Review

Patient blood management to reduce surgical risk

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Background: **Preoperative anaemia and perioperative blood transfusion are both identifiable and preventable surgical risks. Patient blood management is a multimodal approach to address this issue. It focuses on three pillars of care: the detection and treatment of preoperative anaemia; the reduction of perioperative blood loss; and harnessing and optimizing the patient-specific physiological reserve of anaemia, including restrictive haemoglobin transfusion triggers. This article reviews why patient blood management is needed and strategies for its incorporation into surgical pathways.**

Methods: **Studies investigating the three pillars of patient blood management were identified using PubMed, focusing on recent evidence-based guidance for perioperative management.**

Results: **Anaemia is common in surgical practice. Both anaemia and blood transfusion are independently associated with adverse outcomes. Functional iron deficiency (iron restriction due to increased levels of hepcidin) is the most common cause of preoperative anaemia, and should be treated with intravenous iron. Intraoperative blood loss can be reduced with antifibrinolytic drugs such as tranexamic acid, and cell salvage should be used. A restrictive transfusion practice should be the standard of care after surgery.**

Conclusion: **The significance of preoperative anaemia appears underappreciated, and its detection should lead to routine investigation and treatment before elective surgery. The risks of unnecessary blood transfusion are increasingly being recognized. Strategic adoption of patient blood management in surgical practice is recommended, and will reduce costs and improve outcomes in surgery.**

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Introduction

Surgical outcomes and 30-day mortality rates are increasingly being analysed, and are readily available to service commissioners, patients, the media and the general public. Consequently, increased importance is placed on patient selection and optimization for surgery to reduce patient risk. However, anaemia is rarely treated in surgical patients, and blood transfusion is the mainstay of treatment in the perioperative period. Both anaemia and transfusion have been associated with increased morbidity and mortality[1,2].

The term 'blood management' was driven towards the patient's perspective with the formation of the Society for the Advancement of Blood Management (http://www.sabm.org), when it had previously been regarded as managing the supply to blood banks. A paradigm shift towards patient-focused blood management, patient blood management (PBM), has been taking place[3]. PBM is not an intervention *per se*, but goal-oriented patient care based on published evidence and best practice, with cooperative inclusion and empowerment of patients when possible, with the aim of improving clinical outcomes.

PBM focuses on three pillars of care in surgical patients: the detection and treatment of preoperative anaemia; reduction of perioperative blood loss; and harnessing and optimizing the patient-specific physiological reserve of anaemia (including restrictive haemoglobin transfusion triggers)[4] (*Table 1*).

Blood transfusion is common practice and the traditionally accepted solution to surgical anaemia. However, mounting evidence now suggests that this tradition may in fact be causing harm. PBM aims to integrate this evidence base into a readily applicable bundle of interventions to reduce the risk of unnecessary transfusion and optimize patient outcomes after surgery. Blood is a precious resource and its use is not without complications. Throughout the history of transfusion practice, new discoveries have mandated change to improve transfusion

Table 1 Pillars of patient blood management

	Pillar 1 Optimize erythropoiesis	Pillar 2 Minimize blood loss	Pillar 3 Manage anaemia
Preoperative	Diagnose anaemia Identify, evaluate and treat anaemia Treat absolute or functional iron deficiency Consider preoperative autologous blood donation Consider erythropoiesis-stimulating agents if nutritional anaemia is ruled out/treated Refer for further evaluation as necessary	Identify and manage bleeding risk (past medical and family history) Review medications (antiplatelet, anticoagulation therapy) Minimize iatrogenic blood loss Procedure planning and rehearsal	Compare estimated blood loss with patient-specific tolerable blood loss Assess and optimize patient's physiological reserve, e.g. pulmonary and cardiac function Formulate patient-specific management plan using appropriate blood-conservation modalities
Intraoperative	Schedule surgery with optimization of red cell mass	Meticulous haemostasis and surgical techniques Anaesthetic blood-sparing strategies Acute normovolaemic haemodilution Cell salvage/reinfusion Pharmacological haemostatic agents	Optimize cardiac output Optimize oxygenation and ventilation Evidence-based transfusion thresholds
Postoperative	Stimulate erythropoiesis Manage nutrition and correctable anaemia (e.g. avoid folate deficiency, iron-restricted erythropoiesis) Beware of drug interactions that can increase anaemia	Monitor and manage bleeding Avoid secondary haemorrhage Maintain normothermia (unless indicated specifically) Autologous blood salvage Minimize iatrogenic blood sampling loss Haemostasis/anticoagulation management Be aware of adverse effects of medicines Prophylaxis of upper gastrointestical haemorrhage	Maximize oxygen delivery Minimize oxygen consumption Avoid/treat infections promptly Evidence-based transfusion thresholds

safety. Syphilis testing began in 1947 and the discovery of human immunodeficiency virus in the 1980s brought about another paradigm shift: the introduction of routine blood-borne virus screening. Hepatitis C infected as many as 10 per cent of blood transfusion recipients from the 1970s and 1980s[5]. The risks from prions and other unknown pathogens remain an area of concern and research. The Serious Hazards of Transfusion (SHOT) haemovigilance scheme began in 1996, and the UK Department of Health began to issue 'Better Blood Transfusion' health service circulars to implement the lessons being learned.

