bjh guideline

Guidelines on the management of anaemia and red cell transfusion in adult critically ill patients

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Forward

This document aims to summarize the current literature guiding the use of red cell transfusion in critically ill patients and provides recommendations to support clinicians in their day-to-day practice. Critically ill patients differ in their age, diagnosis, co-morbidities, and severity of illness. These factors influence their tolerance of anaemia and alter the risk to benefit ratio of transfusion. The optimal management for an individual may not fall clearly within our recommendations and each decision requires a synthesis of the available evidence and the clinical judgment of the treating physician.

This guideline relates to the use of red cells to manage anaemia during critical illness when major haemorrhage is not present. A previous British Committee for Standards in Haematology (BCSH) guideline has been published on massive haemorrhage (Stainsby *et al*, 2006), but this is a rapidly changing field. We recommend readers consult recent guidelines specifically addressing the management of major haemorrhage for evidence-based guidance. A subsequent BCSH guideline will specifically cover the use of plasma components in critically ill patients.

The World Health Organization (WHO) defines anaemia in men and women as a haemoglobin (Hb) <130 and <120 g/l, respectively, (Beutler & Waalen, 2006; WHO, 2011) and severe anaemia as <80 g/l (Guralnik *et al*, 2004; WHO, 2011). Anaemia is highly prevalent among the critically ill; 60% of patients admitted to intensive care units (ICU) are anaemic and 20–30% have a first haemoglobin concentration (Hb) <90 g/l (Hebert *et al*, 2001a; Vincent *et al*, 2002; Corwin, 2004; Walsh *et al*, 2004a, 2006a). After 7 d 80% of ICU patients have an Hb <90 g/l. Cohort studies indicate a strong association between anaemia and inferior outcomes, especially amongst those with cardiovascular disease (Carson *et al*, 1996; Hebert *et al*, 1997; Kulier *et al*, 2007; Wu *et al*, 2007). Haemodilution, blood loss and blood sampling are the most important initial contributors to anaemia in critical care. Impaired erythropoiesis secondary to inflammation is increasingly important with prolonged illness (Walsh & Saleh, 2006).

Depending upon casemix, 30–50% of ICU patients receive red cell (RBC) transfusions (Walsh *et al*, 2004b; Walsh & Saleh, 2006). Ten percent of all RBCs transfused nationally are given in general ICUs (Walsh *et al*, 2004a). Studies suggest that only 20% of transfusions are to treat haemorrhage (Vincent *et al*, 2002); the majority are given for anaemia. Mean blood consumption ranges from 2 to 4 units per admission.

Methods

The writing group was selected by the BCSH Transfusion Task Force with input from the Intensive Care Society to provide expertise in relevant physiology, pathophysiology, general intensive care and specific subgroups of critically ill patients.

We did not undertake a formal systematic literature review. We agreed *a priori* a range of issues relating to general intensive care patients, and specific sub-groups of patients with relevant co-morbidities. These were subcategories relating to general intensive care, weaning from mechanical ventilation, ischaemic heart disease (IHD), sepsis, and neurocritical care. A MEDLINE database search was conducted from its inception to December 2011 using a range of broad search terms relating to red cell transfusion, critical care, and intensive care. The search strategy is available from the

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authors on request. The search yielded 4856 papers. These were sub-divided according to the pre-defined subcategories and reviewed by sub-group members allocated to each part of the guideline. At least two group members contributed to each subcategory section. Using this approach a total of 508 relevant papers were extracted and reviewed in full. Recent systematic reviews and guidelines produced by other groups were also reviewed where available.

The quality of evidence was judged by predefined Grades of Recommendation, Assessment, Development and Evaluation (GRADE) criteria (Jaeschke *et al*, 2008). Strong recommendations, grade 1, are made when the group was confident that the benefits do or do not outweigh the harm and burden of cost of a treatment. Where the magnitude of benefit is less certain, grade 2, or suggested recommendations are made. The quality of evidence is rated as A – high quality randomized control trials, B – moderate, C – low, D – expert opinion only. The GRADE system is summarized in Table I.

Table I. Summary of the grade recommendations.

Determination of the quality of evidence	
Underlying methodology	
A. Randomized control trial	
B. A downgraded randomized control trial or high quality observational studies	
C. Well-done observational studies	
D. Case series or expert opinion	
Factors that may decrease the strength of evidence	
1. Poor quality of planning and implementation of available randomized control studies, increasing the risk of bias	
2. Inconsistency of results	
3. Indirectness of evidence	
4. Imprecision of results	
5. High likelihood of reporting bias	
Main factors that may increase the strength of the evidence	
1. Large magnitude of effect (direct evidence, relative risk >2, with no plausible confounders)	
2. Very large magnitude of effect with RR >5 and no threats to validity	
3. Dose respondent gradient	
Factors determining strong *versus* weak recommendations	
Quality of evidence	The lower the quality of evidence the weaker the recommendation
Relative importance of outcomes	If values and results vary widely the weaker the recommendation
Baseline risk of outcomes	The higher the risk, the greater the magnitude of effect
Magnitude of relative risk	The greater the benefit the stronger the recommendation
Precision of the estimates of effect	The greater the precision the stronger the recommendation
Cost	The greater the cost the weaker the recommendation

The pathophysiology of anaemia

Global oxygen delivery (DO_2) from the heart to tissues is the product of arterial O_2 content and cardiac output (Barcroft, 1920). Arterial O_2 content is calculated by the O_2 carried by haemoglobin plus the dissolved O_2; in health >99% of O_2 is transported bound to haemoglobin. Tissue hypoxia can occur during critical illness as a result of problems at all stages in the O_2 cascade, including airway and pulmonary disease, inadequate cardiac function and reduced or maldistributed microvascular flow. Anaemia reduces O_2 carrying capacity and there is strong biological plausibility in the belief that it causes tissue hypoxia. When tissue DO_2 falls, O_2 supply is maintained by compensatory mechanisms that increase O_2 extraction. However, there is a critical DO_2 at which these compensatory mechanisms are overwhelmed and O_2 transport becomes directly proportional to O_2 supply. In such circumstances, severe tissue hypoxia is much more likely to occur. Studies using normovolaemic haemodilution indicate that young adults can maintain an O_2 supply at Hb concentrations of 40–50 g/l by increasing cardiac output and O_2 extraction (Weiskopf *et al*, 2006). The heart and brain have high O_2 extraction ratios, which limits these compensatory mechanisms. In addition, O_2 consumption is increased in the critically ill. Therefore anaemia may be less well tolerated during critical illness. An assessment of the risk to benefit ratio of transfusion to improve O_2 carrying capacity is a key consideration to optimise patient outcomes.

Transfusion triggers in general critical care populations

The strongest evidence guiding transfusion policy in adult critically ill patients comes from the Transfusion Requirements In Critical Care (TRICC) study (Hebert *et al*, 1999). Patients with a Hb $\leq$90 g/l were randomized to either a relatively high Hb transfusion trigger of <100 g/l with a target of 100–120 g/l, the 'liberal' group, or a lower trigger of <70 g/l with a target of 70–90 g/l (the 'restrictive' group). Mortality was compared at 30 and 60 d, and a range of secondary outcomes compared. The restrictive group received 54% fewer units of blood and 33% received no blood transfusions in the ICU, whereas all of the liberal group were transfused. Thirty-day mortality in the liberal group was typical of general ICU populations (23·3%), but there was a non-significant trend towards lower mortality for the restrictive group (18·7%, $P = 0{\cdot}11$). In two pre-defined subgroups, younger patients (aged < 55 years) and patients with lower illness severity [Acute Physiology and Chronic Health Evaluation (APACHE) II score < 20], the risk of death during 30-d follow up was significantly lower with the restrictive strategy. For patients aged <55 years those in the restrictive group had a 5·7% mortality vs. 13·0% for those in the liberal group [95% confidence interval (CI) for the absolute difference 1·1–13·5%; $P = 0{\cdot}028$]. Similarly, for patients with an APACHE II score < 20, those in the restrictive group had an 8·7% mortality vs. 16·1% for the liberal group (95% CI for

the absolute difference: 1·0–13·6%; $P = 0·03$). These differences represented a number needed to treat to benefit from restrictive over liberal transfusion of about 13 patients for these sub-groups.

