

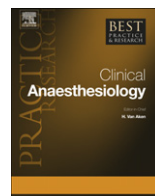


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The three-pillar matrix of patient blood management – An overview



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Allogeneic blood transfusion has had a central role in the development and practice of numerous medical and surgical advances. In recent years, transfusion has no longer been regarded as essential for the management of a wide range of diseases and most uncomplicated elective surgeries in well-prepared patients should now be conducted without the use of transfusions. With the exception of chronic haematopoietic deficiencies, the ‘transplantation’ of allogeneic blood is usually supportive therapy and is generally only required in relationship to complicated major surgery, trauma and until the basic disease processes can be corrected. For most patients it is possible to minimise or avoid blood transfusion by a ‘standard of care’ management of a patient’s own blood by optimising and preserving haematopoietic reserves in conjunction with tolerating the effects of deficiencies. The corollary to avoiding blood transfusion is that potential transfusion hazards need not be considered. This article focusses on the three-pillar matrix of patient blood management. The understanding of basic physiology and pathophysiology is at the core of evidence-based approaches to optimising erythropoiesis, minimising bleeding and tolerating anaemia.

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“Clinicians would be less confident in the safety of blood, and therefore more eclectic in its use, if they kept in mind the many possible weak links in the chain. In the hands of experts it is virtually safe, and very valuable; but there is little doubt that today, many deaths supposed to have occurred ‘in spite of transfusion’ have really been caused by it. In fact, there are few risks in transfusion when the doctor fails to insert a needle or cannula into a vein; they begin to mount once he succeeds”

H. Milner, The Lancet, 1949.¹

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Background

“It is always safe to assume, not that the old way is wrong, but there may be a better way”

Henry Harrower.

The concept of the three-pillar matrix may be a rather cryptic and unusual expression to use in clinical medicine, but the term three pillars has a long and traditional history of being used as a metaphor or analogy and as an ‘aide-mémoire’. It is not difficult to remember three concepts, but when a list extends beyond three there is an increasing likelihood that it will not be remembered and not be used regularly in discourse and clinical practice. The reference to the three pillars of patient blood management as a matrix adds further to the underlying concept that the origins and principles embedded in the three-pillar matrix of patient blood management are ‘motherhood’ statements or ‘no-brainers’.

Although there is an extensive literature on transfusion alternatives for minimising allogeneic red cell transfusions, caution is advisable in the use of the term ‘transfusion alternatives’ as only some are indeed truly alternatives. Patient blood management is sometimes viewed as an intervention or an ‘alternative’ to allogeneic blood transfusion, when in reality patient blood management is sound evidence-based clinical practice. The goal of patient blood management is to improve patient’s clinical outcomes; minimising or avoiding blood transfusion and reducing health costs may be desirable side benefits, but not the primary aim. Appropriately diagnosing and treating anaemia, minimising blood loss and harnessing a patient’s physiological reserves and tolerating anaemia are not ‘alternatives’ to blood transfusion. Indeed, to regard treating iron-deficiency anaemia with iron or not letting a patient bleed unnecessarily as an alternative to red cell transfusions is difficult to comprehend. However, the use of some autologous transfusion techniques, erythropoiesis-stimulating agents and, to some extent, anti-fibrinolytics can be regarded as transfusion alternative interventions that may have benefits, and also may bring with them hazards that need balancing in the same manner as the decision to transfuse. It is important, as with any therapeutic intervention, when making a risk/benefit assessment and balancing all the options that it is done on a ‘level playing field’ and red blood cell (RBC) transfusion should no longer be regarded as the default and ‘safe’ option when there is clinical uncertainty.^{2,3} Fig. 1 illustrates what should be regarded as standard of care versus transfusion alternatives.

It was in the early days of the human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) epidemic that there were numerous tragic medico-legal cases of HIV transmission through blood transfusion in which plaintiffs’ lawyers asked the simple question of the defending clinician “What was the indication for the blood transfusion and what benefit were you anticipating for my client?” In many cases patients died of AIDS when a simple consideration of the three-pillar matrix for patient blood management would have established that there was no role for allogeneic blood

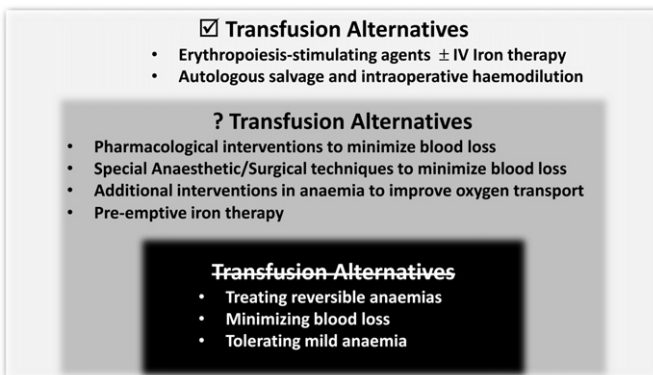


Fig. 1. Standard of care versus transfusion alternatives.

transfusion and the patient was exposed to a fatal hazard of transfusion without evidence for benefit.⁴ For a patient to be exposed to the risk of serious morbidity or mortality without good evidence for benefit is intolerable in modern scientifically based medicine, *primum non nocere*.

