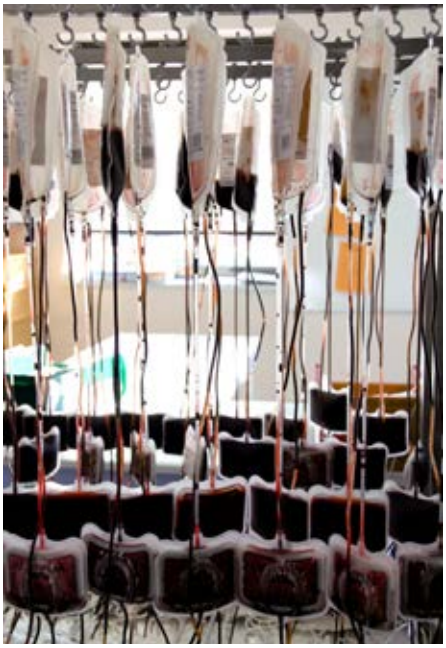
thebmj.com
- Blood Transfusion Outfit (bmj.2.4117.1084)
- Restrictive approach to transfusion best in upper gastrointestinal bleeding (*BMJ* 2013;346:f71)

Do liberal blood transfusions cause more harm than good?

Guidelines and evidence from randomised controlled trials and meta-analyses increasingly support restrictive blood transfusion, but it is being implemented only slowly, explain **Lawrence Tim Goodnough** and **Michael Murphy**. They argue that electronic systems for clinical decision support could improve blood use



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Blood transfusions have been identified as one of the most overused therapies both in the United States and the UK. In England the National Comparative Audit of Blood Transfusion programme has found inappropriate use over several years (table 1) and there have been various initiatives to improve use.[1] Choosing Wisely, a US initiative that supports evidence based care to minimise the harms of overtreatment, has highlighted five recommendations for minimising blood use (box 1).[2]

Audits in England show considerable variation in the use of transfusion for patients having cardiac surgery (fig 1), and studies over 20 years indicate that a substantial amount of blood is being transfused inappropriately in these patients.[3 4] Variation has also been observed in transfusion rates among patients having other types of major surgery,[5] as well as in transfusions among developed countries worldwide (fig 2, thebmj.com). This variation in the use of transfusion has persisted, despite the publication of numerous clinical practice guidelines setting thresholds of 60-80 g/L, which might have been expected to standardise practice (see table on thebmj.com).[6] Here, we look at the evidence for restrictive transfusion policies and discuss how we can increase adoption.

KEY MESSAGES
- Meta-analyses of patients randomised to restricted transfusion have shown reductions in cardiac events, re-bleeding, bacterial infection and mortality.
- Clinical decision tools show promise for education and reduction of transfusion in clinical practice
- The Choosing Wisely Campaign has highlighted five ways of reducing transfusion and waste of blood products
- Further research is needed to resolve uncertainties about transfusion in patients with serious co-morbidities, and how the age and storage of blood affects patient outcomes

Box 1 | Recommendations on blood transfusion for the Choosing Wisely campaign[2]
- Don't transfuse more units of blood than absolutely necessary. A restrictive threshold (70-80 g/L) should be used for most stable patients without evidence of inadequate tissue oxygenation. Single unit red cell transfusions should be the standard for non-bleeding patients
- Don't transfuse red blood cells for iron deficiency without haemodynamic instability
- Don't routinely use blood products to reverse warfarin. This can usually be achieved with vitamin K alone
- Don't perform serial blood counts on clinically stable patients. Blood counts should be obtained only when there is reason to believe that a new clinically important abnormality will be detected
- Don't transfuse O negative blood except to O negative patients and in emergencies to women of child bearing potential with unknown blood group

Restrictive transfusion

Restrictive transfusion is the policy of giving blood transfusions only when the potential benefits are deemed to outweigh potential risks, with the goal of minimising the use of blood.[7] Blood transfusion has long been associated with short and long term risks for patients.[8] Research to improve blood safety and to promote restrictive blood transfusion practices first gained impetus in the 1970s and the 1980s in response to the recognition that hepatitis C virus and HIV were transmitted by blood transfusion.[9] Since then, despite substantial advances in blood safety with respect to infection, evidence has accumulated to indicate that blood transfusion is associated with adverse patient outcomes (box 2).[10] Institutional experience and national databases indicate that a restrictive blood transfusion approach and other measures to minimise the use of transfusion such as pre-operative management of anaemia, are being implemented[11] as best practice.

