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What is really dangerous: anaemia or transfusion?

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Editor's key points

- Paradoxically, both anaemia and transfusion are independently associated with organ injury and increased morbidity.
- Further characterization of the mechanisms of injury is needed to appropriately balance these risks.
- Treatment strategies to optimize haematopoiesis, manipulate physiological responses, and minimize blood loss are necessary to improve outcomes in anaemic patients.

Summary. While complex physiological mechanisms exist to regulate and optimize tissue oxygenation under various conditions, clinical and experimental evidence indicates that anaemia, unchecked, is associated with organ injury and unfavourable outcomes. More data (especially from human studies) are needed to answer questions regarding the optimal approaches to the treatment of acute and chronic anaemia. Meantime, allogeneic blood transfusions remain the most common treatment, particularly in surgical/trauma patients and those with moderate-to-severe anaemia. Clinical studies emphasize the paradox that both anaemia and transfusion are associated with organ injury and increased morbidity and mortality across a wide span of disease states and surgical interventions. Further characterization of the mechanisms of injury is needed to appropriately balance these risks and to develop novel treatment strategies that will improve patient outcomes. Here, we present the current understanding of the physiological mechanisms of tissue oxygen delivery, utilization, adaptation, and survival in the face of anaemia and current evidence on the independent (and often, synergistic) deleterious impact of anaemia and transfusion on patient outcomes. The risks of anaemia and transfusion in the light of substantial variations in transfusion practices, increasing costs, shrinking pool of donated resources, and ambiguity about actual clinical benefits of banked allogeneic blood demand better management strategies targeted at improving patient outcomes.

Keywords: anaemia; blood transfusion; haematocrit; morbidity; mortality; risk factors

Aerobic metabolism allows cells to harness the energy stored in organic molecules more efficiently using oxygen as the final electron receptor, changing oxygen from a toxic by-product of photosynthetic reactions to an essential element of life. In the more complex, multicellular organisms, adequate oxygen delivery to distant tissues cannot be adequately met by simple diffusion and hence elaborate mechanisms based on various haemoglobin (Hb)-related molecules exist to achieve this in a variety of species ranging from plants to humans.[1] The process of life today is undoubtedly reliant on the continuous supply of oxygen to the cells throughout the body, tasked by cardiopulmonary systems, vasculature, and the liquid tissue called blood.

While oxygen delivery is not the sole function of blood, it is among the most critical of all, as demonstrated by the grave consequences of severe acute anaemia (particularly at Hb levels below 50 g litre^{-1}). Anaemia resulting in tissue ischaemia remains a dreaded condition, and thousands of patients receive blood transfusions every day to avoid (or in hope of avoiding) this negative consequence.[2–4] Like many other medical interventions, transfusion, a common treatment of anaemia, is not free of risks. Its routine and widespread use in clinical practice ignores the fact that blood transfusion can be viewed as an organ transplant with known complexities and risks, albeit lacking the rigorous indications of solid transplants. For many patients, the undetermined benefit of transfusions make this clinical decision difficult and it should not be taken lightly.[5 6] Just as a timely organ transplant can be life saving so can appropriate blood transfusion. The issue at hand is the balance between the risks of transfusion and the risks of anaemia, a challenge many clinicians face with inadequate education, information, or both. This is the focus of this review. It should be emphasized here that such a discussion—while indispensable—is incomplete, without consideration of other competing treatments of anaemia and the matters of blood supply and costs.

Oxygen delivery and adaptations in anaemia

Understanding of the role of oxygen in mammalian physiology began with its discovery and early characterization by Scheele, Priestley, and Lavoisier over 200 yr ago,[7] leading to further insights about mechanisms of oxygen sensing, delivery, and utilization.[8 9] Mechanisms to sense changes in oxygen tension and to improve oxygen delivery to tissue facilitated the efficient production of adenosine triphosphate (ATP) molecules,[10 11] with such oxygen-sensing mechanisms becoming more elaborate in increasingly complex organisms, including mammals.[12]

Three key physiological elements became necessary for delivery of oxygen to tissues in mammals: (i) an efficient pump—the heart; (ii) an effective system of oxygen distribution—the circulatory system; and (iii) an efficient oxygen reservoir—Hb, all finely and continuously regulated. As emphasized by Guyton and colleagues,[13] it is the tissues' need for oxygen that regulates cardiac output and regional tissue blood flow; 'tissues regulate their blood flow . . . to maintain oxygen uptake and, in so doing, contribute to regulation of cardiac output'. Besides a functioning cardiovascular system, Hb is the other critical component that is central to the efficient delivery of oxygen to the tissues, and hence, red blood cells (RBCs) and their availability are key to optimal tissue oxygen delivery. As summarized by Singel and Stamler,[14] 'A general principle of physiology holds that cells precisely regulate their primary function. For RBCs, this primary function is delivery of oxygen to tissues'. This section reviews the important mechanisms that ensure oxygen delivery to tissues under physiological conditions.