In minimising or avoiding allogeneic red cell transfusion from a patient's perspective, the clinician's primary responsibility is to manage the patient's own blood as a precious and unique resource that should not be wasted. There is a triad of independent risk factors in surgical patients for adverse clinical outcomes – anaemia, haemorrhage and transfusion – for which there is a plethora of observational data and limited randomised controlled trial (RCT) evidence.^{5–18} Of compelling concern is the strong independent association between red cell transfusions and increased morbidity, mortality, intensive care admission and hospital length of stay. The range of associated morbidities includes bacterial infections (including septicaemia), cardiac and cerebral ischaemic events and impaired renal function. In addition, venous thrombo-embolism, multisystem organ failure, systemic inflammatory response syndrome and acute lung injury have been associated.^{13,19–28}

This triad of risk factors is addressed by the three pillars of patient blood management by appropriately managing preoperative anaemia and maximising red cell mass when possible, minimising haemorrhage and avoiding allogeneic red cell transfusions, that is, tolerance of anaemia. Allogeneic blood transfusion should be considered only when there are no options available. Central to evidence- and problem-based transfusion medicine in relationship to red cell transfusions is the timely diagnosis and management of anaemia.

The unacceptable role of allogeneic blood transfusion as a 'culturally' embedded default therapeutic decision for the management of anaemia and haemorrhage has resulted from failure to address the three pillars of patient blood management:

- 'Anaemia' is common and generally poorly managed, despite good scientific understanding of mechanisms and sophisticated diagnostic methods.^{29,30} In most circumstances anaemia is mild and its significance per se in terms of impacting adversely on clinical outcomes in the absence of confounding co-morbidities is questionable.
- Poor attention to the management of 'haemostasis' is common because of:
 - failure to pre-emptively assess haemostasis and haemorrhagic risk and
 - suboptimal intra-operative surgical and anaesthetic management of bleeding.
- Poor 'tolerance' of mild and moderate degrees of anaemia in the short term:
 - Although there is literature associating anaemia with poorer outcomes in some circumstances, there is a dearth of evidence supporting the proposition that correcting the anaemia with red cell transfusions improves clinical outcomes.^{5,8,9,31,32}

What is an appropriate blood transfusion?

In order to be ready when needed, you must also be ready when not needed.

Ashley Brilliant.

Allogeneic blood transfusion in Western medicine is regarded as a safe and effective clinical intervention and a default therapeutic decision in managing anaemia in the context of clinical uncertainty. The reality is quite different and this practice can no longer be tolerated. Allogeneic blood transfusion has the potential for a greater range of serious hazards than probably any other therapeutic intervention. Suboptimal clinical management results from failing to appropriately address and manage one or more of the three pillars of patient blood management. It has been said in clinical practice that if a test or procedure is readily available and easy to do it will be used frequently, without due consideration for its appropriateness or possible adverse consequences. If a test or procedure is complex, difficult to do and limited in availability, even though of major clinical importance, its practice will be ignored at worst or at best not viewed as optimal standard of care. Unfortunately, the former situation is commonly witnessed with blood transfusions where haemodynamically stable anaemic patients are transfused without due consideration for the risks and appropriate standard of care. By contrast, in critically haemorrhaging patients in whom blood transfusions may be life saving, the

evidence base for the understanding of pathophysiology, the logistics of point-of-care haemostasis testing and debate over optimal blood component therapy frustrate clinical management.

Emphasising that patient blood management is not an alternative to allogeneic blood transfusion begs the question “What is an appropriate allogeneic blood transfusion?”³ The three-pillar matrix of patient blood management goes a long way in answering this question:

- What is the time frame of the decision-making process?
 - Urgent, emergent or elective.
- What is the haemopoietic defect (i.e., diagnosis)?
 - Red cell disorder or haemostatic defect.
- What is, or should be, the standard of care for the patient?
- Is the indication for the transfusion prophylactic for an anticipated emergent problem or therapy for an existing acute or chronic consequence of blood component(s) deficiency?
- Are there alternatives to allogeneic transfusion?
- What blood component is indicated and where should it be obtained?
- Except for serological compatibility, are there any other patient-specific requirements in relationship to the donor blood (e.g., freshest available, leuco-depleted, irradiated, Cytomegalovirus (CMV) negative)?
- How should the component be administered and monitored?
- What are the potential hazards of the blood component therapy, and their severity and risk?
- Can the risk of adverse effects be avoided or minimised?
- What is the overall cost of the haemotherapy?
- Is the patient fully informed of the medical decisions, including blood transfusion, especially in the elective setting?