Overall, there were also lower rates of new organ failures in the restrictive group and a trend towards higher rates of Acute Respiratory Distress Syndrome in the liberal group (7·7% vs. 11·4%). These findings support using transfusions to maintain a Hb of 70–90 g/l. Concerns about the applicability of these results include the introduction of leucodepletion of red blood cells (RBCs), the storage age of RBCs, and risk of selection bias; few patients with cardiac disease were enrolled and there was a high clinician refusal rate.

The results of the TRICC study have been corroborated by two recent studies. The Transfusion Requirements After Cardiac Surgery (TRACS) study found no difference in a composite end-point of 30-d mortality and severe comorbidity in cardiac patients prospectively randomized to a liberal or restrictive transfusion strategy (Hajjar *et al*, 2010). Most recently the 'FOCUS' (Transfusion Trigger Trial for Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair) study of liberal or restrictive transfusion in high-risk patients after hip surgery showed no difference in mortality or mobility in the group assigned to the restrictive transfusion strategy (Carson *et al*, 2011). Importantly, although patients in the FOCUS trial were not critically ill, they were elderly and had a high prevalence of cardiovascular disease. Taken together the recent literature consistently shows no clear advantage with a liberal transfusion strategy. A suggested approach to transfusion in critical care is summarised in Fig 1.

Recommendations

- **A transfusion threshold of 70 g/l or below, with a target Hb range of 70–90 g/l, should be the default for all critically ill patients, unless specific co-morbidities or acute illness-related factors modify clinical decision-making (Grade 1B).**
- **Transfusion triggers should not exceed 90 g/l in most critically ill patients (Grade 1B).**

Alternatives to red cell transfusions

Erythropoietin. Critically ill patients do not generate a physiological increase in erythropoietin concentration in response to anaemia (Corwin *et al*, 1999, 2002, 2007; Hobisch-Hagen *et al*, 2001; Corwin, 2004; Shander, 2004; Hebert & Fergusson, 2006; Belova & Kanna, 2007; Arroliga *et al*, 2009; Bateman *et al*, 2009). Several trials have evaluated the efficacy and effectiveness of erythropoietin administration in critically ill patients. Methodological variations including different patient populations, and varying dosage regimens of both erythropoietin and iron therapy makes interpretation of these trials complicated. It appears on balance that a combination of iron supplementation and erythropoietin therapy can modestly decrease transfusion requirements, but the benefits become negligible when a transfusion trigger of 70 g/l is used (Corwin *et al*, 2007). No difference in patient outcomes has been demonstrated, except for a possible decrease in mortality among trauma patients. Erythropoietin therapy increases deep vein thrombosis, especially when prophylaxis is not used. Erythropoietin is not licenced for use in anaemic critically ill patients.

Recommendation

- **Erythropoietin should not be used to treat anaemia in critically ill patients until further safety and efficacy data are available (Grade 1B).**

Iron therapy. The inflammatory response complicates the interpretation of iron indices in critical illness (Walsh & Saleh, 2006). Tests of iron status typically demonstrate an increased ferritin concentration whilst transferrin levels, the serum iron-to-iron binding ratio and transferrin saturation are decreased. Iron is shifted into macrophages resulting in a functional iron deficiency similar to the anaemia of chronic disease. Evidence of absolute iron deficiency is absent in most patients, and patients do not respond to iron supplementation alone (Walsh *et al*, 2006b; Munoz *et al*, 2008). There are no large randomized trials of iron monotherapy in critically ill patients, and excess iron may increase susceptibility to infection (Maynor & Brophy, 2007). The biochemical characteristics of anaemia in the critically ill are summarized in Table II.

Recommendation

- **In the absence of clear evidence of iron deficiency, routine iron supplementation is not recommended during critical illness (Grade 2D).**

Blood sampling techniques to reduce iatrogenic blood loss

Blood sampling contributes substantially to iatrogenic anaemia during critical illness (Smoller & Kruskall, 1986; Corwin *et al*, 1995; Zimmerman *et al*, 1997). Studies examining the

Table II. Biochemical characteristics of anaemia in the critically ill.

	Change	Comment
Serum iron	Decreased	Similar to the anaemia of chronic disease
Total iron binding capacity	Decreased	
Ferritin	Increased	Positive acute phase protein
Transferrin	Decreased	
Soluble transferrin receptor	Normal	Increase thought to represent iron deficiency or new erythropoiesis
Vitamin B12 and folate	Normal	
Erythropoietin concentration	Slight increase	Inappropriately low for severity of anaemia, may be related to renal impairment and inflammation

magnitude of blood loss associated with routine phlebotomy indicate typical daily blood loss of approximately 40 ml (Foulke & Harlow, 1989; Fowler & Berenson, 2003; MacIsaac *et al*, 2003; Corwin, 2005; Chant *et al*, 2006; Harber *et al*, 2006; Sanchez-Giron & Alvarez-Mora, 2008).

Available evidence suggests that blood conservation devices are infrequently used in the ICU, although few recent studies or surveys have been published (O'Hare & Chilvers, 2001). Several studies have assessed the impact of these devices. Two showed a significant reduction in blood loss, but without an effect on anaemia or RBC use (Foulke & Harlow, 1989; MacIsaac *et al*, 2003; Mukhopadhyay *et al*, 2010). One study (Mukhopadhyay *et al*, 2010) showed a reduction in the severity of anaemia and reduced RBC use with the Venous Arterial blood Management Protection (VAMP) system (Edwards Lifesciences, Irvine, CA, USA). Use of this device was associated with decreased requirements for RBC transfusion (control group 0·131 units vs. active group 0·068 units RBC/patient/d, $P = 0{\cdot}02$). The intervention group also had a smaller reduction in Hb during ICU stay, $14{\cdot}4 \pm 20{\cdot}8$ vs. $21{\cdot}3 \pm 23{\cdot}2$ g/l; $P = 0{\cdot}02$ (Mukhopadhyay *et al*, 2010). No cost-effectiveness evaluations of these systems in routine practice have been published.

The use of small volume paediatric sampling bottles has also been consistently associated with reduced phlebotomy-related blood loss, without affecting assay quality (Harber *et al*, 2006; Sanchez-Giron & Alvarez-Mora, 2008).

Recommendations

- **The introduction of blood conservation sampling devices should be considered to reduce phlebotomy-associated blood loss (Grade 1C).**
- **Paediatric blood sampling tubes should be considered for reducing iatrogenic blood loss (Grade 2C).**

Adverse consequences associated with RBC transfusion in critical care

The need to ensure RBC transfusion is used only where appropriate is emphasized by concerns about adverse consequences (Fig 1). An increasing body of laboratory and clinical research has raised the possibility that stored RBCs have harmful effects, although the clinical consequences remain to be defined. Most cohort studies show associations between transfusion and adverse patient outcomes, including death, organ failure progression, infection and prolonged hospital stay (Marik & Corwin, 2008). However, the importance of residual confounding in these studies is uncertain. The risks of transfusion in the critically ill include those common to all blood transfusions (e.g. errors in administration) and those more specific to individual blood components (e.g. bacterial contamination in platelet transfusions). The key principles of safe administration of blood are summarized in the BCSH Guidelines for the Administration of Blood Components (Harris *et al*, 2009). In critically ill patients, transfusion-associated lung injury (TRALI) and transfusion-associated circulatory overload (TACO) are particularly relevant complications (Dara *et al*, 2005; Rana *et al*, 2006a; Gajic *et al*, 2007a,b; Khan *et al*, 2007). Any adverse events or reactions related to transfusion should be appropriately investigated and reported to local risk management, the Serious Hazards of Transfusion group (SHOT) and the Medicines and Healthcare products Regulatory Agency (MHRA) via the Serious Adverse Blood Reactions and Events (SABRE) system.