Oxygen sensing

Exquisitely sensitive mechanisms for detecting reductions in tissue oxygen delivery exist, potentially as a means of surviving acute blood loss and anaemia. These mechanisms are largely redundant, emphasizing their importance to survival. Oxygen sensors exist at the level of organs (kidney),[15–17] tissues (aortic and carotid body chemoreceptors),[18 19] and cells [hypoxia-inducible factor (HIF)].[20 21] A number of arguments support the importance of these oxygen-sensing mechanisms during acute anaemia: (i) during anaemia, an early decrease in renal tissue oxygen partial pressure (P_{O_2})[16 17 22] triggers an increase in renal erythropoietin (EPO) production to restore Hb concentration;[17 23] (ii) increased chemoreceptor activity is detected during anaemia and contributes to physiological mechanisms (increased cardiac output) and cellular responses that optimize tissue oxygen delivery and protect cells from episodes of hypoxia;[18 19] and (iii) increased expression of hypoxia-sensitive molecules, including HIF, occurs in acute and chronic anaemia at an Hb threshold near 70 g litre^{-1}.[20 21 24] These findings support the hypothesis that adaptive responses to anaemia-induced tissue hypoxia occur to support cellular (and ultimately organism) survival during anaemia.

Respiratory adaptations

Anaemia stimulates respiration resulting in increased minute ventilation. In addition, nitric oxide (NO)-mediated mechanisms improve ventilation–perfusion matching, leading to a characteristic increase in the partial pressure of oxygen in arterial blood (Pa_{O_2}) and Hb oxygen saturation (Sa_{O_2}).[25 26] These responses ensure that optimal Sa_{O_2} is maintained at the time of reduced Hb to maximize blood oxygen content.

Cardiovascular adaptations

During anaemia, hypoxia-sensing cells activate the sympathetic nervous system that, among other mechanisms, increases cardiac output and reduces systemic vascular resistance.[17 19 27 28] These responses are consistently observed in humans and animals and act to maintain a global balance of oxygen delivery and consumption.[27 28] Guyton and Richardson[29] have emphasized the importance of reduced blood viscosity, systemic vasodilation, and increased venous return to maintain adequate cardiac output during acute anaemia. Since these initial observations, data from experimental and clinical studies confirm that additional active and feedback mechanisms are required to maintain cardiac output and increased tissue blood flow (Table 1).[17 19 22 27 30–36] Collectively, these mechanisms ensure that oxygen delivery to the microcirculation and tissues of vital organs is optimized during anaemia.

Increased tissue oxygen extraction during anaemia

Human and animal studies have demonstrated that global and tissue-specific oxygen delivery is maintained during acute anaemia, in part through increased systemic oxygen extraction.[28 35] This mechanism can be less important to organs with high basal oxygen extraction, such as the heart, that are more dependent on increased flow to match increased oxygen consumption during anaemia.[37] In contrast, oxygen extraction in the brain increases from about 30% at baseline to near 50% during anaemia under experimental conditions.[17 35] This increase in oxygen extraction likely depends upon at least three important factors: (i) a right shift of the oxyhaemoglobin dissociation curve to reduce Hb oxygen affinity. This can occur by a number of mediators including low pH, increased 2,3-diphosphoglycerate (2,3-DPG), and NO-mediated signalling events.[38 39] (ii) Increased tissue blood flow which favours increased oxygen diffusion into the tissue;[15] and (iii) increased capillary recruitment and density, which can limit the diffusion distance to cells during anaemia.[24] The primary goal of these mechanisms is to facilitate oxygen diffusion from the microcirculation to tissues, thereby sustaining mitochondrial oxidative phosphorylation (aerobic respiration). Quantitative measurements of tissue P_{O_2} in the microcirculation, tissue, and cells demonstrate that oxygen travels readily down a small gradient.[40] For example, in rat brain, the microcirculatory transmural P_{O_2} gradient is about 0.13 kPa μm^{-1} (Fig. 1).[41] Furthermore,