The core principles of personalised evidence-based patient blood management and transfusion medicine

In the current era of evidence-based medicine it is sometimes forgotten that patients should be treated as individuals and not as statistically ‘average’ patients on the basis of levels of evidence with RCTs as the highest level of evidence. This is not to denigrate the importance of sound evidence from RCTs in patient blood management when appropriate. Examples of where RCTs are important in improving patient outcomes are in establishing valid surrogate end points, ‘transfusion triggers’ and questions surrounding the quality and quantity of blood components that correlate with improved clinical outcomes.^{33–39} However, most of the core principles of the three pillars of patient blood management and the serious hazards of blood transfusion are not based on observational or RCT probabilistic causation. The evidence is from a sound deterministic understanding of causation on the basis of well-established hazards of blood transfusion and physiological knowledge of haemopoiesis and oxygen transport.¹⁷

The concept of personalised medicine is not new and is best epitomised by Sir William Osler in his aphorism: “It is much more important to know what sort of a patient has a disease than what sort of a disease a patient has.”⁴⁰ However, with an overemphasis on frequentist-based statistics dictating the ‘levels of evidence’ for clinical management it is easy to lose sight of the fact that patients may have comorbidities or specific clinical or personal requirements demanding that they should be treated as individuals ($N = 1$) and not as average patients ($N = X$). Indeed, in soundly practiced evidence-based medicine, as originally advocated, this should be the case in that evidence-based medicine integrates best research evidence and knowledge with clinical expertise and patient values. Clinicians and patients form an alliance for optimising individual clinical outcomes and quality of life. This is achieved by

1. The ‘application of established knowledge and research evidence’ from:
 - understanding of normal structure and function,
 - understanding of pathophysiology,
 - patient-centred clinical research,
 - validity of diagnostic methods,
 - classification and natural history of disease,

- prognostic indicators of disease,
- efficacy and safety of therapeutic, rehabilitative and preventive interventions and
- outcome/s of treated disease.

Clinical expertise:

- clinical skills and experience in managing a patient's unique health state with
- appropriate diagnostic methods and
- appropriate therapeutic interventions.

3. Patient values:

- the individual and unique preferences and circumstances,
- concerns and expectations a patient brings to the clinical interaction and
- meaningful informed consent, especially when time permits.

It is as a result of the explosion of knowledge about the human genome that there has been a resurgence of interest in personalised medicine.⁴¹ The practice of personalised medicine is based on Bayesian statistics in which the starting point is a sound deterministic understanding of human physiology and pathophysiology applied to the diagnosis and management of individual patients with input from appropriate and rigorous evidence from frequentist-based statistics.^{42,43}

This Bayesian analysis can be expressed as follows:

[Known facts from physiology/pathophysiology + Levels of evidence from Evidence Based Medicine (EBM)] + [Patient-specific information] = [New information for clinical decision making]

The key components of personalised medicine are achieved by making every effort to ensure the following:

1. optimising diagnosis,
2. optimising therapeutic benefit,
3. matching therapy to the patient,
4. monitoring for compliance and efficacy of therapy,
5. preventing/minimising hazards of therapy,
6. pre-empting possible disease complications by prevention or early recognition and
7. optimising patient empowerment and consent.

In patient blood management each of these components needs to be addressed in relationship to the three-pillar matrix. Although protocols and standard clinical pathways are appropriate in many circumstances, some patients having complex co-morbidities and difficult-to-manage variables require highly customised clinical and personal management. Fig. 2 illustrates the spectrum of clinical management in circumstances in which protocols are appropriate to highly specialised individualised patient management. The aim of clinical protocols is to deskill a clinical pathway in an algorithmic generic manner without jeopardising efficacy and patient outcomes.

Experiences and lessons learnt from personalised blood management of patients who refuse allogeneic blood transfusion

“If you have the same kind of trouble I have, please seek help immediately!”

Ashley Brilliant.

In acute haemorrhagic shock or critical anaemia the first of the three pillars, the total red cell mass, is depleted to a life-threatening degree at which point survival is increasingly unlikely without allogeneic blood transfusions unless the primary cause is controlled.⁴⁴ The management of patients who, usually for religious reasons, refuse blood transfusion presents the clinician with a challenge and is one of the best examples of personalised medicine. Unless they are able to receive clinical care from physicians experienced in, and who have the resources for, treating such patients an increased rate of