Transfusion-associated circulatory overload (TACO)

SHOT defines TACO as acute respiratory distress with pulmonary oedema, tachycardia, increased blood pressure, and

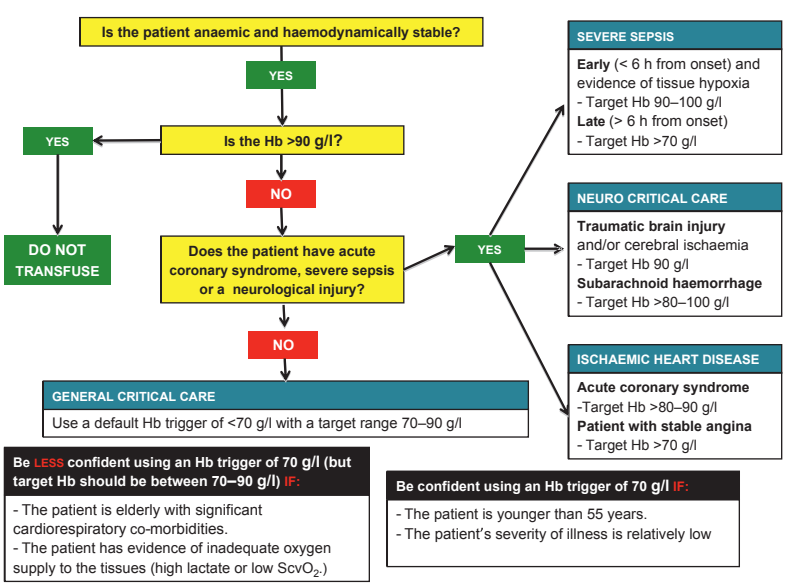

Fig 1. A suggested approach to transfusion in critical care. $ScvO_2$, central venous oxygen saturation.

evidence of a positive fluid balance after a blood transfusion (Taylor *et al*, 2010). Assessing the true incidence of TACO is difficult due to the lack of a consensus definition. A single large study evaluating the incidence of TACO in critically ill patients, defined the condition as the onset of pulmonary oedema within 6 h of transfusion with a PaO_2:FiO_2 ratio of <300 mmHg or SaO_2 of <90% on room air, bilateral infiltrates on a chest radiograph in the presence of clinically evident left atrial hypertension (Rana *et al*, 2006b). The different criteria used in these studies may account for the reported differences in incidence, varying from one in every 357 units of RBCs transfused, to the 2009 SHOT report (Taylor *et al*, 2010), which identified 34 cases of TACO, 33 attributable to RBCs, but only five cases confirmed as highly likely.

Transfusion-related acute lung injury (TRALI)

TRALI is defined as the onset of pulmonary oedema within 6 h of transfusion with a PaO_2:FiO_2 ratio of <300 mmHg in room air, bilateral infiltrates on a chest radiograph in the absence of left atrial hypertension. TRALI was first reported in 1951 but did not receive widespread recognition until more aggressive transfusion support became established (Silliman *et al*, 2005). It is difficult to recognize and can occur after transfusion of plasma, platelets or RBCs. Rana *et al* (2006a) estimated the incidence of TRALI as in one in every 1271 transfusions. Blood donors in confirmed cases are typically multiparous women who have developed leucoagglutinins during pregnancy. Many Blood Transfusion Services have introduced a policy of sourcing plasma from male donors, which has reduced the incidence of TRALI (Chapman *et al*, 2009). When suspected, TRALI should be investigated systematically; a suggested procedure is summarized in Table III.

Recommendations

- **Pre-transfusion clinical assessment should be undertaken including assessment of concomitant medical conditions that increase the risk of TACO (cardiac failure, renal impairment, hypoalbuminaemia, fluid overload) (Grade 1D).**
- **Attention to the rate of transfusion together with careful fluid balance and appropriate use of diuretic cover (e.g. furosemide) can reduce the risk of TACO (Grade 1D).**
- **Patients developing acute dyspnoea with hypoxia and bilateral pulmonary infiltrates during or within 6 h of transfusion should be carefully assessed for the probability of TRALI and patients should be admitted to a critical care area for supportive treatment and monitoring (Grade 1D).**
- **Any adverse events or reactions related to transfusion should be appropriately investigated and reported via systems for local risk management, and also to National Haemovigilance Schemes (Grade 1D).**

Table III. TRALI v TACO – clinical features and investigation.

Feature	TRALI	TACO
Temperature	↑	No change (unless already elevated or other explanation, e.g. new sepsis)
Blood Pressure	↓/−	↑/−
Neck veins/central venous pressure	No change	Can be distended/CVP ↑
Auscultation	Crepitations, wheeze rare	Crepitations +/− S3 often wheeze as well
Pulmonary artery occlusion pressure	Normal	Elevated
Improvement after diuretic	No	Yes
White blood cell count	Transient ↓ (unless other cause of elevation, e.g. sepsis; inflammation)	No change

TRALI, transfusion-associated lung injury; TACO, transfusion-associated circulatory overload (Data from Skeate & Eastlund, 2007).

RBC storage duration

Cohort studies have explored the relationship between the age of blood and clinical outcomes, including hospital-acquired infections and mortality. Interpretation of these studies is difficult because of the problems of confounding and also lack of control of the RBC storage duration. Several, but not all, studies have found associations between the transfusion of older RBCs and adverse clinical outcomes (Zallen *et al*, 1999; Mynster & Nielsen, 2001; Offner *et al*, 2002; Koch *et al*, 2008; Petillä *et al*, 2011). There are no completed randomized trials comparing standard issue RBCs with either fresher RBCs or older RBCs; several are in progress (Lacroix *et al*, 2011). Current storage regulations are based on RBCs recovering effective O_2-carrying function within 24 h of transfusion into the patient. The maximum duration of storage varies from 35 to 42 d between countries. Typically, ICU patients receive RBCs stored for 2–4 weeks, in part because blood banks often issue older RBCs as they tend to be transfused shortly after issue. RBC storage results in changes that potentially impair O_2 release (2,3 DPG depletion) and limit capillary transit (decreased nitric oxide production; membrane changes; decreased deformability; increased adherence to endothelium). Accumulation of bioactive substances (cytokines, lipid mediators) in the supernatant could also have adverse effects, especially in countries transfusing non-leucodepleted RBCs (Tinmouth *et al*, 2006).

Recommendation

- **The evidence base is insufficient to support the routine administration of 'fresher blood' to critically ill patients (Grade 2B).**

Critically ill patients with sepsis

Severe sepsis is the commonest reason for admission to the ICU in the UK, accounting for 30% of cases (Harrison *et al*, 2006), with mortality ranging from 10% to 40% (Angus *et al*, 2001). Sepsis is associated with impaired tissue DO_2 through a range of mechanisms, including respiratory failure, poor cardiac function and abnormalities of microvascular flow. The physiological rationale for using blood transfusions is to correct reductions in O_2-carrying capacity in anaemic patients.

Early stages of sepsis. Tissue hypoxia is common during the early stages of sepsis. Resuscitation strategies include respiratory and cardiovascular support. The aim is to correct a low DO_2 and meet tissue O_2 demands. Evidence of benefit from RBC transfusion in early sepsis comes from a single centre study of goal-directed resuscitation (Rivers *et al*, 2001). Both groups in the study received fluid boluses and vasopressor drugs to achieve resuscitation targets comprising a central venous pressure ≥ 8 cm H_2O and mean arterial pressure ≥ 65 mmHg. The goal-directed therapy group were monitored during the first 6 h of treatment by measuring the central venous oxygen saturation ($ScvO_2$). In cases where the $ScvO_2$ was <70%, patients received blood transfusions to maintain a haematocrit (Hct) of 0·30 (Hb $\approx$ 100 g/l) and/or dobutamine to increase cardiac output (Rivers *et al*, 2001). This intervention decreased the absolute risk of death in hospital by 16% (30·5% vs. 46·5%). One major difference between the groups was the early use of blood (64·1% vs. 18·5%). As this was a complex intervention it is difficult to attribute clinical benefit to a single component. However, when patients are anaemic and there is evidence of inadequate DO_2 during early sepsis, a target Hb of 100 g/l is probably advisable. In early sepsis, $ScvO_2$ <70%, mixed venous oxygen saturation (SvO_2) <65%, or lactate concentration >4 mmol/l are widely considered consistent with the existence of tissue hypoxia although this may not be the case for patients with later, more established sepsis. Ongoing clinical trials are evaluating the importance of early goal-directed therapy in sepsis.

