideration of lost circulating volume may be useful in guiding transfusion management. Table II provides a classification of hypovolaemic shock according to percentage

blood loss and the associated clinical signs (Baskett, 1990).

Need for transfusion based on estimation of lost circulating volume. This is the prime consideration in patients with acute blood loss:

- 15% loss of blood volume (750 ml in an adult): no need for transfusion unless blood loss is superimposed on pre-existing anaemia or when the patient is unable to compensate for this quantity of blood loss because of severe cardiac or respiratory disease.
- 15–30% loss of blood volume (800–1500 ml in an adult): need to transfuse crystalloids or synthetic colloids; the need for red cell transfusion is unlikely unless the patient has pre-existing anaemia, reduced cardiorespiratory reserve or if blood loss continues.
- 30–40% loss of blood volume (1500–2000 ml in an adult): rapid volume replacement is required with crystalloids or synthetic colloids, and red cell transfusion will probably be required.
- 40% loss of blood volume (> 2000 ml in an adult): rapid volume replacement including red cell transfusion is required.

Need for transfusion based on consideration of the concentration of haemoglobin. The concentration of haemoglobin should be considered along with other factors such as the rate of blood loss:

- Red cell transfusion is not indicated when estimates of actual and anticipated haemoglobin concentrations are > 10 g/dl.
- Red cell transfusion is indicated when the haemoglobin concentration is < 7/g/dl. Red cell transfusions should be given in relation to the rate of ongoing red cell loss. If the patient is otherwise stable, 2 units of red cells should be transfused in adults (or the equivalent in children according to size), and then the clinical situation and haemoglobin concentration should be reassessed.
- The correct strategy for transfusion of patients with haemoglobin concentrations between 7 and 10 g/dl is less clear. Clinicians often transfuse red cells, although available evidence suggests that this is often not justified.
- In patients who may tolerate anaemia poorly, e.g. patients over the age of 65 years and patients with cardiovascular or respiratory disease, consider adopting a higher concentration at which transfusions are indicated, e.g. when the haemoglobin concentration becomes < 8 g/dl.

Consideration of the risk of further bleeding resulting from abnormal haemostasis. Abnormal haemostasis associated with acute blood loss is usually caused by thrombocytopenia or platelet dysfunction and should be treated with platelet concentrates according to current guidelines (BCSH, 1988, 1992). Coagulopathies that require replacement of clotting factors are less common, and again should be treated according to currently available guidelines (BCSH, 1988). Studies in anaemic uraemic patients have shown that increasing the haemoglobin concentration with either red blood cell transfusions or erythropoietin corrects the prolonged bleeding time often seen in these patients (Livio *et al*, 1982; Boneu & Fernandez, 1987), but similar data on shortening of the bleeding time by correction of anaemia are not available in other clinical settings.

The advice of a haematologist should be sought about the appropriate investigation and management of abnormal haemostasis, including the use of platelet and coagulation factor replacement before invasive procedures.

(2) Anaemia in critical care. The same target values should be applied as for acute blood loss. Overtransfusion may increase mortality in this group; 30-d mortality was no worse in patients receiving a 'restrictive' transfusion strategy (trigger haemoglobin concentration < 7 g/dl) than in patients receiving a 'liberal' transfusion strategy (trigger haemoglobin concentration < 10 g/dl), and was lower in less acutely ill patients (Hebert *et al*, 1999).

In terms of the general management of critically ill patients, the importance of adequate volume replacement, maintenance of blood pressure and the use of inotropic drugs to maintain a normal cardiac output continues to be emphasized (Hinds & Watson, 1995). A recent systematic review of randomized controlled trials suggested that crystalloids should be used in preference to colloids for fluid resuscitation of patients with acute hypovolaemia (Schierhout & Roberts, 1998), but the crystalloids versus colloids debate continues, and reviews of the effectiveness of specific colloids are being prepared by the Cochrane Injuries Group (Watts *et al*, 1998). Colloids have the potential disadvantage of causing hypersensitivity, including occasional severe anaphylactoid reactions, and exacerbating any haemostatic problems and the hypotension attributable to blood loss (Salmon & Mythen, 1993; Watts *et al*, 1998).

(3) Peri-operative transfusion. The objective should be to manage the patient so that transfusion is not needed. Specific measures that may be appropriate are the investigation and treatment of anaemia, e.g. resulting from iron deficiency, before elective surgery, discontinuation of antiplatelet drugs, reversal of anticoagulation, consideration of the various strategies of autologous transfusion (BCSH, 1993, 1997) and the use of pharmacological agents to reduce surgical bleeding.