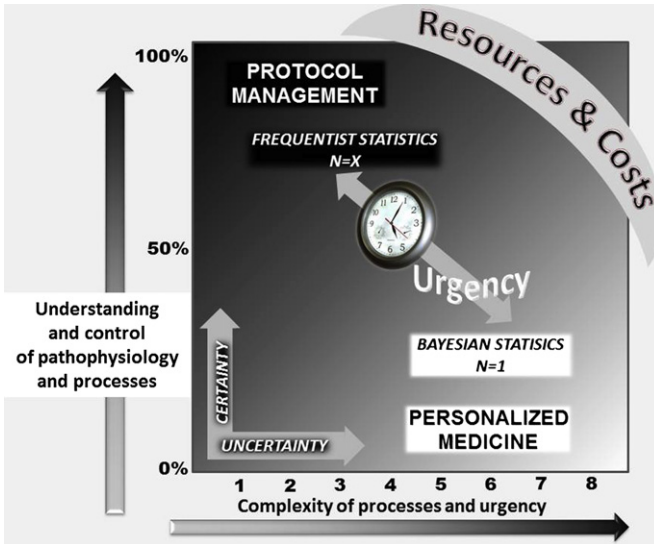


Fig. 2. The spectrum of clinical management in circumstances ranging from those in which protocols are appropriate to highly specialized individualized patient management.

mortality and morbidity is an inevitable consequence.⁴⁵ Case studies in the literature have demonstrated survival of such patients, defying much of the physiological principles taught in medical school.^{46–50}

Stemming from these experiences with Jehovah's Witness (JW) patients there has been a reassessment of the body's ability to compensate for profound depletion of the blood-oxygen-carrying capacity and for clinicians to 'tolerate' anaemia without immediate transfusion of red cell concentrates.⁵¹ This has been particularly so in elective surgical settings where there is evidence that JW patients have equivalent or better clinical outcomes in many elective surgical settings in which transfusion has been regarded as an integral component of clinical care for successful patient outcomes.^{52–54}

It is as a result of these experiences that the appropriateness of red cell transfusions in anaemic haemodynamically stable patients is being questioned.⁵⁵ There are an increasing number of studies supporting the proposition that anaemic patients managed with a restrictive transfusion protocol have at least similar, if not better, clinical outcomes compared with clinician-directed liberal transfusion policies.^{33,34}

A case–control study comparing JW patients with patients accepting blood transfusion undergoing elective cardiac surgery has confirmed the experiences of clinicians who regularly manage JW patients who were observed to have better clinical outcomes in terms of postoperative recovery.⁵³ This recent study found that not only was the postoperative recovery better than that of transfused patients, but also the JW patients had higher haemoglobin levels preoperatively, lost less blood at surgery and had higher haemoglobin levels postoperatively. The only reasonable interpretation of these findings is that the JW patients received a different standard of care. An obvious corollary to this and other observational studies and the RCTs of restricted RBC transfusion protocols is that many patients are unnecessarily exposed to the serious risks of allogeneic blood transfusion. Although these hazards may be rare and unlikely to occur in small studies, they are 'common' for patients unfortunate enough to be victims in the non-research 'real-world' clinical context.

In many ways it has been through experiences with the JW patients that the 'new' transfusion paradigm has come about. It is a return of the patient focus with evidence-based transfusion medicine and patient blood management viewing a patient's own blood as a valuable and unique natural resource that should be conserved and managed appropriately. In addition, altruistically donated blood is a valuable, unique and costly resource, held in trust that it will be used as therapy only when there is evidence for potential benefit, potential harm will be minimised and there are no feasible transfusion alternatives.

The role of clinical practice guidelines and protocols

“Arriving at one point is the starting point to another”

John Dewey.

The gradual move in recent years from blood product focus to a patient problem focus is highlighting the important role of clinical practice guidelines and clinical management protocols.^{19,56} Some years ago the author lectured at an international blood regulators’ conference on the subject of ‘Clinicians as Gatekeepers: What Is the Best Route to Optimal Blood Use?’ The talk concluded with the statement: “*There is an urgent need for a paradigm shift away from obsession with the supply and safety of homologous blood to patient blood management. Until this occurs we will continue to look for gatekeepers who either keep gates shut when they should be open or open them when they should be closed.*”⁵⁷

Major work in the development of patient blood management clinical practice guidelines has occurred in Australia under the auspice of the National Blood Authority with inputs from the clinical community, organisations, colleges and societies. These guidelines have been based on key principles for developing guidelines and approved by the National Health and Medical Research Council (NH&MRC) with systematic identification and synthesis of the best available scientific evidence. The reader is referred to the modules currently freely available on the Internet from the Australian Government National Blood Authority website at www.nba.gov.au. There are currently four modules available including critical bleeding/massive transfusion, and perioperative, medical and critical care. Obstetric and paediatric/neonatal modules are currently in development.

Towards an understanding of the fundamentals of the three pillars of patient blood management

The maintenance of adequate microcirculatory function requires circulation of blood of the appropriate composition, achieved by an effective cardiac output, which in turn is dependent on an adequate intravascular blood volume and its return to the heart. In focussing on the first of the three pillars it is essential to have a sound understanding of the physiology of blood volume, red cell mass and plasma volume regulation and the pathophysiological changes occurring in the context of a variety of clinical settings.^{58–61}

Eighty percent of the total blood volume is contained in the circulation’s highly flexible venous capacitance. An appropriate relationship must exist between the size of the venous compartment and the blood volume in order to ensure adequate venous return to the heart. Factors regulating the relationships between red cell mass and plasma volume in determining the venous haematocrit remain surprisingly unclear. Most scientific literature relating to total blood volume is found in relation to shock and resuscitation, the plasma volume literature relates to salt and water homeostasis and hypertension and red cell mass literature relates to haematological disorders. To the casual observer it may appear that the red cell mass and plasma volume are independent variables.