Table 1 Cardiovascular adaptations in anaemia to ensure optimal oxygen delivery to vital organs. Hb, haemoglobin; P_{O_2}, partial oxygen pressure

Adaptive mechanism	Details and observations supportive of the mechanisms
Aortic chemoreceptors	Aortic chemoreceptor activation of sympathetic and parasympathetic innervations of the heart required to ensure the effective increase in cardiac output (through increased heart rate and stroke volume) associated with acute anaemia[19 32]
Cardiac β-adrenergic receptors	Acute cardio-selective β-blockade impairs the cardiac response to acute anaemia resulting in profound tissue hypoxia, indicating the importance of stimulation of cardiac β-adrenergic receptors to support the increase in cardiac output observed during anaemia[17]
Vasoconstriction of splanchnic vasculature	Active vasoconstriction of the splanchnic vasculature can contribute to the increase in venous return and preload observed during anaemia[33]
Preferential vasodilation of vital organs	Anaemia-induced increase in cardiac output is preferentially distributed to organs of primary importance to survival by actively regulated and adrenergically mediated vasodilation and hence, improved perfusion in these organs.[34] Examples: As much as six-fold increase in coronary circulation and blood flow to supply oxygen for the increase in myocardial oxygen consumption[27 31 36] Preferential increase in cerebral blood flow during acute anaemia[31 35]
Preferential maintenance of tissue P_{O_2} in vital organs	In normovolaemic mammals, tissue P_{O_2} is preferentially maintained in the heart and brain during acute anaemia, as reflected by the observation that the Hb threshold for tissue hypoxia (reduced tissue P_{O_2}) is lower in the brain and heart, relative to other 'less vital' organs such as the liver and kidney, which become hypoxic at higher Hb levels[17 22 35]

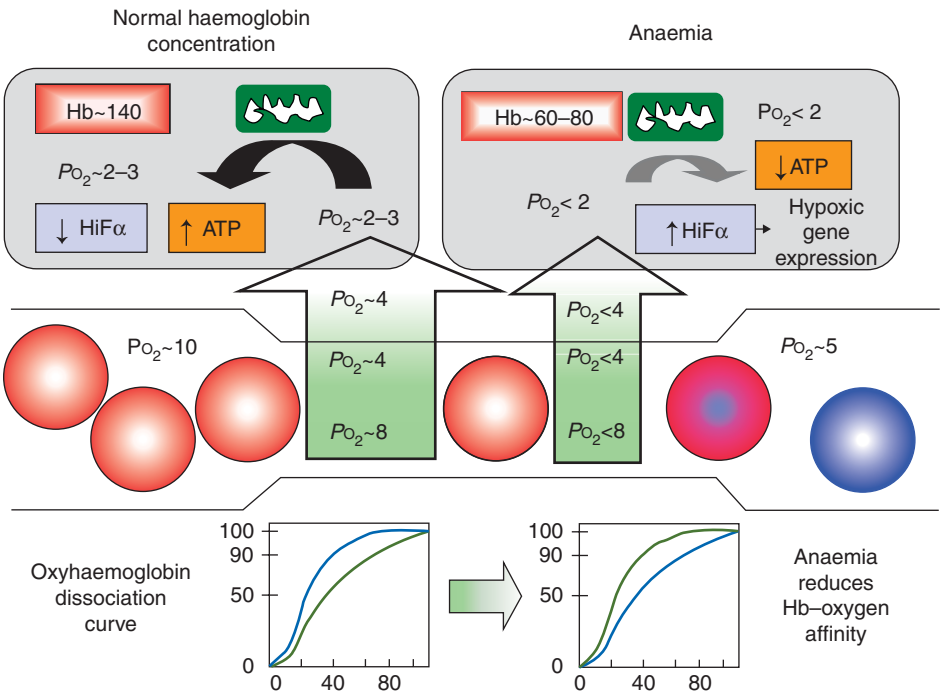

Fig 1 Comparison of oxygen transport from the microcirculation at physiological Hb concentrations and during anaemia.[40–45] ATP, adenosine triphosphate; Hb, haemoglobin in g litre^{-1}; HIFα, hypoxia-inducible factor alpha; P_{O_2}, partial pressure of oxygen in kPa.