PBM is the culmination and formalization of such approaches to apply the best current evidence to the practice of blood transfusion. It has been adopted by the World Health Organization[6], and has been proposed by the National Blood Transfusion Committee in the UK. In recent years, it has developed in a sporadic manner in Europe[7]. Recommendations have since been released for the implementation of PBM in the National Health Service (NHS), with the aim of decreasing avoidable and inappropriate transfusions of blood and blood products, and optimizing patient care[8].

The benefits of PBM appear to be clear, particularly in surgery, to address the triad of independent risk factors that affect outcome in surgical patients: anaemia, blood loss and transfusion. Significant direct and indirect cost savings can be achieved in the surgical setting[9], and early data suggest that implementation of PBM strategies is associated with improved clinical outcomes[10].

This article reviews why PBM is needed, and how several strategies can be incorporated simply and readily into surgical pathways. Although much evidence for PBM has arisen from the surgical specialties in which bleeding risk is highest, such as cardiac surgery, this article focuses on the application of PBM to non-cardiac surgery. Major transfusion protocols are not discussed; the focus is on elective clinical practice.

Methods

Recent studies investigating the three pillars of patient blood management were identified in PubMed using the keywords 'patient blood management', 'bleeding' 'transfusion' and 'preoperative anaemia'. Studies

Table 2 General risks of transfusion

Hazard	Mechanism
Transfusion-related immunomodulation	Immune mediators accumulate in stored blood
Transfusion-associated circulatory overload	Precipitation of congestive cardiac failure or acute left ventricular failure
Transfusion-related acute lung injury	Immune-mediated: donor antibodies react with recipient white blood cells, creating leucoagglutinates that are trapped within the lung
	Non-immune-mediated: endothelium suffers an initial insult (e.g. sepsis, surgery or trauma), attracting neutrophils that are activated by biologically active compounds in stored blood
	Injury caused by both mechanisms leads to capillary leak, and neutrophil extravasation and activation
Haemolytic transfusion reactions	Immediate: donor red blood cell membrane antigens react with existing antibodies within recipient's plasma
	Delayed: re-exposure to antigen-positive red blood cells in an alloimmunized recipient with specific antibodies causes a reaction
Acute non-haemolytic transfusion reactions	Febrile: recipient white cell antibodies react to donor leucocyte antigens
	Allergic: soluble donor antigens react in an already sensitized recipient
Post-transfusion purpura	Previous sensitization produces antibodies that attack donor platelet antigens as well as destroying circulating natural platelets
Transfusion-associated graft *versus* host disease	Donor lymphocytes proliferate in an immunocompromised recipient, attacking host cells as 'foreign'
Infection[13]	Viral: estimated risk of infectious donation entering UK blood supply – hepatitis B, less than 1 in 1·2 million donations; HIV, 1 in 7 million, hepatitis C, < 1 in 28 million
	Bacterial: 7 cases reported to SHOT, 1996–2012
	Prion: 4 reported cases of vCJD transmission by transfusion in the UK (all before the introduction of universal leucoreduction of red blood cells in 1999). No practical test for screening donors yet available

HIV, human immunodeficiency virus; SHOT, Serious Hazards Of Transfusion; vCJD, variant Creutzfeldt–Jakob disease.

related to the perioperative setting were focused on, and supplemented by current national guidelines and recommendations.

Hazards and risks of blood transfusion

Blood transfusion is typically regarded as the solution to anaemia and blood loss in surgery. Aside from the use of transfusion to replace acute blood loss, surgical patients receive either preoperative, perioperative or postoperative 'top up' blood transfusions. Although blood transfusion is a highly efficient and effective service, there is increasing evidence to suggest that intraoperative blood transfusions increase risk[11], and lead to a dose-dependent increase in morbidity and mortality[2]. Even a single unit of transfused red blood cells (RBCs) has been shown significantly to increase 30-day mortality, composite mortality, pneumonia and sepsis[12].

The hazards of transfusion include immunomodulatory effects, risks of circulatory overload, transfusion reactions and infective complications. The immunomodulatory effects of transfused blood include increased cancer recurrence, metastasis and postoperative infection (*Table 2*). The effect of storage on RBCs has been of concern, although the recent ABLE (Age of Blood Evaluation) trial reported no significant difference in hazard of death after receiving transfused fresh blood cells *versus* standard-issue blood cells (hazard ratio (HR) 1·1, 95 per cent c.i. 0·9 to 1·2; $P = 0·38$)[14]. Trials are ongoing in this area, including a randomized clinical trial[15] of standard-issue *versus* fresher RBCs in intensive care patients.

In a systematic review of over 20 000 patients with colorectal cancer, Acheson and colleagues[16] found that 58·8 per cent of patients received a blood transfusion. Blood transfusion was associated with increased all-cause mortality (odds ratio (OR) 1·72, 95 per cent c.i. 1·55 to 1·91; $P < 0·001$) and an increased OR for cancer-related mortality, combined recurrence–metastasis–death, postoperative infection and surgical reintervention, with a mean(s.d.) duration of observation of 62·8(28·8) months in the analysed studies.