The haematocrit of blood in the macrocirculation is higher than that calculated from measurement of the red cell mass and plasma volume (i.e., body haematocrit). In a normal stable state the relationship of the body haematocrit to the venous haematocrit is approximately 0.9. This F-cell ratio represents variations in the red cell mass distribution within the vascular space.⁶² Circulating blood haemodilutes in the microcirculation. Individual organs of the body autoregulate microcirculatory flow and haematocrit by vasomotion, by which tissue perfusion cycles with only a third of the microcirculation perfusing at any one time allowing transcapillary to and fro movement and economies for the circulatory system.

The splanchnic circulation has a central role as the cardiovascular volume ‘buffer’ to maintain a functional relationship between the total circulating blood volume and the size of the vascular compartment. When blood volume is centralised as a result of venoconstriction the pattern of neuro-humoral responses resembles those occurring with hypertransfusion. Unless the venoconstriction is relieved, re-establishing an appropriate relationship between the size of the vascular compartment and the blood volume can be achieved only by reducing plasma volume with resultant haemoconcentration. This plasma volume contraction is achieved by salt and water shift into the interstitial space and the

lymphatic system and/or a diuresis. This transcapillary efflux, in which atrial natriuretic peptide and endothelin have a role, occurs in the systemic circulation with protection of the pulmonary system, to avoid excess lung water. The spleen also has a role in plasma volume reduction, by rapidly moving plasma into the lymphatic system which has its own capacitance. Mechanisms by which venous compliance may be reduced via increased sympathetic nervous system activity include hypoxia, exercise, cold exposure and mental/physical stress. Sympathetic activation or the infusion of alpha receptor agonists, such as noradrenaline, leads to a reduction in the total circulating blood volume as a result of plasma volume contraction and haemoconcentration. Sympathetic antagonists and other vasodilators result in redistribution of the blood volume and expansion of the plasma volume by interstitial fluid influx resulting in haemodilution.

Sudden requirements for increases or decreases in total intravascular blood volume can only be effectively achieved by alteration in plasma volume as the red cell mass cannot be acutely altered in a non-haemorrhaging patient. This is in contrast to when chronic stresses are placed on the system – the red cell mass component of the intravascular blood volume can be appropriately regulated by increased or decreased erythropoiesis under the influence of erythropoietin. It is thus evident that acute maintenance of an appropriate relationship between the volume of the intravascular compartment ('the vessel') and the absolute intravascular blood volume ('the fluid') results in acute changes in haematocrit as plasma volume adapts. In some circumstances these changes in haematocrit due to haemoconcentration or haemodilution may be appropriate to the stimulus, whereas in other circumstances the changes in haematocrit are 'unavoidable' by-products to permit a 'higher priority' acute volume adaptation to occur. An understanding of the physiological and pathophysiological factors influencing the venous haemoglobin level is important as elevation in the haemoglobin level does not necessarily represent an increase in the total red cell mass nor does a transient elevation indicate dehydration (Table 1).

The optimal haematocrit

The reference range for haematocrit is relatively wide and there is difficulty in defining a 'normal' population as fitness status, smoking habits, alcohol intake, body mass index and stress may all influence haematocrit. Within the reference range for haematocrit a person's total red cell mass correlates with aerobic capacity (i.e., VO_{2max}) rather than the measured circulating oxygen-carrying capacity in the venous system (i.e., haemoglobin per unit volume).^{60,63}

The peripheral venous haemoglobin concentration is generally used as the red cell transfusion 'trigger' and has also been used in research trials of restrictive transfusion protocols. Haemoglobin concentration is not a good measure of the overall oxygen-carrying, -delivery and -unloading capacity of the haematological component of oxygen transport. Ideally, a rapid measurement of total red cell mass, haemoglobin and red cell membrane molecular structure and function would be a better guide to the complexities of the blood's ability to carry out its oxygen-transporting functions.⁶⁴ In addition, this information should be interpreted in relationship to measurements of cardiopulmonary function and individual organ microcirculation and function. As this is not possible in the real world of day-to-day clinical practice, the clinician needs to rely on clinical assessment in conjunction with information gleaned from easily measured functional and structural parameters of oxygen transport. This being the case, the venous haemoglobin concentration will remain the commonly used parameter; it is thus important that the many factors that may impact on its interpretation need to be high in the clinician's consciousness when making decisions to tolerate anaemia or administer a red cell transfusion.^{65–68}

There are several physiological and pathophysiological settings in which venous haemoglobin levels need to be interpreted in context. The following is a summary of considerations that should be taken into account when assessing the physiological and clinical interpretation of a patient's venous haemoglobin level.