Use of blood worldwide has begun to fall over the past three years in many countries (fig 2). For example, use in the United States has fallen by about 3% annually since 2010.[7] And in the UK the demand for red blood cell units, which steadily increased during the 1990s, has fallen since 2000 (fig 3).[1] Several factors may have driven this, including successive Department of Health, National Blood Transfusion Committee, and NHS Blood and Transplant (NHSBT) initiatives to improve patient blood management[12]; the National Comparative Audit of Blood Transfusion programme; concern about the transmission of variant Creutzfeldt-Jakob disease by transfusion; the costs of blood units provided by blood services; and hospital costs such as compatibility testing, administration of blood, and the management of any complications. However, the continuing variation in the use of blood suggests that overall usage could be reduced further.

Evidence for restricted transfusion

Although the risks of transfusing blood are known and can be quantified, any benefits are

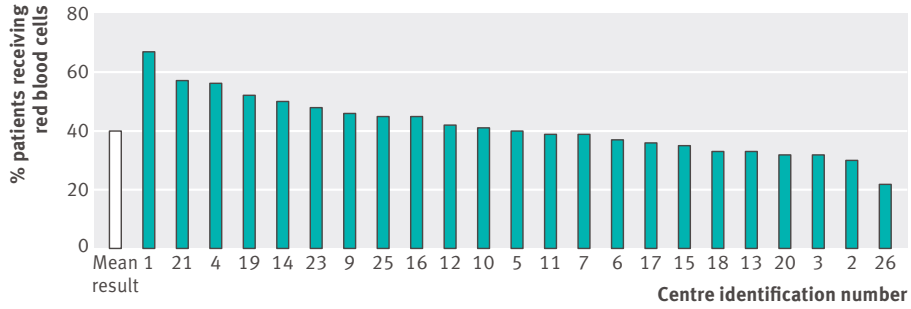

Fig 1 | Variation in use of red blood cell transfusions between centres doing primary coronary artery bypass surgery in England, 2011[3]

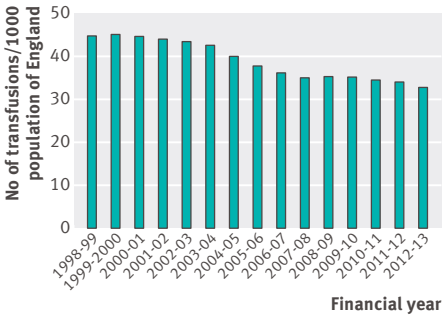

Fig 3 | Units of red cells issued from NHS Blood and Transplant per 1000 population, England, 1998-99 to 2013-14[1]

less certain and not easily quantifiable. A 2012 Cochrane meta-analysis of 19 trials in over 6000 patients compared restrictive transfusion to liberal transfusion strategies.[13] Patients randomised to restrictive transfusions had a lower in-hospital mortality (relative risk=0.77, 95% confidence interval 0.62 to 0.95), but there was no difference in 30 day mortality (0.85, 0.70 to 1.03). A more recent meta-analysis found that a restrictive red blood cell transfusion strategy aiming to allow a haemoglobin concentration as low as 70 g/L reduced cardiac events, rebleeding, bacterial infections, and mortality.[14]

Randomised controlled trials in various clinical settings provide good evidence for restrictive transfusion. Three non-inferiority trials in adults in intensive care units,[15] having cardiothoracic surgery[16] or having repair of hip fracture[17] showed that patients could tolerate a restrictive transfusion strategy with haemoglobin concentrations of 70-80 g/L. Clinical outcomes in patients on the restrictive strategy were equivalent to those in patients transfused to maintain concentrations >100 g/L. A fourth study in adults with upper gastrointestinal bleeding found that a more restrictive transfusion practice (transfusion when haemoglobin was < 70 g/L) had improved rebleeding rates and 45 day mortality compared with patients transfused to maintain concentration > 90 g/L.[18] A fifth trial in children in critical care found that a threshold of 70 g/L was safe in patients who were haemodynamically stable.[19]