In the UK, over 2 million units of RBCs were transfused in 2012, with more than 2600 adverse events included in the 2012 SHOT report[17]. This included major morbidity in 134 patients, four deaths where transfusion contributed to death and five other deaths where transfusion was possibly contributory. Separate to this is the cost of transfusion; the cost per unit of RBCs is €169 (£122, exchange rate 14 June 2015), at an overall cost of provision to the NHS of €300 million (£217 million). However, the cumulative total NHS costs (including nursing time, patient transport, treatment costs, etc.) are estimated to be nearly three times this at €878 (£635) per unit transfused. In the UK, audits of transfusion rates by operation and hospital are planned, and preoperative anaemia has been proposed as a Key Performance Indicator.

Pillar 1: detection and treatment of preoperative anaemia

Anaemia is a potentially correctable risk in surgery

Anaemia, defined as an insufficient circulating RBC mass, with a haemoglobin concentration of less than 130 g/l for men and below 120 g/l for women, is common in surgical practice. Its prevalence is generally between 20 and 40 per cent in surgical populations, and over 60 per cent in some studies of colorectal surgery[18]. The effect of anaemia is well known; even mild anaemia leads to impaired functional capacity, physical performance and a reduced quality of life[19]. This situation is significant in the surgical population, with ever more elderly patients, and patients with co-morbidities such as cardiac and pulmonary disease, undergoing increasingly complex surgery[20]. Normal levels of oxygen delivery are maintained at a haemoglobin concentration of between 60 and 100 g/l as the reduced blood viscosity leads to increased blood flow. Beyond this, tissue hypoxia and organ dysfunction become apparent.

Preoperative anaemia is not simply an abnormal laboratory value, but an important modifiable risk factor for perioperative morbidity and mortality that compounds the stress of surgery. Mounting data from a series of studies have shown anaemia to be an independent risk factor for increased morbidity and mortality in cardiac[21] and non-cardiac[22–24] surgery.

Recently, several authors have looked at the effect of anaemia on outcomes using the database from the American College of Surgeons National Surgical Quality Improvement Program® (NSQIP®). NSQIP® prospectively collects preoperative patient data, risk factors and laboratory results, perioperative complications and 30-day postoperative outcomes for patients undergoing major surgery in more than 200 participating hospitals (https://www.facs.org/quality-programs/acs-nsqip). In a detailed multivariable logistic regression analysis of 227 425 patients undergoing elective major non-cardiac surgery, 69 229 patients had preoperative anaemia[1]. Preoperative anaemia was associated with a 35 per cent increased risk of one major postoperative complication and a 42 per cent increased risk of death. This effect of preoperative anaemia was independent, adjusted for over 60 potential confounders and present for even mild anaemia, with the additional effect of a relationship between anaemia severity and outcome: a severity–response curve (*Fig. 1*). In a study of 310 311 veterans from 132 centres, Wu and co-workers[25] showed that anaemia (in predominantly elderly men) was associated with an increased risk of 30-day postoperative mortality and cardiac events in elective and emergency surgery. In a smaller subgroup of 23 348 elective open and laparoscopic colectomies, Leichtle and colleagues[26] found that preoperative anaemia was associated with the adverse composite outcome of myocardial infarction, stroke, renal insufficiency and 30-day mortality.

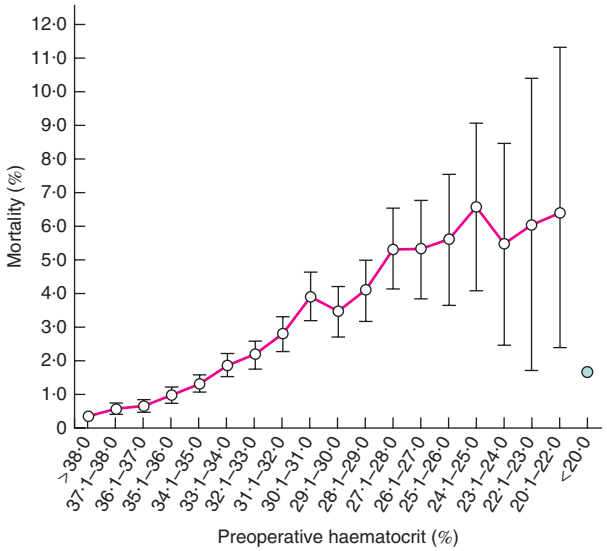

Fig. 1 Mortality rate per unit (per cent) preoperative decrease in haematocrit from normal baseline (over 38 per cent). Error bars represent 95 per cent c.i.; the shaded circle represents data that were too minimal to be analysed (previously unpublished graph from data presented in Musallam *et al.*[1])

In a secondary analysis of 39 309 patients undergoing non-cardiac surgery in the European Surgical Outcomes Study (EuSOS)[27], multivariable analysis showed that patients with severe or moderate anaemia had a higher in-hospital mortality rate than those with a normal preoperative haemoglobin concentration: OR 2·28 (95 per cent c.i. 2·06 to 3·85) and 1·99 (1·67 to 2·37) respectively.

Detection of preoperative anaemia

The significance of preoperative anaemia appears underappreciated, and its detection should lead to routine investigation and treatment. The Network for Advancement of Transfusion Alternatives (NATA) guidelines[28] recommend that the haemoglobin level is measured 28 days before scheduled surgery in patients undergoing elective orthopaedic surgery. European Society of Anaesthesiology guidelines[29] recommend that patients at risk of bleeding be assessed for anaemia 4–8 weeks before surgery. This leaves adequate time to investigate and manage diagnosed anaemia without resorting to blood transfusion or delaying surgery.