Later stages of sepsis. The evidence base for RBC transfusions in patients managed during the later stages of critical illness resulting from sepsis is complex. The use of intravenous fluids, RBC transfusion and inotropic and/or vasopressor therapies to achieve 'supra-normal' values for DO_2 has been discredited (Hayes *et al*, 1994; Gattinoni *et al*, 1995). Current evidence suggests that using RBC transfusions to achieve a Hb higher than 70–90 g/l has no clinical benefit once the patient has established organ failure beyond the early resuscitation period. A subgroup analysis of patients with severe infection in the TRICC trial failed to show benefit from liberal transfusion, with more deaths in the liberally transfused group (30-d mortality: restrictive group 22·6% vs. liberal group 29·7%; Hebert *et al*, 1999). Cohort studies have also examined the association between RBC transfusion and clinical outcomes in septic patients. Studies carried out before the introduction of leucodepletion reported associations between RBC transfusion and higher mortality, whereas those performed after leucodepletion have reported lower mortality, raising the possibility that this may influence the risk to benefit profile of transfusion in these patients (Hebert *et al*, 1999; Vincent *et al*, 2002, 2008; Corwin *et al*, 2004). Ongoing trials are comparing restrictive *versus* liberal transfusion practice for patients with sepsis.

Best transfusion practice when a patient with established critical illness develops a second episode of severe sepsis during an ICU stay, such as bacteraemia or ventilator-associated pneumonia, is uncertain – no prospective trials are available to guide management in this situation. Under these circumstances clinicians should use changes in available physiological indicators of O_2 supply-demand balance, such as lactate, acid-bases status, $ScvO_2$ and SvO_2 together with clinical judgement to guide transfusion practice. Current evidence does not support transfusion to a Hb > 90–100 g/l.

Recommendations

- **In the early resuscitation phase in patients with severe sepsis, if there is clear evidence of inadequate DO_2, transfusion of RBCs to a target Hb of 90–100 g/l should be considered (Grade 2C).**
- **During the later stages of severe sepsis, a conservative approach to transfusion should be followed with a target Hb of 70–90 g/l (Grade 1B).**

RBC transfusion in neurological critical care

Cerebral DO_2 is derived from the cerebral blood flow (CBF) and the arterial O_2 content. Following brain injury, several factors converge to impair cerebral DO_2, including hypoxaemia, hypovolaemia, raised intra-cranial pressure (ICP), vasospasm, failure of cerebral autoregulation and disruption of flow-metabolism coupling (Mendelow, 1988). The cerebral tissues compensate for a fall in DO_2 by increasing their oxygen extraction ratio (O_2ER), but this compensatory mechanism has limits and damaged brain tissue with a high O_2ER is particularly vulnerable to ischaemia and secondary injury. Measurement of brain tissue O_2 partial pressure (Pb_tO_2) confirms that cerebral ischaemia is consistently associated with poor outcomes following brain injury and maintaining adequate DO_2 to prevent cerebral ischaemia is central to the management of critically ill neurological patients. Although anaemia is common in patients admitted to the ICU following brain injury, the manipulation of the Hct to maintain cerebral DO_2 remains contentious. While increasing the Hct increases O_2 carrying capacity, there is an inverse relationship between Hct and blood viscosity and

high Hct levels have been shown to reduce CBF and may predispose to cerebral ischaemia (Pendem *et al*, 2006).

There are few prospective studies that have attempted to define the optimal Hct in critically ill neurological patients and current understanding is largely drawn from single centre observational studies and expert opinion. While the use of a restrictive transfusion strategy may improve outcomes in most critically ill adults, it remains unclear whether these findings can safely be applied to neurocritical care patients (Hebert *et al*, 1999; Vincent *et al*, 2002; Corwin *et al*, 2004). There is little evidence that blood transfusion improves outcome in anaemic patients with brain injury and transfusion itself appears to be associated with unfavourable outcomes in several studies. The evidence is considered in the context of traumatic brain injury (TBI), subarachnoid haemorrhage (SAH) and ischaemic stroke.

Traumatic brain injury

Delayed cerebral ischaemia is a major cause of secondary injury following TBI (Dhar *et al*, 2009). Clinical markers of cerebral oxygenation are predictive of unfavourable outcome in these patients (Gopinath *et al*, 1994; Valadka *et al*, 1998; van den Brink *et al*, 2000). Maintenance of adequate cerebral DO_2 and prevention of cerebral ischaemia is essential (Elf *et al*, 2002; Patel *et al*, 2002; Al Thanayan *et al*, 2008). Strategies to maintain CBF focus largely on maintaining adequate cerebral perfusion pressure and the avoidance of excessively raised ICP. The Brain Trauma Foundation (BTF) has published widely adopted guidelines on the management of the above parameters (BTF, 2007). These guidelines make no recommendation on the optimal Hb target to maximize cerebral DO_2.

A number of observational studies suggest that anaemia is associated with poor outcomes following TBI (Angus *et al*, 2001; Rivers *et al*, 2001; Hollenberg *et al*, 2004; Harrison *et al*, 2006; Dellinger *et al*, 2008; Sanchez-Giron & Alvarez-Mora, 2008; Bennett-Guerrero *et al*, 2009) but the association of anaemia with mortality is not a universal finding (Carlson *et al*, 2006; Schirmer-Mikalsen *et al*, 2007). Whilst RBC transfusion improves cerebral oxygenation in most anaemic patients with TBI, the increment is frequently small and $PbtO_2$ actually appears to decrease in some patients following transfusion (Smith *et al*, 2005; Leal-Noval *et al*, 2006; Zygun *et al*, 2009). It has been speculated that this variation in clinical effect may be attributable to the storage age of blood, but this remains unproven (Leal-Noval *et al*, 2008).

The influence of RBC transfusion on the outcome of TBI is unclear. Transfusion itself is associated with poor outcome, but in cohort studies this could be due to confounding (Carlson *et al*, 2006; Salim *et al*, 2008). A retrospective subgroup analysis of the TRICC study, which included 67 patients with moderate to severe TBI, suggested no significant improvement in mortality in patients randomized to a liberal (Hb 100–120 g/l) as compared to restrictive (Hb 70–90 g/l) transfusion strategy (Hebert *et al*, 1999; McIntyre *et al*, 2006). Although underpowered, this suggests a restrictive transfusion strategy may be safe in this group of patients.

The Lund approach to the management of TBI uses a combination of measures to preserve the normal colloid and osmotic pressure across the disrupted blood brain barrier following TBI, including RBC transfusion to maintain a Hb > 100 g/l; a small single-centre non-randomized study has suggested improved outcomes using this approach, but the use of this technique remains controversial (Eker *et al*, 1998). In summary, there is insufficient evidence to reach an evidence-based conclusion on the optimal Hb target.