Although evidence from meta-analyses and these five trials is persuasive, there remains some uncertainty. For example, evidence from controlled trials of transfusions for anaemia in critical care patients with heart disease or acute coronary syndromes is less robust. A multicentre trial of 110 patients randomised to receive blood transfusions at haemoglobin concentrations of <80 g/L or 100 g/L found that the liberal transfusion strategy was associated with a lower mortality but with similar rates of myocardial infarction or unscheduled coronary artery bypass surgery.[20] A more liberal approach in the management of anaemia may therefore be warranted in patients at risk,[21] such as those with acute coronary syndromes. Most recently a multicentre randomised trial of sepsis patients who received one unit of red blood cells when haemoglobin was ≤ 70 g/L or ≤ 90 g/L found no difference in 90 day mortality (43% *v* 45%, P=0.44).[22]

Although some have called for an absolute haemoglobin threshold for transfusion based on these trials,[23] it is important to incorporate clinical judgment into transfusion decisions, taking into account patient risk factors and comorbidities. Given the increasing evidence that shows blood transfusions are poorly effective and possibly harmful, the guiding principle for transfusion therapy should be "less is more." Guidelines instruct clinicians to take account of individual patient circumstances before deciding on transfusion.[6] Most guidelines agree that transfusion should not take place when the haemoglobin concentration is >100 g/L but should be considered at concentrations <70-80 g/L (see table on thebmj.com).

Storage

Understanding the basic science that underpins the evidence is complex. Intuitively, if a patient has anaemia (reduction in red blood cell mass), the temptation is to correct it with transfusion; it is difficult to reason why patient outcomes with liberal transfusion are worse. Some of the lack of efficacy of blood may be down to storage. Transfused blood cells show imperfections, known as storage lesions, such as a decrease in membrane deformability and metabolic changes.[24] Longer duration of storage of red blood cells has been associated with increased morbidity as well as short and long term mortality in patients having open heart surgery.[25] However, the recently completed RECESS trial found no difference in morbidity (multiorgan system dysfunction) or mortality in adults having cardiopulmonary

Table 1 | Summary of the inappropriate use of blood from audits of blood use in England[1]

Audit	Year	No of hospitals	No of cases audited	Inappropriate use	Guidelines for audit standards
Red cell transfusion	2002	All 13 hospitals in Northern Ireland	360	19% of patients inappropriately transfused and 29% overtransfused	BCSH, 2001: clinical use of red cell transfusion
Red cells in hip replacement	2007	139/167 (83%)	7465	48% of patients	British Orthopaedic Association 2005
Upper gastrointestinal bleeding	2007	217/257 (84%)	6750	15% of RBCs, 42% of platelets, 27% of FFP	British Society of Gastroenterology 2002
Red cell transfusion	2008	26/56 (46%) hospitals in two regions	1113	19.5% of transfusions	BCSH, 2001: clinical use of red cell transfusion
Fresh frozen plasma	2009	186/248 (75%)	5032	43% of transfusions to adults, 48% to children, 62% to infants	BCSH, 2004: clinical use of fresh frozen plasma, cryoprecipitate, and cryosupernatant
Platelets in haematology	2011	139/153 (91%)	3296	27% of transfusions	BCSH, 2003: use of platelet transfusions
Cryoprecipitate	2012	43/82 (52%) from 3 regions	449	25% of transfusions	BCSH, 2004: clinical use of fresh frozen plasma, cryoprecipitate, and cryosupernatant

BCSH=British Committee for Standards in Haematology (guidelines available on www.bcshguidlines.org).

Box 2 | Potential risks of blood transfusion

- Infectious agents—for example, hepatitis viruses, HIV, West Nile virus, bacteria (platelets only), cytomegalovirus, syphilis, dengue fever virus, malaria, new variant Creutzfeldt-Jakob disease
- Transfusion reactions
- Medical errors (wrong blood given because of mislabelled specimen or patient misidentification)
- Transfusion associated acute lung injury
- Transfusion associated circulatory overload
- Iron overload
- Immunomodulation
- Clinical effects due to storage of blood

Table 2 | Transfusion practices and patient outcomes for patients treated in Stanford hospital and clinics after introduction of computerised decision support in 2010[34]

	2009	2010	2011	2012	2013
Units of red blood cells transfused	30 194	25 304	23 136	23 008	22 991
% of patients transfused	21.9	18.9	17.8	17.5	17.0
Death rate/1000 discharges*	2.8	2.6	2.5	2.5	2.4
No of readmissions within 30 days/1000 discharges	10.7	11.5	11.0	10.6	10.5
Mean length of stay (days)*	5.63	5.55	5.52	5.59	5.49
All patients					
Admission haemoglobin (g/L)	116	117	116	116	115
Discharge haemoglobin (g/L)	109	108	107	107	106
Transfused patients					
Admission haemoglobin (g/L)	100	99	97	97	95
Discharge haemoglobin (g/L)	98	95	91	91	88