There are various reasons for anaemia in surgical patients. The increasingly elderly surgical population is

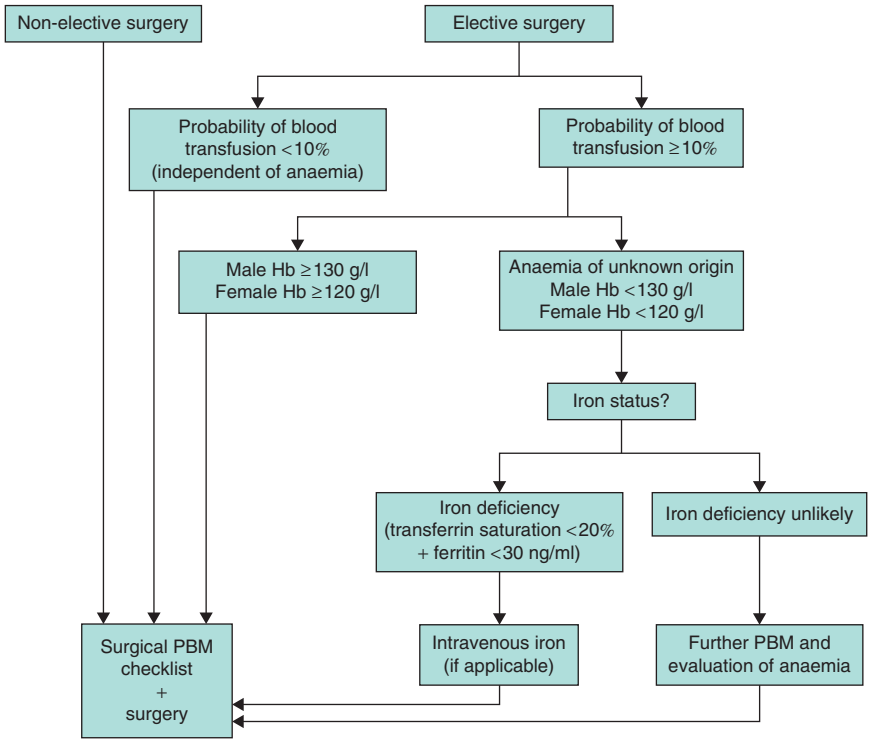

Fig. 2 Preoperative patient blood management (PBM) algorithm. Hb, haemoglobin (adapted from Meybohm *et al.*[34])

frequently anaemic. Patients can have anaemia of chronic disease (both unexplained and due to co-morbidities), or anaemia owing to nutritional deficiencies, blood loss or a combination of these. Iron deficiency is the most prevalent nutritional deficiency worldwide[19]. A state of both absolute and functional iron deficiency can occur. Absolute iron deficiency is defined by the lack of stored iron.

Functional iron deficiency is defined as the occurrence of iron-restricted erythropoiesis in the presence of normal or even increased amounts of stored body iron[30]. This results from impaired iron transport, or chronic inflammation that prevents the uptake and transport of iron in situations where iron demand exceeds supply, such as haemoglobinopathy, chronic haemolytic anaemia or the use of erythropoiesis-stimulating agents (ESAs). Transferrin, a protein that binds and transports iron, can be functionally blocked from carrying out its role owing to increased levels of hepcidin, a hormone produced in the liver that is regulated by iron stores and erythropoietic activity. Hepcidin levels are also increased in inflammatory states. Hepcidin increases iron storage by inhibiting the transport of iron into the plasma from hepatocytes and macrophages, and from duodenal enterocytes after ingestion. Thus, hepcidin prevents the uptake of dietary iron from the gastrointestinal tract, leading to iron-restricted erythropoiesis and functional iron deficiency; such a state is the commonest cause of anaemia in patients undergoing cardiac surgery[31]. In general surgical patients, chronic disease, inflammatory disease and malignancy are common precipitants of functional iron deficiency[32]. Functional iron deficiency is the most common cause of anaemia of chronic disease, and is present in around 50 per cent of anaemic surgical patients.

Treatment strategies

British Society of Gastroenterology guidelines[33] for the management of iron deficiency anaemia state that all patients should have iron supplementation to correct anaemia and replenish body stores, and that parenteral iron can be used when oral preparations are ineffective or not tolerated. A cut-off risk of bleeding of 10 per cent is useful in determining those patients in whom elective surgery should be postponed if anaemic (*Fig. 2*).

Oral iron is a longstanding, low-cost treatment for anaemia. Total body stores of iron are 3–4 g in healthy people. The bioavailability of ferrous iron is only 10–15 per cent. This is reduced further by poor absorption resulting from the downregulation of duodenal absorption by inflammation, infection and chronic disease. A

systematic review[35] has demonstrated that oral iron may reduce the proportion of patients requiring blood transfusion. However, enteral iron is absorbed at a rate of 2–16 mg per day, and 3–6 months of treatment can be required to provide 1000–2000 mg to replenish the physiological reserve of iron. Reduced uptake is one of the main reasons why oral iron often fails to ameliorate anaemia in surgical patients. Compliance can also be poor owing to the common side-effects of gastrointestinal disturbance, including abdominal pain, diarrhoea and constipation. Meta-analysis[36] has shown that oral iron has an OR of 2·32 (95 per cent c.i. 1·74 to 3·08; $P < 0·001$) compared with placebo for gastrointestinal side-effects.