Recommendations

- **In patients with TBI the target Hb should be 70–90 g/l (Grade 2D).**
- **In patients with TBI and evidence of cerebral ischaemia the target Hb should be >90 g/l (Grade 2D).**

Subarachnoid haemorrhage

Anaemia is consistently associated with unfavourable outcome in patients with SAH and it is uncertain whether transfusion improves outcome (Naidech *et al*, 2006, 2007; Wartenberg *et al*, 2006; Kramer *et al*, 2008). While transfusion improves cerebral DO_2 in anaemic patients with SAH, it may decrease brain tissue oxygenation in others (Smith *et al*, 2005). Transfusion has been associated with reduced mortality in two observational studies (Dhar *et al*, 2009; Sheth *et al*, 2011). A small prospective randomized feasibility study, in which patients with SAH were randomized to a Hb target of either >100 or >115 g/l, has suggested only a trend towards improved secondary outcomes, reduced infarction rate and greater rates of functional independence with restrictive transfusion, but large randomized studies are lacking. Retrospective studies have suggested an association between RBC transfusion and poor outcome (Smith *et al*, 2004; De Georgia *et al*, 2005; Kramer *et al*, 2008; Tseng *et al*, 2008). Conversely haemodilution, targeting a Hct of approximately 0·30, has been used in combination with induced hypertension and hypervolaemia (triple-H therapy) in the treatment and prevention of cerebral vasospasm following SAH (Lee *et al*, 2006). Definitive studies demonstrating the efficacy of triple-H therapy are lacking, and it is unclear whether reduced blood viscosity and/or reduced Hb are responsible for the benefits reported (Dankbaar *et al*, 2010).

The optimal Hb in patients with SAH has not been defined. It remains unclear whether the use of RBC transfusion improves (or worsens) outcomes.

Recommendation

- **In patients with SAH the target Hb should be 80–100 g/l (Grade 2D).**

Ischaemic stroke

Observational studies in patients with ischaemic stroke suggest that the effect of Hct on outcome is u-shaped, with both high and low Hb associated with unfavourable outcome (Diamond *et al*, 2003; Kramer *et al*, 2008). Although high Hcts predispose to cerebral ischaemia and reduced reperfusion, RCTs have failed to show significant benefit from modest haemodilution (Asplund, 2002; Allport *et al*, 2005). An observational study examining CBF in patients with ischaemic stroke suggests that cerebral DO_2 is maximal with a Hct of 0·40–0·45, a similar range to that in healthy volunteers (0·42–0·45; Kusunoki *et al*, 1981; Gaehtgens & Marx, 1987). Diamond's study of 1012 patients with ischaemic stroke demonstrated that the most favourable outcomes occurred in patients with Hcts of approximately 0·45 (Diamond *et al*, 2003). The impact of transfusion in anaemic patients admitted to the ICU following ischaemic stroke has not been evaluated.

There is insufficient evidence to recommend a specific lower Hb target (or transfusion trigger) in patients admitted to neurocritical care following ischaemic stroke.

Recommendation

- **In patients presenting to the ICU with an acute ischaemic stroke the Hb should be maintained above 90 g/l (Grade 2D).**

RBC transfusion for patients with ischaemic heart disease

Anaemia is a risk factor for adverse cardiovascular events and death for patients with acute and chronic IHD (Hajjar *et al*, 2010; Carson *et al*, 2011). It is unknown if RBC transfusion modifies this relationship. Coronary perfusion occurs primarily during diastole, especially to the left ventricle, which has highest O_2 demand. The O_2ER of the coronary system is high, meaning that matching the increased O_2 demand requires an increase in coronary blood flow. Anaemia decreases the O_2 content of blood per unit volume and occlusive coronary disease restricts blood flow; these factors increase the risk of ischaemia. During critical illness, cardiac work can also be significantly increased as a result of the increased global O_2 requirements, while hypotension and tachycardia may reduce diastolic coronary blood flow. There is, therefore, biological plausibility that anaemia is tolerated poorly by patients with IHD.

Chronic ischaemic heart disease. Two cohort studies of perioperative and critically ill patients found an association between anaemia and mortality in patients with IHD (Carson *et al*, 1996; Hebert *et al*, 1997). In both studies a Hb below 90–100 g/l was associated with excess mortality. These observations were corroborated by others demonstrating associations between anaemia and higher mortality in general surgical populations, particularly among older patients (Wu *et al*, 2001; Kulier *et al*, 2007). In the TRICC trial, there were no excess adverse cardiac events in the patients managed with a restrictive transfusion strategy. The proportion of patients who suffered a myocardial infarction (MI) post-randomization was higher in the liberal group (0·7% vs. 2·9%, $P = 0·02$), and overall cardiac adverse events were also higher (13·2% vs. 21·0%, $P < 0·01$). In a *post hoc* subgroup analysis of 257 patients who were documented as suffering from IHD at baseline, there was a non-significant trend towards lower 30-d mortality among patients managed with the liberal strategy (difference in 30-d survival 4·9% (95% CI 15·3% to −5·6%); these data suggested possible benefit from liberal blood use in patients with known IHD, but the sub-group analysis was underpowered. In contrast, the recently published FOCUS study in elderly patients undergoing hip fracture surgery, which compared a liberal strategy (Hb < 100 g/l) with a restrictive strategy (symptomatic anaemia or Hb < 80 g/l), found no difference in mortality or cardiovascular complications despite 40% of patients having IHD (Carson *et al*, 2011). Similarly, the TRACs study compared similar liberal and restrictive transfusion strategies in patients undergoing elective cardiac surgery and found no differences in 30-d mortality or severe morbidity between the groups (Hajjar *et al*, 2010). Although these trials were not in critically ill patients, both included patients at high risk of coronary events.

Acute coronary syndromes. There are no large randomized trials of transfusion strategies for patients with acute coronary syndromes (ACS). A recent small pilot study in 45 patients compared liberal and conservative transfusion approaches in patients with an acute myocardial investigation (Cooper *et al*, 2011). The primary outcome measure of in-hospital death, recurrent MI or worsening of congestive cardiac failure occurred in eight patients in the liberal group and three in the conservative arm (38% vs. 13%; $P = 0·046$). The majority of our current evidence is based on the physiological rationale for maintaining a higher blood O_2 content, and data from cohort studies. Anaemic patients developing an ACS have worse outcomes (Guralnik *et al*, 2004). An older population, the widespread use of antiplatelet therapy, together with potential blood loss during percutaneous revascularization procedures, have increased the prevalence of anaemia among patients with ACS. Wu *et al* (2001) analysed approximately 79 000 US patients in the Medicare database aged >65 years presenting with acute MI. After statistical adjustment for confounding, transfusion improved 30-d mortality for patients with a Hct < 0·33%; the benefit of transfusion appeared highest among those patients with most severe anaemia (Wu *et al*, 2001). In separate cohort studies, data were analysed from trials of non-transfusion interventions for ACS (Rao *et al*, 2004; Yang *et al*, 2005). Although anaemia was associated with worse patient outcomes, these studies found no benefit from transfusion at lower Hb, and transfusion was associated with worse outcomes. Wu *et al*

(2001) compared the impact of transfusion in patients with ST segment elevation myocardial infarction (STEMI) and non-STEMI. In this cohort, anaemia (Hb < 140 g/l) was associated with increased mortality in STEMI and RBC transfusions were associated with decreased risk. Conversely, for non-STEMI cases, anaemia (<110 g/l) was associated with increased mortality, but RBC transfusions were associated with increased risk. More recent cohort studies also did not find clinical benefit from transfusion when the Hb was >80–90 g/l (Aronson *et al*, 2008; Alexander *et al*, 2009). All cohort studies are limited by confounding, and the quality of evidence is low.

Recommendations

- **Anaemic critically ill patients with stable angina should have a Hb maintained >70 g/l, but transfusion to a Hb > 100 g/l has uncertain benefit (Grade 2B).**
- **In patients suffering from ACS the Hb should be maintained at >80–90 g/l (Grade 2C).**

Weaning

Weaning consists of liberation from mechanical ventilation and extubation. Strategies to improve the speed and success of weaning are of particular relevance because they are likely to be both clinically effective and cost saving. Depending on case-mix, up to 25% of patients exhibit delayed weaning, and 5–10% continue to require ventilation at 30 d (Make, 1995; Ely *et al*, 1996). Extubation failure is associated with a sevenfold increase in mortality (Epstein *et al*, 1997; Jurban & Tobin, 1997).

Weaning failure can be associated with an imbalance in O_2 supply and demand. As weaning commences, DO_2 maybe reduced by a lower Hb and a lower cardiac output while increases in maximal O_2 uptake (VO_2) occur due to the extra work of independent breathing (Walsh & Maciver, 2009). Two studies have shown an association between anaemia and a failure to wean (Ouellette, 2005; Silver, 2005). Increasing DO_2 by increasing the Hb using transfusion potentially improves arterial O_2 content and is the physiological basis of using RBC transfusion to assist weaning.