quantitative measurement of P_{O_2} in the microvasculature, interstitial tissue, and neuropil of rat brain demonstrates that there is a continuous oxygen gradient from the arteriole (~10 kPa) to the capillary (~6 kPa) and then to the interstitial tissue (~4 kPa) and into cells (~3 kPa in neuropil) (Fig. 1).[42 43] Experimental data suggest that once oxygen is present in the tissue, there is very little resistance to its diffusion into cells.[44] New quantitative data suggest that the P_{O_2} in mitochondria is much higher than previously estimated, allowing the mitochondria to generate ATP under aerobic conditions and also function as a primary oxygen sensor.[45]

Metabolic adaptation to acute anaemia

Human and animal studies have demonstrated that overall balance of systemic oxygen delivery and consumption is preserved[27 28 35 45 46] or slightly decreased during anaemia.[47] However, in some experimental models, myocardial oxygen consumption can double, in the context of preserved global oxygen delivery.[27 36] Given the increase in myocardial oxygen utilization, some organs must reduce their tissue oxygen consumption during acute anaemia to maintain global oxygen utilization. Such mechanisms are also activated during atmospheric hypoxia,[47] and can contribute to the intracellular adaptive changes that promote survival during acute anaemia. These mechanisms are dependent in part on HIF-mediated metabolic cellular adaptations.[11] Thus, numerous mechanisms exist to optimize the balance between oxygen supply and demand in acute anaemia. The next step in understanding the adaptive responses to anaemia involves understanding the adaptive cellular responses to anaemia-induced tissue hypoxia.

Assessment of anaemia-induced tissue hypoxia in the brain

Experimental studies have focused on the brain, a vital organ with a high metabolic requirement that is at risk of injury during acute and chronic anaemia. In direct opposition to an earlier hypothesis that acute anaemia leads to fortuitous cerebral hyperaemia and increased tissue P_{O_2} (luxury perfusion),[48] strong clinical experimental data suggest that the brain and other organs are at risk of anaemia-induced tissue hypoxia and possible injury.[49–53] Experimental studies have demonstrated that cellular elements within cerebral tissue respond to a small reduction in tissue P_{O_2} by stabilizing HIF-α, an oxygen-sensitive transcription factor, resulting in transcription of a number of hypoxia-adaptive molecules.[17 20 21 24]

HIF has been described as the master regulator of hypoxia sensing[10 11] and hypoxic cell signalling.[54] HIF promotes transcription of a large number of hypoxia-response genes responsible for cardiovascular adaptation to hypoxia;[55] increased erythropoiesis (through EPO);[56] promotion of angiogenesis [through vascular endothelial growth factor (VEGF)];[24 57] and a metabolic switch to increase glucose transport and glycolytic (anaerobic) metabolism.[11 58] Therefore, evidence of increased HIF-α expression in the brain during anaemia at clinically relevant Hb concentrations ($\sim$60–80 g litre^{-1}) provides strong evidence of anaemia-induced tissue hypoxia at the cellular level. The associated increased expression of HIF-responsive elements, including EPO, VEGF, and CXCR4, suggests that anaemia elicits hypoxic changes in gene expression that might be adaptive and cytoprotective. Anaemia-induced increases in HIF occur in both acute and chronic models of anaemia and have been associated with cognitive decline in old animals, possibly as an 'adaptive' form of survival mechanism, or as a 'maladaptive' sign of hypoxic brain injury.[20 21 24]

Perils of anaemia

The World Health Organization (WHO) defines clinical anaemia based on Hb thresholds of 130 g litre^{-1} in men, 120 g litre^{-1} in non-pregnant women, and 110 g litre^{-1} in pregnant women.[59] Anaemia is generally caused by reduced production of RBCs, increased destruction of RBCs, blood loss (acute or chronic), or a combination of these factors.[60] Acute haemorrhage can result in hypovolaemia and circulatory collapse (shock) due to the lost volume. Exsanguination occurs mostly in combat injury or trauma[61] and remains a leading cause of maternal mortality across the world.[62] Other aetiologies (e.g. gastrointestinal or internal bleeding due to rupture vessels) also occur.[63 64] Unless the circulatory volume is resuscitated and bleeding is controlled, the condition most often will result in imminent death. Volume loss can normally be managed using i.v. fluids,[65] but the resultant acute severe anaemia can be more challenging to manage, particularly in massively bleeding cases commonly complicated by coagulopathy and transfusion of large amounts of blood.[66]