Intravenous iron, however, has been shown to be effective in correcting anaemia in iron-deficient patients, with significantly lower odds of gastrointestinal side-effects[36]. Total-dose infusions of iron can now be administered in as little as 15 min. There are several intravenous iron preparations available, including iron dextrans, iron polymaltose, ferumoxytol, ferric carboxymaltose, iron sucrose, ferric gluconate and iron isomaltoside[37]. Historically, parenteral iron preparations were associated with high rates of adverse events including anaphylaxis. Many reactions were related to dextran-containing preparations, commonly because antibodies to dextran can be produced from exposure to dental caries. Modern carbohydrate preparations have a significantly improved safety profile. There is good evidence for their safety and efficacy in a range of conditions, including the perioperative setting[24]. A systematic review[38] demonstrated an increase in haemoglobin concentration and reduced risk of RBC transfusion (relative risk (RR) 0·74, 95 per cent c.i. 0·62 to 0·88) with intravenous iron, especially when used with ESAs or in patients with lower ferritin concentrations, but without significant difference in mortality or serious adverse events. It must be noted that this involved only a few trials in the perioperative setting and further adequately powered studies with clinically meaningful endpoints are required.

Erythropoiesis-stimulating agents

Recombinant erythropoietin (rEPO) has longstanding use to stimulate erythropoiesis in patients on dialysis. Within 5 days of treatment an increase in RBC proliferation in bone marrow is evident. A Cochrane review[39] of rEPO in patients with colorectal cancer failed to show any significant change in haemoglobin level with preoperative use of rEPO, or a decrease in the number of patients receiving allogeneic blood. However, a systematic review[40] of patients undergoing orthopaedic and cardiac surgery showed a reduction in the proportion of patients receiving allogeneic blood transfusions. A more recent meta-analysis[41] showed a significant risk reduction in patients who received preoperative rEPO among patients undergoing cardiac surgery: RR 0·53 (95 per cent c.i. 0·32 to 0·88; $P < 0·010$) without autologous blood donation and 0·28 (0·18 to 0·44; $P < 0·001$) with autologous blood donation.

The NATA guidelines[28] for orthopaedic surgery recommend that ESAs be used for anaemic patients in whom nutritional deficiencies have been ruled out or corrected, or both. Use of intravenous iron together with an ESA has been shown to improve the ESA response before surgery[42]. However, there are safety concerns regarding the use of perioperative ESAs[43]. Potentially harmful effects include hypertension, and thrombotic and ischaemic events, possibly as a consequence of higher haemoglobin concentrations, and possibly as secondary effects of the ESA on other cells, including stimulation of tumour growth[44]. Caution should be exercised when considering the use of ESAs, and conservative dosing regimens are advised.

Pillar 2: reduction in perioperative blood loss

Multimodal approach to coagulopathy and haemorrhage

Reducing perioperative blood loss requires a multimodal approach, encompassing anaesthetic and surgical technique, pharmacological interventions and cell salvage. Antiplatelet and anticoagulant therapy is increasingly being continued into the perioperative period to reduce perioperative cardiovascular risk, and this must be balanced against the risk of bleeding on an individual basis[45]. The haemostatic management of intraoperative bleeding requires careful monitoring of coagulation, including the use of point-of-care testing and protocols for the use of blood products and coagulation factor concentrates. A multimodal approach to coagulopathy and haemorrhage must be employed, requiring liaison between the surgical, anaesthetic and haematology teams as appropriate. A detailed review of perioperative coagulation management is beyond the scope of this article, but recent reviews[46–48] have focused on this.

The choice of surgical technique can reduce intraoperative blood loss; laparoscopic and minimally invasive surgical techniques, such as robotic urological surgery, are associated with reduced bleeding. The position of the patient during surgery can also influence bleeding. Venous return can be obstructed, leading to vessel engorgement and increased venous pressure at the operative site, increasing bleeding. This is particularly true in lumbar spinal surgery where the patient is in the prone position,

increasing intra-abdominal compression and epidural vessel engorgement. Efforts should be made to ensure that venous drainage is maintained by careful positioning.

Neuraxial anaesthesia has been shown to reduce bleeding, probably owing to systemic hypotension and decreased venous tone resulting from sympathetic blockade[49]. Avoidance of hypervolaemia and hypertension reduces surgical bleeding, as well as improving operating conditions.

The triad of hypothermia, acidosis and hypocalcaemia must be avoided. Maintenance of normothermia, and avoidance of acidosis and hypocalcaemia are priorities to maintain haemostasis. Below 35°C, platelet function is affected and the efficiency of enzymatic clotting factors impaired. A decrease in temperature of 1°C increases blood loss by approximately 16 per cent and increases the RR of transfusion by approximately 22 per cent[50].