Gender

- Females have lower blood volumes and reference ranges for haemoglobin levels. Females are also more likely to be transfused than males.^{69,70}

Table 1

Summary of considerations in addressing the three pillars of patient blood management in the perioperative setting.

1st pillar Optimise erythropoiesis	2nd pillar Minimise blood loss & bleeding	3rd pillar Harness & optimize physiological reserve of anaemia
Preoperative		
Identify and manage patients with anaemia in a timely manner	Identify and manage bleeding risk Minimising iatrogenic blood loss Procedure planning and rehearsal Preoperative autologous blood collection in selected cases	Assess/optimize patient's physiological reserve and risk factors Compare estimated blood loss with patient-specific tolerable blood loss Patient-specific blood management plan including appropriate blood conservation Restrictive transfusion strategies
Intraoperative		
Time surgery when erythropoiesis has been optimised	Meticulous haemostasis and surgical techniques Blood-sparing surgical techniques Anaesthetic blood conserving strategies Maintain normothermia unless specifically indicated Autologous blood options – salvage, haemodilution Pharmacological/haemostatic agents	Optimize cardiopulmonary function Restrictive transfusion strategies
Postoperative		
Stimulate erythropoiesis if necessary	Monitoring and management of post-operative bleeding Rapid warming/maintain normothermia, unless hypothermia specifically indicated Autologous blood salvage if appropriate Minimising diagnostic blood sampling Haemostasis/anticoagulation management Prophylaxis of upper GI haemorrhage where appropriate Minimize infections	Tolerance of anaemia Maximize oxygen delivery Minimize oxygen consumption Restrictive transfusion strategies

Age

- In the elderly there are significant alterations in blood volume regulation mechanisms due to alterations in the autonomic nervous system and thirst mechanisms. Total blood volume decreases with age and the ability of the adrenergic system of older subjects to respond and adapt to environmental challenges and medical interventions is blunted.^{71,72}

Pregnancy

- During pregnancy there is a range of physiological changes in the circulation, the principle one being an increase in total blood volume. If these changes do not occur placental development may be impeded and foetal growth retardation may be a consequence. As a result of the larger vascular compartment, plasma volume and red cell mass are both increased, plasma volume more than red cell mass. The net effect is haemodilution and reduced blood viscosity.^{73,74}

Aerobic fitness

- Aerobically fit individuals commonly have haemoglobin levels in the lower range and there is a poor correlation between the haemoglobin concentration in the peripheral blood and the total red cell mass. This is commonly referred to as 'sports anaemia'.^{75,76}

Altitude

- A classical form of stress polycythaemia in which plasma volume contracts is seen in acute hypoxic stress of altitude. The initial response to acute hypoxia is an increase in sympathoadrenal activity manifest as increased cardiac output, vasoconstriction, centralisation of the blood volume and subsequent haemoconcentration.⁵⁸ [with references].

Physiological and pathophysiological adrenergic stress

- The term ‘acute haematological stress response’ has not been well defined as there are probably a variety of haematological stress responses depending on the stimulus. The term is best used in relation to adrenergic activation as seen in the fight/flight response. The acute haematological stress response results in plasma volume contraction and haemoconcentration and, in some cases, polycythaemia. This may occur as a physiological response to environmental hypoxia or psychological stress and can also be seen secondary to a range of diseases. These conditions include acute hypoxia, respiratory failure, acute neurological catastrophes (strokes and sub-arachnoid haemorrhage), acute coronary syndromes, atrial tachycardias and pheochromocytoma, to mention a few. It is important that the acute haematological stress response is recognised as major fluctuations in the venous haemoglobin levels may result when there has been no change in the total red cell mass, especially as the stimulus resolves, and be misinterpreted as dehydration if the haemoglobin is elevated and blood loss if there is a relatively sudden reduction.^{58,65,77} [with references].

Acute-phase response, anaemia of injury and chronic disease

- The acute-phase response follows release of cytokines and is a manifestation of post-insult host defences and healing responses. It is important that these two acute haematological responses are delineated as they are probably activated relatively independently (but sequentially in some cases), by different stimuli and different temporal sequences. The acute haematological stress response is more related to the acute adrenergically mediated ‘fight–flight’ reaction. During the acute haematological stress response, haemoconcentration and priming of the haemostatic system (platelets and coagulation factors) occur in response to a real or potential insult. By contrast, the acute-phase response is associated with haemodilution, ensuring the maintenance of blood fluidity and maintenance of microcirculatory flow, presumably to ensure delivery of the inflammatory and healing responses. The acute-phase response may progress to a more chronic phase with the development of the anaemia of chronic disease. The anaemia of chronic disease is not a primary diagnosis in its own right, but a normal secondary response to an infectious or inflammatory disease and should not be ‘corrected’. The anaemia of chronic disease is a component of the acute/chronic-phase response and there are numerous reactive changes which occur in the blood in response to infectious, inflammatory or malignant disease, which are all part of the host defence and healing mechanisms.⁷⁸