*P < 0.05.

bypass who received blood stored for a median of either 7 days or 28 days.[26 27] The Age of Blood Evaluation (ABLE) trial is studying critical care patients randomised to receive either standard issue red blood cell units or units stored for ≤7 days with a primary outcome of 90 day all cause mortality.[28] These results will provide further insight into whether storage lesions affect patient outcomes.

Action to reduce transfusion

A recent meta-analysis of 18 randomised controlled clinical trials showed that cohorts treated according to a restrictive transfusion strategy had a reduced risk of healthcare associated infection compared with those treated according to a liberal transfusion strategy.[29]

One way to implement a strategy is with mandatory clinical decision aids. A systematic review[30] of clinical decision support found that 68% of the interventions improved clinical practice in various clinical settings. Electronic ordering with a clinical decision support tool can alert clinicians to inappropriate orders and facilitate audit. Clinical decision tools have been shown to reduce inappropriate blood transfusion, although data are limited.[31 32]

Computerised ordering systems also allow collection of clinical information relevant to the indication for transfusion, and doctors can then receive a "best practices alert" based on the patient's most recent haemoglobin measurement as well as a link to relevant literature.[33] Such systems seem to be associated with improved blood use.[34] Ideally, the tool should also provide a mechanism to capture the reasons for overriding alerts to provide an understanding of apparent inappropriate transfusions. This could be useful for further education.

Clinical decision tools in general do have limitations. For example, decisions are made by teams not individuals; guidelines and evidence may not be fully developed to support best practice recommendations; patient populations may be too heterogeneous for a one size fits all best practice alert; or improved patient outcomes may not be demonstrably linked to the clinical decision support intervention.[35] However, the children's and adult hospitals at Stanford University Medical Center improved blood use from 2010 to 2013 after implementing computerised ordering symptoms with decision tools (table 2).[33 36 37] Before the initiation of clinical decision support, 57-66% of orders for red blood cells were for patients with a pretransfusion haemoglobin above 80 g/L; this figure fell to 30% after the system was introduced despite concurrent increases in the number of patients discharged, patient days at risk, case mix complexity, volumes of selected surgeries, and solid organ and stem cell transplantations. The authors estimated that annual net savings were £980 000 (€1.2m; $1.5m) in red blood cell purchase costs alone. These changes to restrictive transfusion practices have been associated with hospital-wide lower inpatient mortality and lengths of stay.[37]

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A similar clinical decision support system is being implemented at Oxford university hospitals.[38] In haematology, where the system was first implemented, the proportion of non-compliant red blood cell transfusion and platelet transfusion requests fell over six months (from 62.4% to 33.3% for red blood cells (P<0.01) and from 46.4% to 13% (P< 0.001) for platelets, unpublished observations).

Further evidence comes from a multi-institutional implementation of clinical decision support for patients having cardiothoracic surgery, in which haemoglobin transfusion threshold levels dropped from 81 g/L to 76 g/L after implementation; the percentage of patients transfused postoperatively decreased from 50.3% to 40.8%; mean red blood cell units transfused postoperatively decreased from 1.6 to 1.2 units; and postoperative surgical site infections fell from 3.1% to 1.1% of patients.[39]

The future

Blood use in hospitals is under renewed scrutiny not only in relation to clinical patient outcomes but also because of the potential for substantial cost savings. A unit of red blood cells costs £121 in England, and there are the further costs of laboratory testing, storage of blood, administering blood, and monitoring patients.

Recent studies suggest that the use of computerised ordering with clinical decision support may help implement restrictive transfusion practices. Further work is needed to understand how to further configure these systems to optimise their influence on clinicians' behaviour. In addition, the remit for tools for clinical decision support in blood management could be expanded to include algorithms for the investigation and management of anaemia, and the use of measures to reduce blood use in surgery.

Further research is also needed to resolve continuing uncertainties surrounding the optimal management of anaemic patients with serious comorbidities such as cardiac and respiratory disease, the use of plasma products and platelets in patients with haemostatic problems, and whether fresh blood is associated with better clinical outcomes than stored blood.

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