Pharmacological treatments

Antifibrinolytic drugs

The antifibrinolytic drugs tranexamic acid (TXA) and ε-aminocaproic acid are lysine analogues that reversibly inhibit fibrinolysis by binding the lysine-binding sites on plasminogen, limiting the activation of plasmin, which cleaves fibrin strands. A Cochrane review[51] of antifibrinolytic drugs found that TXA produced a RR of RBC transfusion of 0·61 (95 per cent c.i. 0·53 to 0·70) and concluded that 'the lysine analogues are effective in reducing blood loss during and after surgery, and appear to be free of serious adverse effects'. Prophylactic use of TXA has been shown to reduce perioperative blood loss in cardiovascular, major orthopaedic and liver transplantation surgery, urological, gynaecological and obstetric surgery[52]. The dosing regimens vary, but a dose of 1 g is sufficient for most adults, with no evidence to support the use of high doses[53]. The CRASH-2 (Clinical Randomization of an Antifibrinolytic in Significant Haemorrhage) trial[54] showed that early (within 3 h of traumatic injury) administration of TXA (1 g followed by a 1-g infusion over 8 h) significantly reduced the risk of death from haemorrhage and all-cause mortality in traumatic bleeding. Importantly, the mortality rate rose if the dose was given after 3 h[54].

Aprotinin reduces fibrinolysis by inhibiting plasmin. It was withdrawn from clinical use following a multicentre trial[55] that showed an increase in mortality with its use. However, this finding has been disputed in further analysis of that trial and its subsequent meta-analyses, leading to requests for relicensing of aprotinin in both Europe and Canada, on the basis that its benefits in reducing blood loss and transfusion associated with cardiac surgery outweigh its risks[56].

Topical haemostatic agents

Fibrin sealants are composed of the clotting agents fibrinogen (with or without factor XIII) and thrombin (plus calcium), which promote haemostasis when applied to wound surfaces, in a manner similar to the final common pathway of the coagulation cascade. These can be sprayed or applied in liquid form. A Cochrane review[57] of fibrin sealant use reported a relative reduction in the rate of exposure to allogeneic RBC transfusions by 37 per cent (RR 0·63, 95 per cent c.i. 0·45 to 0·88). TXA is also used in topical form, in a saline solution or as a gel. A systematic review[58] of a range of surgical specialties demonstrated a reliable reduction in surgical bleeding (RR 0·71, 95 per cent c.i. 0·69 to 0·72; $P < 0·001$) and the risk of receiving a blood transfusion, although noted that the effect on thromboembolic events in this group was uncertain.

Autotransfusion

Cell salvage

RBCs are salvaged from the operative field using a double-lumen suction device, with anticoagulants added to the aspirated blood. This is then stored in a reservoir, before being centrifuged to separate out the components. The RBCs are washed and filtered, removing biochemical debris, including free haemoglobin, white blood cells and plasma. These are suspended in normal saline for retransfusion, with a haematocrit of 50–70 per cent. Some 200 ml of cell-salvaged RBCs equates to 1 unit of blood. Cell salvage has been demonstrated to be cost-effective compared with transfusion[59]. Cell salvage efficiency can be reduced by the concomitant use of antifibrinolytic agents and haemostatic products. Modern systems allow the suction device to be used independently, with the centrifuge consumables used only if sufficient blood is aspirated for processing and return; this reduces cost while ensuring that the capability to salvage shed RBCs is available.

Use of intraoperative cell salvage should be encouraged to reduce the need for allogeneic blood transfusion and should be considered for operations with an anticipated blood loss greater than 1000 ml[60]. However, if anticipated blood loss is greater than 500 ml the authors recommend consideration of cell salvage, because blood loss often exceeds this amount, and suctioning of blood with a compatible suction circuit, with the option to centrifuge and reinfuse if sufficient amounts are retrieved. A Cochrane review[61] found that the use of cell salvage reduced the relative rate of allogeneic RBC transfusion by 38 per cent (RR 0·62, 95 per cent c.i. 0·55 to 0·70), saving on average 0·68 units of allogeneic RBCs per patient (weighted mean difference −0·68; 95 per cent c.i. −0·88 to −0·49).

In orthopaedic surgery, the risk reduction was 55 per cent[61].

Retransfused blood can potentially be harmful owing to the presence of other substances aspirated from the surgical field, including bacteria and malignant cells. However, studies[62,63] have shown that, despite the aspiration of microbiologically contaminated blood, there is no increase in positive cultures or postoperative infection, even though the washing phase is unable to eliminate all bacteria. European Society of Anaesthesiology guidelines[29] suggest that the decision to use salvaged blood potentially contaminated with bacteria or malignant cells should be made on an individual basis. In a recent Cochrane review[61], mortality, reoperation for bleeding, infection, wound complications, non-fatal myocardial infarction, thrombosis, stroke and length of hospital stay were not increased by cell salvage; indeed, fewer patients who had undergone cell salvage developed infection or wound complications. Because retransfused washed RBCs from cell salvage provide no plasma, clotting factors or platelets, additional haemostatic therapies (such as platelets or fresh frozen plasma) may be required.

Acute normovolaemic haemodilution

Acute normovolaemic haemodilution involves the donation of whole blood by the patient immediately before surgery, and its simultaneous replacement with crystalloid or colloid to maintain normovolaemia, aiming for a haematocrit of 20–30 per cent. The aim is twofold: to dilute circulating RBCs and plasma components, reducing the amounts lost during surgical bleeding; and to provide fresh whole blood for retransfusion at the end of surgery, providing RBCs, clotting factors and platelets to maintain haemostasis and oxygen delivery. A meta-analysis[64] of this technique concluded that there are only modest benefits from this technique and did not support its adoption, although it may be more cost-effective than cell salvage[59].