Schonhofer *et al* (1998) studied normal and chronic obstructive pulmonary disease (COPD) patients and noted that transfusion reduced the work of breathing in the COPD group. A small, five patient case series by the same author suggested transfusion may be beneficial in weaning ventilated anaemic COPD patients (Schonhofer *et al*, 1998). However, larger studies in a more heterogeneous group of ventilated patients have shown either no benefit from transfusion, or suggested that it is associated with a worse outcome (Schonhofer *et al*, 1998; Hebert *et al*, 2001b; Vamvakas & Carven, 2002; Levy *et al*, 2005). The two largest studies are subgroup analyses of other studies – TRICC and CRIT (Hebert, 1998; Hebert *et al*, 2001b; Corwin *et al*, 2004). Both provide weak evidence because they were not designed to evaluate weaning or the effect of RBC transfusion on weaning duration. Vamvakas and Carven (2002), suggested that transfusion was associated with an increased duration of mechanical ventilation. Available evidence does not allow strong recommendations specific to transfusion and weaning from mechanical ventilation, but existing data do not support the use of a liberal transfusion strategy.

Recommendation

- **Red cell transfusion should not be used as a strategy to assist weaning from mechanical ventilation when the Hb is >70 g/l (Grade 2D).**

Conclusion: the blood transfusion anaemia paradox

Anaemia is prevalent in the critically ill and is associated with adverse outcomes. At present there are no clinically or cost-effective alternatives to RBC transfusion for rapidly increasing the Hb and restoring O_2 carrying capacity. The prospective and observational data that is available consistently suggests that transfusion of RBCs when the Hb is within the 70–90 g/l range has no beneficial effect on clinical outcomes either in the general critical care population, or in specific patient sub-groups for whom a physiological rationale for reduced anaemia tolerance exists. Importantly, it is currently uncertain whether the lack of effectiveness of blood transfusions in this population is because anaemia itself does not affect outcomes or because the risks associated with current stored red cell transfusions out weigh physiological benefits. In the future, large well designed, prospective randomized control trials are required to further evaluate the risk to benefit balance of RBC transfusion in a range of acute conditions resulting in critical illness.

Summary of recommendations

General intensive care

- A transfusion threshold of 70 g/l or below, with a target Hb range of 70–90 g/l, should be the default for all critically ill patients, unless specific co-morbidities or acute illness-related factors modify clinical decision-making (Grade 1B).
- Transfusion triggers should not exceed 90 g/l in most critically ill patients (Grade 1B).

Alternatives to red cell transfusion

- Erythropoietin should not be used to treat anaemia in critically ill patients until further safety and efficacy data are available (Grade 1B).

- In the absence of clear evidence of iron deficiency, routine iron supplementation is not recommended during critical illness (Grade 2D).

Blood sampling techniques

- The introduction of blood conservation devices should be considered to reduce phlebotomy-associated blood loss (Grade 1C).
- Paediatric blood sampling tubes can be effective for reducing iatrogenic blood loss (Grade 2C).

TRALI and TACO

- Pre-transfusion clinical assessment should be undertaken including concomitant medical conditions that increase the risk of TACO (cardiac failure, renal impairment, hypoalbuminaemia, fluid overload; Grade 1D).
- Attention to the rate of transfusion together with careful fluid balance and appropriate use of diuretic cover (e.g. furosemide) can reduce the risk of TACO (Grade 1D).
- Patients developing acute dyspnoea with hypoxia and bilateral pulmonary infiltrates during or within 6 h of transfusion should be carefully assessed for the probability of TRALI and patients should be admitted to a critical care area for supportive treatment and monitoring (Grade 1D).
- Any adverse events or reactions related to transfusion should be appropriately investigated and reported via systems for local risk management, and also to National Haemovigilance Shemes (Grade 1D).

Red cell storage duration

- The evidence base is insufficient to support the administration of 'fresher blood' to critically ill patients (Grade 2B).

Sepsis

- In the early resuscitation of patients with severe sepsis, if there is clear evidence of inadequate DO_2, transfusion of RBCs to a target Hb of 90–100 g/l should be considered (Grade 2C).
- During the later stages of severe sepsis, a restrictive approach to transfusion should be followed with a target Hb of 70–90 g/l (Grade 1B).

Neurocritical care

- In patients with TBI the target Hb should be 70–90 g/l (Grade 2D).
- In patients with TBI and evidence of cerebral ischaemia the target Hb should be >90 g/l (Grade 2D).
- In patients with SAH the target Hb should be 80–100 g/l (Grade 2D).
- In patients presenting to the ICU with an acute ischaemic stroke the Hb should be maintained above 90 g/l (Grade 2D).

Ischaemic heart disease

- In patients suffering from ACS the Hb should be maintained at >80 g/l (Grade 2C).
- Anaemic critically ill patients with stable angina should have a Hb maintained >70 g/l (Grade 2C).

Weaning

- Red cell transfusion transfusion should not be used as a strategy to assist weaning from mechanical ventilation when the Hb is >70 g/l (Grade 2C).

Disclaimer

While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology nor the publishers accept any legal responsibility for the content of these guidelines.

Appendix 1

Summary of the literature used to write the guideline and provide the key recommendations

Study	Design and setting	Main result
Phlebotomy and blood conservation devices		
Foulke and Harlow (1989)	Prospective single centre study of 151 patients following introduction of paediatric phlebotomy tubes for sampling	Daily blood loss reduced from 62·6 ± 4 to 43·6 ± 3 ml Total diagnostic blood loss 316 ± 81 vs. 168 ± 18 ml, representing an average 17% decreased transfusion requirements
Corwin *et al* (1995)	Retrospective, single centre study	23% of patients admitted to the ICU for >7 d, 85% were transfused (9·5 ± 0·8 units) Patients receiving blood transfusion were phlebotomized 61–70 ml/d Low Hct was only identified in <25% of patients
MacIsaac *et al* (2003)	Randomized controlled trial of 160 patients (80 in intervention arm, 80 controls) Unblinded exposure to blood conservation device (VAMP Plus system, Baxter Healthcare)	Both groups similar Hb on ICU admission VAMP patients lost significantly less blood than controls
Chant *et al* (2006)	Retrospective single centre observational study of 155 patients	Mean daily phlebotomy volume 13·3 ± 7·3 ml Small increases in average phlebotomy by 3·5 ml/d were associated with a doubling in the odds of being transfused at day 21
Harber *et al* (2006)	Randomized control study following a highly conservative phlebotomy protocol	16% of ANZICS ICUs return dead space volume Median blood loss fell from 40 to 8 ml $P < 0{\cdot}001$
Sanchez-Giron and Alvarez-Mora (2008)	Prospective, observational study of 246 patients Unit introduced small volume, 'paediatric' blood sampling tubes	Median sampling loss reduced from 19·9 to 5·1 ml All tests could be performed and no additional tests were required
Mukhopadhyay *et al* (2010)	Before and after intervention study in a medical ICU, assessing the impact of a restrictive transfusion strategy adopted and data on Hb prior to and after the introduction of the VAMP were assessed	Use of the blood conservation device decreased requirements for RBC transfusion. The device also resulted in a smaller decrease in Hb in ICU
Red cell storage duration		
Purdy *et al* (1997)	Single centre, retrospective cohort study: 31 patients Non-leucocyte deplete blood	First study to suggest a correlation between mortality and the age of transfused RBCs 32 patients with sepsis admitted during the study time frame, 12 survived. 31 transfused Baseline characteristics between the survivors and non-survivors were not statistically significant Median age of units transfused to survivors was 17 vs. 25 d in non-survivors
Zallen *et al* (1999)	Single centre, retrospective analysis of prospectively collected database: 63 patients	Age of transfused RBCs is an independent risk factor for MOF 63 patients identified, 23 developed MOF No difference in ISS and transfusion requirement between MOF −ve and MOF +ve patients, MOF +ve patients were significantly older 46 ± 4·7 vs. 33 ± 2·3 years Mean age of transfused blood was older in MOF +ve patients, 30·5 ± 1·6 vs. 24 ± 0·5 d Multivariate analysis identified age of transfused RBCs in the first 6 h as an independent risk factor for MOF
Vamvakas and Carven (2000)	Retrospective cohort study: 268 patients	Study does not support an association between transfusion of old blood and clinical mortality