In situations where dangerously low Hb levels need to be quickly raised, RBC transfusions remain the mainstay management of severely anaemic patients. However, there are certain situations in which transfusion is not an option despite severe anaemia. Examples include patients of the Jehovah's Witness faith who refuse blood transfusions on religious grounds, those with alloantibodies and haemolytic anaemia who cannot be transfused with allogeneic blood, and situations in which blood is not available such as combat or injury in remote locations.[67] In the absence of transfusions, interventions such as sedation and neuromuscular block (to minimize oxygen demand), haematinic agents, delivery of high oxygen concentration and hyperbaric oxygen therapy (to increase the level of plasma-dissolved oxygen),[68] and investigational therapeutics such as artificial oxygen carriers[67 69] can save the life of these patients when severely anaemic, with reports documenting survival of patients with Hb levels as low as 10–20 g litre^{-1} without sequela.[67 69 70] The published record belongs to a 53-yr-old victim of several stab wounds who survived a nadir Hb of 7 g litre^{-1} [haematocrit (Hct) of 2.2%] without receiving blood transfusions due to unavailability of cross-matched blood.[71]

Nonetheless, case series of such patients often provide a solemn account of the grave consequences of acute severe anaemia and critical Hb levels where blood oxygen delivery cannot keep up with tissue oxygen demand. In a study of 300 Jehovah's Witness patients undergoing major non-cardiac surgeries, 30 day in-hospital mortality was 100%, 54%, 25%, 34%, and 9% in patients with postoperative nadir Hb levels of 11–20, 21–30, 31–40, 41–50, and 51–60 g litre^{-1}, respectively. After adjustment for age, cardiovascular disease, and Acute Physiology and Chronic Health Evaluation II (APACHE II) score, the odds ratio (OR) of death for each 10 g litre^{-1} decrease in Hb level was 2.5 [95% confidence interval (CI), 1.9–3.2].[72] In a subset of 256 patients with morbidity data, the composite outcome

of 30-day mortality or morbidity (defined as serious cardiac events, bacteraemia, pneumonia, or deep wound infection) occurred in 100%, 92%, 53%, 58%, and 29% of the patients with the above postoperative Hb levels. The adjusted OR for the composite outcome was 2.1 (95% CI, 1.7–2.6) for every 10 g litre^{-1} decrease in postoperative Hb.[72] Conversely, there was no death in the 30 day period in patients with Hb levels of 70–80 g litre^{-1} and the composite morbidity was observed in 9% of patients.[72] Another study reported a mortality of 33% in 117 surgical Jehovah's Witness patients with postoperative Hb of 60 g litre^{-1} or less. Interestingly, the median time between the lowest Hb measurement and death was 1 day in patients with nadir Hb of 20 g litre^{-1} or less, while it was 11 days for those with lowest Hb between 41 and 50 g litre^{-1}, indicating a window of opportunity to effectively manage these patients.[73] The leading causes of death in these patients were bleeding, respiratory failure, renal failure, sepsis, myocardial infarction, and arrhythmia, with many patients experiencing a combination of morbidities.[73] Similarly, in our case series of patients with severe anaemia who could not be treated with transfusion, mortality rate was 60% in those with Hb between 20 and 30 g litre^{-1} who were not treated with an Hb-based oxygen carrier.[67] Figure 2 depicts the estimated risk of mortality at various Hb levels derived from our data.[67] Based on the available observations, it has been suggested that the mean fatal Hb level (i.e. mean Hb level associated with anaemia-induced mortality) in humans is around 25 g litre^{-1} and possibly (although still subject to debate) higher in the presence of cardiovascular disease.[74]

As discussed previously, several adaptive mechanisms exist to maintain adequate oxygen delivery to tissues in anaemia. With exacerbation of anaemia, these mechanisms begin to fail at various points and risk of tissue ischaemia and injury increases. Tolerance of individual organs to anaemia varies and dictates complications of anaemia. Given their high oxygen demands, the heart and central nervous system are at particular risk. For example, evidence that the brain is vulnerable during acute and chronic anaemia is provided by numerous examples of brain dysfunction and injury. Acute and chronic anaemia are both associated with cognitive dysfunction that partially resolves after treatment of anaemia.[75 76] Although the mechanisms of anaemia are divergent, cerebral injury has been associated with anaemia caused by iron deficiency,[77] malaria,[78] sickle-cell disease,[79 80] and acute severe anaemia during coronary artery bypass procedures.[51]