Postoperative measures

Efforts should continue to minimize blood loss in the postoperative period. The same basic measures to avoid coagulopathy should be employed. Blood loss into drains is an area of interest. In orthopaedic surgery, the use of drains has been shown to increase blood transfusion rates[65]. In keeping with many enhanced recovery programmes, postoperative surgical drain use is decreasing. Cell salvage can also be used after operation[60], with retransfusion of blood from drains, particularly in major orthopaedic surgery.

As well as blood lost during surgery, the inflammatory and stress response to surgery can reduce erythropoiesis in a similar manner to that of functional iron deficiency of chronic disease. Patients who are either anaemic or non-anaemic (who may nonetheless be iron-deficient) before surgery have been shown to respond well to intravenous iron in the postoperative period, with a reduction in the incidence of postoperative anaemia, compared with oral iron supplementation[66].

Pillar 3: harnessing patient-specific physiological reserve of anaemia

A patient-specific plan should be made before surgery to predict the likely intraoperative blood loss. This should involve consideration of both transfusion thresholds and tissue oxygenation, but also methods to minimize blood loss and monitor haemostasis during surgery.

Restrictive transfusion thresholds

There is an increasing body of evidence demonstrating that restrictive transfusion thresholds are not inferior to liberal transfusion thresholds and that the use of 'top-up' transfusions is ineffective in stable patients. The landmark TRICC (Transfusion Requirements In Critical Care) study[67], published in 1999, showed that a restrictive strategy (maintaining haemoglobin concentration in the range 70–90 g/l, transfusing RBCs if it fell below 70 g/l) was at least as effective as a liberal strategy (maintaining haemoglobin concentration at 100–120 g/l, transfusing RBCs if it fell below 100 g/l) in critically ill patients, although those with acute myocardial infarction and unstable angina were excluded from the study.

In the 15 years since that work, further studies have supported these findings and clinical practice has moved inexorably towards a less liberal transfusion strategy. A restrictive threshold of less than 80 g/l after hip fracture surgery was compared with a liberal threshold of 100 g/l in patients with a history or risk factors for cardiovascular disease. The primary outcome was death or inability to walk across a room without human assistance at 60-day follow-up. The liberal transfusion strategy did not reduce mortality rates or functional capacity in these patients[68]. In a long-term follow-up of this cohort, mortality did not differ significantly between the restrictive and liberal transfusion groups[69].

In a Cochrane review[70] of over 6000 patients it was concluded that restrictive transfusion thresholds (where the mean difference in postoperative haemoglobin concentration was 14·8 (95 per cent c.i. −1·92 to −1·03) g/l lower than in the liberal transfusion group) should be supported for most patients, including those with pre-existing

Table 3 Important studies of transfusion thresholds

Reference	Haemoglobin (g/l)		Population	Outcome
	Restrictive strategy	Liberal strategy		
Hébert *et al.*[67] Transfusion Requirements In Critical Care (TRICC) trial (1999)	70	100	Critically ill patients	Restrictive strategy as safe as a liberal strategy, except perhaps in patients with ischaemic heart disease
Carson *et al.*[68] Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS) trial (2011)	80	100	Patients with high risk or history of cardiovascular disease after hip fracture surgery	Liberal transfusion strategy not superior in terms of morbidity or mortality
Villanueva *et al.*[71] (2013)	70	90	Severe acute upper gastrointestinal bleeding	Significantly improved outcomes in restrictive group, including mortality
Holst *et al.*[73] Transfusion Requirements In Septic Shock (TRISS) trial (2014)	70	90	Patients with septic shock in intensive care	Restrictive group had similar mortality and ischaemic event rates
Murphy *et al.*[72] Transfusion Indication Threshold Reduction (TITRe2) trial (2015)	75	90	Non-emergency cardiac surgery	Restrictive strategy not superior; increased death rate in restrictive group

cardiovascular disease. Indeed, restrictive transfusion strategies were associated with a statistically significant reduction in hospital mortality (RR 0·77, 95 per cent c.i. 0·62 to 0·95), but not 30-day mortality (RR 0·85, 0·70 to 1·03). The authors recommend that, in patients who do not have acute coronary artery disease, blood transfusion can probably be withheld in the presence of haemoglobin levels as low as 70–80 g/l as long as there is no notable bleeding[70]. Similar findings were made in upper gastrointestinal bleeding where a restrictive transfusion strategy increased the 6-week survival probability (95 *versus* 91 per cent; HR for death with restrictive transfusion 0·55, 95 per cent c.i. 0·33 to 0·92; $P = 0·02$)[71]. In cardiac surgery, however, the recently published TITRe2 (Transfusion Indication Threshold Reduction) trial[72] demonstrated uncertainty of restrictive strategies in unstable cardiac patients, reporting a beneficial impact of liberal transfusion to a haemoglobin concentration of more than 90 g/l on mortality following cardiac surgery (4·2 *versus* 2·6 per cent in restrictive *versus* liberal group; HR 1·64, 95 per cent c.i. 1·00 to 2·67; $P = 0·045$). Interestingly, in a similar study[73] of critically ill patients with septic shock, a restrictive transfusion threshold of 70 compared with 90 g/l led to similar numbers of ischaemic events, severe adverse events and requirement for life support. The RR of death in the lower-threshold group was 0·94 (95 per cent c.i. 0·78 to 1·09; $P = 0·44$). In the TITRe2 study[72] concurrent infection was common (more than 25 per cent in both groups). Based on these recent results, it would seem that the mechanism of the intervention by blood transfusion in these settings may be different and not related only to the change in haemoglobin mass.