Medications

- The impact of venodilators causing haemodilution and vasoconstrictors causing haemoconcentration is not commonly recognised clinically as a reason for significant fluctuations in haemoglobin levels with changes in total red cell mass.^{79,80}

Diabetes

- Diabetics have significant reductions in blood volume and total red cell mass, but the venous haematocrit is usually in the reference range.^{81,82}

Cigarette smoking

- Smokers, as a group, have a higher mean haematocrit level than non-smokers. This is commonly due to contraction of the plasma volume. Acute changes in smoking habits, especially cessation when admitted to hospital or in relationship to elective surgery, will result in fluctuations in the haemoglobin level.⁸³

The initial approach to anaemia

“The way out of trouble is never as simple as the way in!”

Ed How.

1. What is the lower limit of ‘normal’ for haemoglobin in this patient?
2. Is anaemia an expected or unexpected finding?
3. Does the degree of anaemia require immediate intervention?
4. Should the finding of anaemia delay elective surgery?
5. What stresses will be placed on oxygen transport in relation to urgent or elective surgery?
6. Is the cause of the anaemia apparent from the clinical findings or initial blood count report?
7. Is the anaemia interacting with other defects in oxygen transport to produce or accentuate the clinical features of associated disease (respiratory, cardiac or vascular disease)?

Establishing the cause of anaemia

Establishing a definitive diagnosis for the cause of an anaemia, or at least collecting the appropriate samples, before therapy is initiated is important. It is unusual for the cause of a significant degree of anaemia to remain undiagnosed after appropriate investigation has been undertaken. The initial investigation of anaemia is relatively simple. With currently available automated haematology analysers a patient’s anaemia can be classified relatively easily on the basis of red cell indices. However, there will always be exceptions and difficult diagnostic problems. The multifactorial anaemias and patients with rare haematological disorders can create difficulty. However, in the majority of circumstances anaemia can be broadly classified into normochromic normocytic, hypochromic microcytic and normochromic macrocytic. The non-haematologist is not expected to be able to analyse all anaemias in detail. The laboratory will usually be able to help with further investigations on the basis of the original blood count. It is important that a logical sequence of investigations be carried out, guided by constant re-analysis of the patient’s clinical history and physical findings. The peripheral blood indices and film provide a high-yield, low-cost guide to the cause of most anaemias. On the basis of these initial results more specifically directed and expensive investigations can be requested, in most cases to confirm the provisional diagnosis.

In the context of preoperative assessment the physician needs to decide:

1. Is the anaemia related to the patient’s current condition?
2. Is the anaemia correctable in the short term and by what means?
3. If the anaemia is not correctable is transfusion appropriate?
4. What effect may anaemia have on the current anaesthetic and surgical management of the patient?

Unless there is a primary disorder of the marrow or some influence suppressing marrow function, most anaemias are correctable, without transfusion, within a period of 2–3 weeks. If surgery is urgent, transfusion may be necessary, but risk/benefit analysis needs to include consideration of the other two pillars of patient blood management. Specifically, is a transfusion indicated as immediate therapy on the basis that the anaemia per se is a primary factor in the patient’s failing oxygen transport? If this is not the case, a transfusion would be prophylactic in nature and may be preventable if the other two pillars of Patient Blood Management (PBM) are included in the decision making. It should also be remembered that, if transfusion is necessary for preoperative anaemia, the correction will only be transient and anaemia may

recur in the postoperative weeks. Even if there is an underlying correctable anaemia to which appropriate attention is given, the stimulus for the marrow to respond is reduced by correction of the peripheral blood haemoglobin level and marrow function may be suppressed by the operation and any postoperative complications. It is thus important that any anaemia which is acutely corrected by transfusion should be adequately followed up after surgery for definitive diagnosis and therapy. It is all too common for patients to re-present with anaemia some weeks after surgery when it is found that either a clear diagnosis for the anaemia was not established or an appropriate follow-up therapy had not been given.

Application of the three-pillar matrix of patient blood management

“All that is wrong cannot be righted. Be sure the wrongs are rightly sighted”

Francis D. Moore.

The application of the three-pillar matrix in day-to-day clinical practice will depend on

- the medical or surgical context,
- the age and sex of the patient,
- the time frame for managing the primary clinical problem – urgent, emergent or elective,
- the reversibility and treatability of the primary disease,
- the presence of co-morbidities,
- the availability and costs of alternatives to blood transfusion and
- specific patient preferences.