Appendix 1 (*Continued*)

Study	Design and setting	Main result
Mynster and Nielsen (2001)	Single centre prospective observational study: 740 patients	Transfusion of leucocyte-depleted RBCs <21 d old may be an independent risk factor for recurrence of colorectal malignancy Survival of patients who exclusively received blood <21 d old was 2·5 vs. 3·7 years when compared to those patients ($P = 0·12$) who received any blood and 4·6 years for those who received no blood Among patients who underwent curative resection, 532, the hazard ratio of disease recurrence was 1·5 (95% CI; 1·1–2·2) in those transfused vs. 1 (95% CI 0·7–1·4)
Offner *et al* (2002)	Prospective cohort study, enrolled patients with an ISS score >15: 61 patients	Transfusion of older blood is associated with increased infection after major injury Major infections developed in 32 patients ISS not significantly different between patients who did and did not develop an infection For each unit of blood transfused over 14 d old the risk of infection increased by 13% Dose response and increased duration of storage increased the risk of infection
Gajic *et al* (2004)	Retrospective analysis of database: 181 patients	Thrombocytopenia and transfusion of fresh frozen plasma are associated with ALI, not the age of RBCs 181 patients identified, no difference in the average age of RBCs between those who developed ALI and those who did not; 18·5 vs. 17·5 d ($P = 0·22$) Transfusion of FFP associated with an OR of 3·2 of developing ALI ($P = 0·023$)
Walsh *et al* (2004b)	Prospective double-blind randomized control trial: 22 patients Patients randomized to either units ≤ 5 d old or units ≥ 20 d old, if Hb <90 g/l	Transfusion of stored leukocyte-depleted RBCs to euvolaemic, anaemic critically ill patients has no clinically significant adverse effects on gastric tonometry or global indexes of tissue perfusion
Murrell *et al* (2005)	Prospective cohort study: 275 patients	The quantity of aged blood is an independent risk factor associated with longer length of ICU care but not mortality Patients who received older blood had a significantly longer ICU stay (RR 1·15, 95% CI: 1·1–1·2) Transfusion of older blood, did not have a significant impact on mortality rate (OR 1·2, 95% CI: 0·87–1·64)
Hebert *et al* (2005)	Double-blind, multicentre, randomized controlled study: 57 patients Patients randomized to receive RBCs ≤ 8 d old *versus* conventional therapy	There were no differences in prolonged respiratory, cardiovascular or renal support. This trial does not demonstrate a detrimental impact of increased red cell storage Median storage time was 4 d in the experimental group and 19 d in the intervention group 73% of patients received RBCs with storage times that corresponded to their allocation more than 90% of the time Group receiving blood ≤ 8 d old received $5·5 \pm 3·3$ units compared to $3·3 \pm 3·3$ units in the intervention arm 27% of patients had a life-threatening complication in the intervention group compared to 13% in the standard group, $P = 0·31$

Appendix 1 (*Continued*)

Study	Design and setting	Main result
van de Watering *et al* (2006)	Single centre, retrospective study: 2732 patients	No justification for the maximum storage time of blood on survival or ICU length of stay. No independent effect of storage time
Koch *et al* (2008)	Retrospective study 2872 patients received blood <14 d old 3130 patients received blood >14 d old	In patients undergoing cardiac surgery transfusion of red cells >2 weeks old was associated with an increased risk of death and significant postoperative complications 2872 patients received 8802 units of blood <14 d old 3130 patients received 10 872 units of blood >14 d old Patients given older blood had a greater mortality 2·8% vs. 1·4%, $P = 0·004$ Patients given older blood were more likely to receive prolonged ventilatory support 9·7% vs. 5·6%, $P < 0·001$ Patients given older blood were more likely to have renal failure 2·7% vs. 1·6%, $P = 0·001$
Petillä *et al* (2011)	Retrospective, multicentre observational study in 47 ICUs, Included 757 critically ill adult patients	In critically ill patients in Australia and New Zealand, exposure to older RBCs is independently associated with an increased risk of death Comparing quartiles, mean maximum red cell age 22·7 d; mortality 121/568 (21·3%) vs. mean maximum red cell age 7·7 d hospital mortality 25/189 (13·2%). An absolute risk reduction of 8·1% (CI 2·2–14%) After adjustment for APACHEII score and other blood component transfusion, pre-transfusion Hb and cardiac surgery the OR for death for patients exposed to the older three quartiles of blood was 2·01 (CI 1·07–3·77)
Adult studies evaluating the impact of transfusion on mortality and morbidity in sepsis		
Lorente *et al* (1993)	Prospective, case–control, crossover study: 16 patients Dobutamine and PRBC transfusion VO_2 assessed	VO_2 depends more on blood flow than total DO_2
Marik and Sibbald (1993)	Prospective controlled intervention study: 23 patients Transfusion of 3 units of RBCs and VO_2 measured	No improvement in VO_2 with transfusion despite increased DO_2
Gramm *et al* (1996)	Prospective case-series: 19 patients Transfusion of 2 units RBCs in patients on a surgical ICU	In patients with a normal lactate, transfusion had no impact on VO_2 although DO_2 was increased
Hebert *et al* (1999)	Randomized controlled trial: 838 patients Randomization to one of two transfusion strategies *Liberal* – Hb maintained above 100 g/l *Restrictive* – Hb maintained at 70–90 g/l	A restrictive transfusion strategy is as effective and preferable to a liberal transfusion strategy in critically ill patients, with the exception of ischaemic heart disease
Rivers *et al* (2001)	Single centre, randomized control study: 263 patients Combined series of interventions, including targeting Hct > 0·30%	Early Goal Directed Therapy associated with improved outcome. Mortality 30·5% vs. 46·5% ($P = 0·009$)
Hebert *et al* (2003, 1999)	Retrospective before and after cohort study: 14 786 patients	Significant reduction in mortality rate 6·19% vs. 7·03% $P = 0·04$ Lower mortality post-leucodepletion
Sakr *et al* (2007)	Prospective observational study: 35 patients Transfusion of 1–2 units of RBCs	Sublingual circulation globally unaltered by RBC transfusion in septic patients
Sakr *et al* (2010)	Multicentre, retrospective case series: 5925 patients	Blood transfusion associated with a lower mortality in patients with sepsis over the age of 66 years

Appendix 1 (*Continued*)