Thus, a transfusion threshold of 70 g/l can be recommended; however, a threshold of 90 g/l should be considered in patients with ischaemic heart disease or those undergoing cardiac surgery. It should be noted that both these thresholds are restrictive in comparison with historical practice (*Table 3*).

Single-unit transfusions

Single-unit transfusions are strongly recommended in stable patients without bleeding, whereby each unit transfused is an independent clinical decision, documented in the patient notes, with the patient reassessed after each transfusion and the incremental haemoglobin concentration noted. Such policies encourage decision-making regarding the appropriateness of transfusion and haemoglobin target. A policy of transfusing RBCs in single-unit aliquots improves RBC utilization and decreases patient exposure to allogeneic blood[74]. Adopting such a practice is good evidence-based medicine, but it will require significant educational programmes to overcome the provider and system barriers to changing entrenched practice[75].

Maintaining tissue oxygen delivery

Tissue oxygen delivery is greatly influenced by haemoglobin concentration. Physiologically the body responds to a reduced haemoglobin and blood oxygen content by sensing oxygen levels at a cellular level, via vascular chemoreceptors and in hypoxia-sensitive organs[76]. The body responds to anaemia by increasing cardiac output, vasodilatation, increasing minute ventilation, and

Table 4 Surgical patient blood management checklist

Sign in (before induction of anaesthesia)
Preoperative haemoglobin within normal range
Consideration of withholding antiplatelet and anticoagulant medication
Consideration of minimally invasive or laparoscopic technique
Point-of-care testing available
Time out (before surgical excision)
Careful patient positioning to maintain venous drainage
Patient warming > 36°C
Use cell salvage whenever blood loss > 500 ml is possible; set up collection reservoir and process if sufficient blood actually collected
Tranexamic acid 1 g to all patients undergoing surgery where blood loss is likely or possible
Availability of prothrombin complex concentrates and fibrinogen concentrates; use of topical haemostatic agents
Sign out (before patient leaves operating room)
Restrictive transfusion thresholds implemented (haemoglobin 70–80 g/l depending on patient characteristics and haemodynamics)
Maintain oxygen delivery, targeting oxygen saturation levels > 95 per cent
Single-unit blood transfusion policy; reassessing haemoglobin level and clinical need between units
Postoperative drain or cell salvage

optimizing the oxygen saturation of haemoglobin in the lung and its extraction at the tissues.

Increasing oxygen delivery and reducing oxygen demand can meet the balance needed to compensate for lower haemoglobin concentrations secondary to blood loss and dilution. This can be achieved by increasing the arterial oxygen content of blood by increasing the fraction of inspired oxygen, which increases the amount of haemoglobin-bound oxygen and also the concentration of oxygen dissolved in the blood. Cardiovascular function can be optimized by the use of vasopressors such as noradrenaline (norepinephrine) to maintain organ perfusion, including coronary perfusion pressure, in the face of compensatory vasodilatation secondary to acute anaemia[77]. Consideration should be given to the adverse effects of postoperative pain and infection on tissue oxygen delivery and increased demand, with prevention and prompt treatment.

Conclusion

PBM presents an opportunity to ameliorate a recognized surgical risk and improve patient outcomes. Its implementation within the NHS has now been recognized as necessary for patient and economic benefit, as demonstrated by the introduction of new NHS-led national recommendations. Traditional practice has been to maintain a haemoglobin concentration or haematocrit based on arbitrary values (for example, less than 100 g/l or haematocrit 30 per cent, the so-called 10/30 rule) established in the 1940s. The decision to transfuse blood should not be a reflex reaction to a defined haemoglobin concentration or haematocrit, as it often was in the past, but a considered risk–benefit decision taken on an individual patient basis. The pillars of PBM help structure the interventions and decisions relating to anaemia and blood transfusion, but more importantly represent a paradigm shift towards a more considered approach to blood transfusion, acknowledging its risks, preventatives and alternatives.

The arguments for making this change are broad. They are both ethical and evidence-based. Failure to treat newly diagnosed anaemia is unacceptable, and clinicians must recognize the risks of transfusion, and convey this to their patients. They are economic owing to the increasing cost of transfusion and its related resource implications, and the scarcity of supply, as demand outstrips donation. The ethics of using this precious resource in the most appropriate manner, as desired by donors, must be considered. The legal ramifications of adverse events, including transfusion-transmitted infection of pathogens, both known and unknown (such as variant Creutzfeldt–Jacob disease), must also be considered.

PBM should become a routine part of surgical practice to reduce risk and improve outcomes in the same way as safer surgical checklists have been employed (*Table 4*). Its implementation is likely to become a target of service commissioners attempting to improve performance and patient safety, while increasing efficiency and reducing costs.

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