The same approach to the management of acute haemorrhage during surgery should be applied as for acute blood loss (above). There is no case for transfusion back to a 'normal' haemoglobin level either before or after surgery, and to avoid transfusion when the haemoglobin concentration is > 10 g/dl is in line with current good practice. The voluntary participation of surgical teams in regular audit of their peri-operative transfusion practice with collection of data, such as units transfused and discharge haemoglobin concentrations, is a useful way of building up a shared understanding of the range of practice among the participating teams and of the practice of individual teams. This approach should provide the opportunity to examine in detail the techniques used by teams using the least blood and the clinical outcomes associated with their practice (McClelland, 1994).

(4) Chronic anaemia. The cause of anaemia should be established, and treatment with red cell transfusions should

not be given where effective alternatives exist, e.g. treatment of iron deficiency, megaloblastic anaemia and autoimmune haemolytic anaemia, unless the anaemia is life threatening. In principle, red cell transfusions for patients with chronic anaemia should be given at intervals to maintain the haemoglobin just above the lowest concentration that is not associated with symptoms of anaemia, but it may be difficult to determine what this concentration is for individual patients. Many patients with chronic anaemia are apparently asymptomatic with a haemoglobin concentration > 8 g/dl but, when patients' symptoms have been formally evaluated using functional assessment scales, those with haemoglobin concentrations > 12 g/dl reported less fatigue and better quality of life (Cella, 1997).

An alternative treatment for chronic anaemia is recombinant erythropoietin, which has been used for treating anaemia in some patients with cancer (Oster *et al*, 1990; Platanias *et al*, 1991; Spivak, 1994), myeloma (Ludwig *et al*, 1990; Osterborg *et al*, 1996), myelodysplasia (Hellstrom-Lindberg, 1995; Rose *et al*, 1995; Italian Cooperative Study Group, 1998) and non-Hodgkin's lymphoma (Osterborg *et al*, 1996). It has been found to be safe and effective in increasing haemoglobin concentrations and produces a sustained increase in the haemoglobin concentration rather than the fluctuating concentrations associated with regular transfusion. The high cost of the drug has limited its use. Further economic analyses are required to compare the use of red cell transfusions and recombinant erythropoietin in the management of chronic anaemia (Griggs & Blumberg, 1998).

The goals of transfusion in β-thalassaemia include suppression of erythropoiesis and inhibition of increased gastrointestinal iron absorption as well as correction of anaemia. 'Hypertransfusion' programmes that cause substantial iron loading have been supplanted by regimens in which the haemoglobin concentration is no more than 9·5 g/dl before transfusion; such regimens provide adequate bone marrow suppression and lower rates of iron overload (Olivieri, 1999).

Long-term transfusion programmes are also used in sickle cell disease to reduce the risk of stroke in children at high risk (defined by trans-cranial Doppler studies), in patients with a previous stroke and to reduce vaso-occlusive events during pregnancy (Castro, 1999). A recent randomized trial found that an aggressive preoperative transfusion strategy involving exchange transfusions did not reduce the number of post-operative vaso-occlusive complications compared with top-up transfusions to a haemoglobin concentration of 10 g/dl, and had the disadvantage that red cell alloimmunization was twice as common (Vichinsky *et al*, 1995). Transfusion is not routinely indicated for patients with sickle cell disease when the haemoglobin concentration is < 7 g/dl; it is suggested that specialist centres are contacted for specific advice about individual patients.

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APPENDIX: AUDIT MEASURES FOR THE CLINICAL USE OF RED CELL TRANSFUSIONS

- each blood bank should have a maximum blood order schedule (MSBOS), and compatible blood should not generally be made available for surgery where the usage is $< 50\%$ of the units provided
- the MSBOS should be reviewed at least annually according to the current blood usage for elective surgery
- local guidelines should be drawn up for peri-operative transfusion and audited; guidelines should also be drawn up for other situations in which acute haemorrhage is common, e.g. gastrointestinal bleeding, obstetrics and trauma
- comparison of the use of blood for common surgical procedures, e.g. primary total hip replacement and coronary artery bypass surgery, between surgeons and hospitals should be carried out
- documentation of transfusion in the medical notes, including the indication for transfusion, the date of transfusion, the number and type of units transfused and any adverse effects and how they were managed, must be routine (BCSH, 1999). Ideally, the notes should also include an assessment of the effectiveness of the transfusion, for example in relieving symptoms of anaemia and in raising the haemoglobin concentration. These records should be audited.