Approaches to patient blood management, in many clinical settings, continue to evolve. The ‘low hanging fruit’, where the most evidence for achieving practice changes and the greatest benefits have been demonstrated in improving patient outcomes, is in relationship to elective surgery. Although the principles are similar, approaches to patients with critical bleeding, haematology/oncology disorders and gastrointestinal haemorrhage are currently an area of intense interest and research. Fig. 3 summarises a generic approach based on the three pillars of patient blood management that can be applied

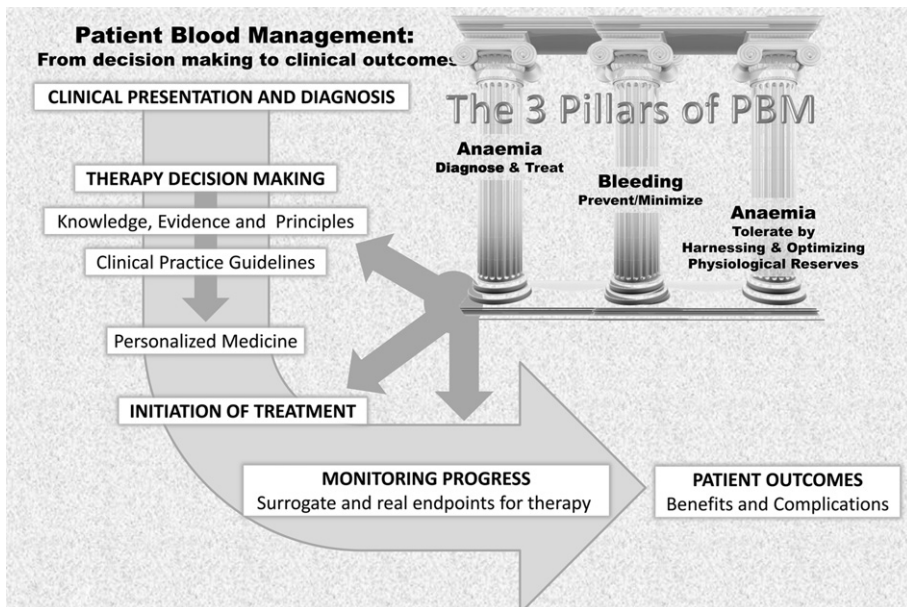


Fig. 3. The three pillars of patient blood management: From decision making to clinical outcomes.

to any clinical setting. This article concludes with a summary of the well-established and successful experience in the surgical setting that has been best developed and applied in the Western Australia Patient Blood Management Program.¹⁸ Table 1 is based on this programme's approach to perioperative patient blood management addressing the three pillars pre-, intra- and postoperatively.

Summary

For too long the benefits of allogeneic blood transfusion in improving patient outcomes have been assumed in many clinical settings. The evidence base for this practice is wearing thin and many patients receiving the labile blood components (red cells, platelets and fresh-frozen plasma) are being unnecessarily exposed to morbidity or mortality without good evidence for benefit. The decision-making process for blood component therapy can be difficult and much debate continues in relation to the indications for the use of various blood components. However, with the move from donor blood product focus to patient blood management and attention to the three-pillar matrix, there are good common sense and scientific reasons to adopt a non-transfusion default position when there is questionable evidence for clinical efficacy in improving patient outcomes. Focussing on the three-pillar matrix by maximising red cell mass, minimising bleeding and tolerating anaemia requires coordinated contributions from several medical disciplines, allied health professions and administrators. Although protocols and standard clinical pathways are appropriate in many circumstances, some patients require highly customised clinical and personal management. From the professional health-care perspective management is best summarised in the Latin proverbial analogy of a beehive, "*una apis, nulla apis*" – "one bee is no bee." For the patient it is personalised medicine in the classical Oslerian tradition.

Practice points

- Appropriately diagnosing and treating anaemia, minimising blood loss and harnessing a patient's physiological reserves and tolerating anaemia are not 'alternatives' to blood transfusion.
- Venous blood haemoglobin levels may not correlate well with total red cell mass and oxygen-transporting and delivery-capacity.
- Aerobic capacity correlates better with total red cell mass than with venous blood haemoglobin level.
- Preoperative anaemia in elective surgical settings should be managed as a high priority as failure to do so correlates with higher red cell transfusion rates.
- Most 'transfusion alternatives' should be 'standard of care'.
- Controlling critical haemorrhage and minimising surgical blood loss should be a high priority.
- Tolerating anaemia and harnessing the reserves in the oxygen transport system require a sound knowledge of physiology and pathophysiology in assessing co-morbidities.

Research agenda

- Better measurable and applicable parameters of the haematological components of oxygen transport, delivery and consumption to assist the clinician in the 'when to transfuse decision'.
- Continued research efforts in the development of haemoglobin substitutes.
- Continuous research to identify the composition of 'the ideal cell free plasma volume expander' with the appropriate colloid activity, viscosity, electrolyte composition, volume of distribution and half-life.
- Further developments in the technology and application of point-of-care haematological assessment of haemostasis.
- Patient blood management in the non-surgical setting.

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