Study	Design and setting	Main result
Vincent *et al* (2008)	Multicentre, retrospective case series: 3147 patients	Increased 30-d survival following transfusion in 821 matched pairs ($P = 0{\cdot}004$)
Hollenberg *et al* (2004)	Practice guideline	Target Hb 80–100 g/l → should consider higher threshold if evidence of impaired O_2 delivery
Dellinger *et al* (2008)	Practice guideline 'Surviving sepsis guidelines'	In the first 6 h of resuscitation target Hct > 0·30% If $ScvO_2 < 70\%$ or $SvO_2 < 65\%$
Green *et al* (2008)	Practice guideline	If $ScvO_2 < 70\%$ – transfuse to Hct > 0·30%
Transfusion in neurocritical care		
Robertson *et al* (1995)	Retrospective, single centre study: 102 patients	Lower Hb associated with unfavourable Glasgow outcome scale at 6 months
Smith *et al* (2004)	Retrospective, single centre study: 441 patients	Intraoperative transfusion associated with worse outcome at 6 months Postoperative transfusion possibly associated with vasospasm
McIntyre *et al* (2006)	Retrospective, single centre study: 67 patients	30 d mortality 17% in restrictive group vs. 13% in the liberal group $P = 0{\cdot}64$
Carlson *et al* (2006)	Retrospective, single centre study: 169 patients	Number of days Hct < 0·30% associated with better outcome Lowest Hct associated with worse outcome
Naidech *et al* (2006)	Retrospective, single centre study: 245 patients	Admission Hb and decline in Hb during admission correlated with a poor outcome
Van Beek *et al* (2006)	Post hoc analysis of several RCTs, multicentre: 3872 patients	Lower Hb associated with a higher risk of death or long-term severe neurological impairment at 3–6 months: OR = 0·69, CI 0·6–0·81)
Wartenberg *et al* (2006)	Retrospective, single centre study: 576 patients	Anaemia associated with worse outcome at 3 months
Schirmer-Mikalsen *et al* (2007)	Retrospective, single centre study: 133 patients	Single Hb < 80 g/l did not predict adverse outcome
Steyerberg *et al* (2008)	Post hoc analysis of RCTs: combined 3554 patients	Lower Hb associated with poor 3- and 6-month outcomes. OR 143 vs. 108 g/l = 0·78, CI 0·7–0·87
Duane *et al* (2008)	Retrospective, single centre study: 788 patients	Lowest Hb in first 72 h associated with greater mortality. OR = 0·86 RBC transfusions not associated with mortality but increased incidence of nosocomial infection
Salim *et al* (2008)	Retrospective, single centre study: 1150 patients	RBC transfusion associated with increased mortality OR 2·2, $P = 0{\cdot}004$ and increased complications OR 3·7, $P = 0{\cdot}0001$
George *et al* (2008)	Retrospective, single centre study: 82 patients	RBC transfusion predicted mortality
Naidech *et al* (2008)	Retrospective, single centre study: 611 patients	Higher 2 week Hb associated with better outcome
Kramer *et al* (2008)	Retrospective, single centre study: 245 patients	Nadir Hb < 100 g/l, associated with increased mortality Transfusion associated with mortality OR 4·3, 95% CI 2·5–9·1; $P < 0{\cdot}01$
Tseng *et al* (2008)	Post hoc analysis of 2 RCTs: 160 patients	Transfusion associated with worse outcomes
Broessner *et al* (2009)	Cohort study 292 patients	Transfusion not associated with an increased ICU mortality nor a worse outcome at 6 months
De Georgia *et al* (2005)	Retrospective, single centre study: 166 patients	Transfusion associated with worse outcome in patients who demonstrated vasospasm OR 2·9, CI 1·1–7·8)
Ischaemic heart disease		
Hebert *et al* (1997)	Retrospective: 4470 patients	Patients who died in the ICU had a lower Hb than survivors, 95 g/l ± 26 vs. 104 g/l ± 23, $P = 0{\cdot}03$ Patients with cardiac disease trend towards an increased mortality when Hb < 95 g/l 55% vs. 42%, $P = 0{\cdot}09$ The mortality rate fell when patients with IHD were transfused

Appendix 1 (*Continued*)

Study	Design and setting	Main result
Hebert *et al* (2001a)	Randomized control trial: 257 patients	No difference in mortality between two arms 23% vs. 23% $P = 1{\cdot}0$
	Subgroup analysis of the TRICC study Hebert *et al*, 1999	Amongst the subset of patients with IHD there was a non-significant trend towards increased mortality, $P = 0{\cdot}3$
Wu *et al* (2001)	Retrospective study of Cooperative Cardiovascular Project database: 78 974 patients >65 years	Patients with lower Hct values on admission had higher 30-d mortality rates Blood transfusion was associated with a lower short term mortality in patients with a Hct < 30% and maybe effective in patients with a Hct as high as 33% Patients transfused with a Hct > 36% had an increased 30-d mortality
Rao *et al* (2004)	Retrospective analysis of data collected in three large cardiology secondary intervention trials	2401 patients received at least 1 unit of RBCs, patients who received transfusion were older and had more co-morbid illness, 8% vs. 3%; $P < 0{\cdot}001$ Blood transfusion in the setting of ACS is associated with higher mortality and this relationship persisted after adjustment for other predictive factors and timing of events
Sabatine *et al* (2005)	Retrospective review: 39 922 patients	Reverse J-shaped relationship observed between baseline Hb and major adverse cardiovascular events Anaemia is a powerful and independent predictor of major adverse cardiovascular events in patients across the spectrum of ACS
Yang *et al* (2005)	Retrospective review, 85 111 patients	Non-CABG patients who received RBCs had a greater risk of death 11·5% vs. 3·8% Transfusion is common in ACS; patients who undergo transfusion are sicker at baseline and experience a higher risk of adverse outcomes
Singla *et al* (2007)	Prospective cohort study	Transfusion in anaemic patients admitted with suspected ACS led to a significant increase in 30-d recurrent MI or death OR 3·05, 95% CI 1·8–5·17, $P < 0{\cdot}001$
Hajjar *et al* (2010)	Prospective, randomized controlled study, compared a restrictive and liberal transfusion strategy in 502 patients undergoing elective cardiac surgery	30 d all cause mortality 10% vs. 11%. However, relatively high 'restrictive' threshold
Carson *et al* (2011)	Prospective, randomized controlled study compared a liberal vs. restrictive transfusion strategy in patients with or who had risk factors for cardiovascular disease undergoing hip fracture surgery	Rates of death 7·6 vs. 6·6 The rates of complications were similar in the two groups
Studies focusing on the question the role of red cell transfusion to aid weaning from mechanical ventilation		
Schonhofer *et al* (1998)	Tertiary referral centre: 20 patients Patients received 1 unit of RBCs for each 10 g/l that their Hb was <110 g/l	Red cell transfusion in anaemic patients with COPD leads to a significant reduction in the work of breathing and minute ventilation
Hebert *et al* (2001b)	Heterogenous population of critically ill patients. Subgroup analysis of the TRICC study: 713 patients	Duration of mechanical ventilation in the liberal and restrictive arms 8·3 ± 8·1 vs. 8·3 ± 8·1 d respectively Relative risk of extubation success in patients ventilated for >7 d 1·1 (CI: 0·84–1·45, $P = 0{\cdot}47$) No evidence that a liberal transfusion strategy decreased the duration of mechanical ventilation
Vamvakas and Carven (2002)	Retrospective cohort study: 416 patients	Allogeneic blood transfusion may impair postoperative pulmonary function

Appendix 1 (*Continued*)

Study	Design and setting	Main result
Levy *et al* (2005)	284 medical/surgical ICUs: 4892 patients	More patients receiving mechanical ventilation received transfusions, 49% vs. 33%, $P < 0{\cdot}0001$ Ventilated patients appear to be transfused at higher thresholds and the justification for this practice is yet to be elucidated
Rana *et al* (2006a)	4 medical/surgical ICUs: 1351 patients	Incidence of TRALI 1 in 534 to 1 in 1271 transfusions Incidence of TACO 1 in 356 transfusion Pulmonary oedema frequently occurs after transfusion
Walsh and Maciver (2009)	Clinical practice scenarios, survey of practising intensivists opinions	UK intensivists believe a more liberal transfusion is required for patients failing to wean from mechanical ventilation

Note: 95% CI, 95% confidence interval; ACS, acute coronary syndrome; ALI, acute lung injury; ANZICS, Australian and New Zealand Intensive Care Society; CABG, coronary artery bypass graft surgery; COPD, chronic obstructive pulmonary disease; DO_2, oxygen delivery; FFP, fresh frozen plasma; ICU, intensive care unit; IHD, Ischaemic Heart Disease; ISS, injury severity score; MI, nyocarial infarction; MOF, multiple organ failure; OR, odds ratio; PBRC, Packed red blood cells; RCT, randomized controlled trial; RR, relative risk; $ScvO_2$, central venous oxygen saturation; SvO_2, mixed venous oxygen saturation; TACO, transfusion-associated circulatory overload; TRALI, transfusion-associated lung injury; TRICC, Transfusion requirements in critical care; VAMP, Venous Arterial blood Management Protection; VO_2, maximal oxygen uptake.

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