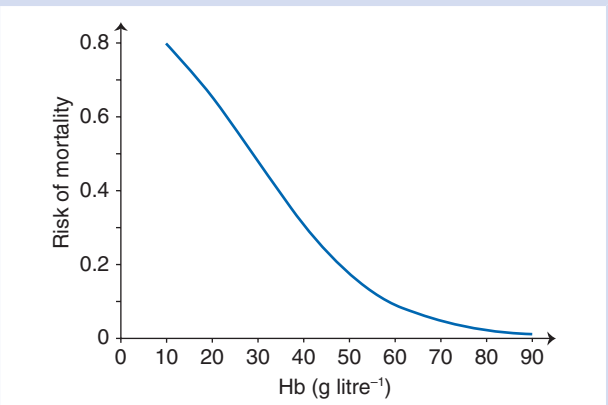

Fig 2 Estimated risk of death at various Hb concentrations. Data are based on a subset of patients (n=19) who could not be transfused, and had agreed to receive an Hb-based oxygen carrier because or in anticipation of severe anaemia, but did not receive the product for various reasons.[67] Risk of mortality for each Hb concentration was calculated using an equation obtained from running a logistic regression model with final status (dead/alive) as the dependent and Hb as the independent variables.

Although anaemia is commonly present in various in-patient and out-patient populations, with some particularly at higher risk (e.g. elderly, critically ill, and those undergoing major orthopaedic surgery or chemoradiotherapy), anaemia is often much less severe than the extreme cases described above. Yet, several lines of evidence support the clinically detrimental effects of anaemia (even when mild to moderate) in various patient populations (see Table 2 for a summary of recent studies).[81–116] Studied populations include general populations, elderly, patients undergoing surgeries (cardiac, orthopaedic, etc.), transplant recipients, critically ill patients, and patients with medical conditions such as chronic renal disease, stroke, acute coronary disease, heart failure, diabetes mellitus, and dementia. Anaemia is associated with several unfavourable outcomes, including higher short- and long-term mortality, increased risk of fractures, renal disease, heart failure, cardiovascular events, readmissions, poorer graft outcome, worse functional status, and lower quality of life.

Perils of transfusion

Given the risks of anaemia, proper management, including timely screening, diagnostic work-up, and efforts to treat the underlying aetiologies, is needed. Treatment can usually be accomplished most effectively using haematinics when the patient is not at risk of ischaemia or when enough time is available before a high-blood-loss elective procedure.[117] Misconceptions exist with regard to the time required for such treatments to exert their effect: while allowing more time is usually preferred (e.g. 4 weeks ahead of elective procedures), when appropriately used, haematinic agents in combination with simple strategies to preserve the patient's own blood (as simple as avoiding unnecessary diagnostic phlebotomies and reducing the drawn blood sample volume)[118] can quickly ameliorate anaemia even within short periods of time.[119]

RBC transfusion is the quickest way to raise Hb concentration and it has been rightfully credited with saving lives of thousands since the fateful day in 1921 when Percy Lane Oliver, honorary secretary of the Red Cross at Camberwell, received an urgent call from a nearby hospital in need

Table 2 Recent studies evaluating clinical outcomes of anaemia in various patient populations. The non-systematic search included the PubMed-indexed English-language manuscripts published between August 2009 and August 2011. WHO criteria: anaemic if Hb <120 g litre^{-1} for women and Hb <130 g litre^{-1} for men. CABG, coronary artery bypass grafting; CHF, chronic heart failure; CPB, cardiopulmonary bypass; Hb, haemoglobin; Hct, haematocrit; HF, heart failure; HR, hazard ratio; ICH, intracerebral haemorrhage; ICU, intensive care unit; MI, myocardial infarction; NA, not applicable; OR, odds ratio; PCI, percutaneous intervention; STEMI, ST-segment elevation myocardial infarction

Study	Population	Anaemia prevalence (and definition)	Findings on anaemia
Cardiac surgeries			
Carrascal and colleagues[105]	227 80-to-90-yr-old patients who underwent CPB	41.9% (WHO criteria)	In multivariate analysis, immediate postoperative Hct $<24\%$ (OR 2.78, $P=0.039$) and transfusion (OR 10.57, $P<0.01$) were independent predictors for in-hospital mortality
De Santo and colleagues[108]	1214 patients undergoing CABG	28% in preoperative period (WHO criteria)	Anaemia was an independent predictor of acute kidney injury (OR 2.06)
Ranucci and colleagues[96]	3003 patients undergoing CPB without receiving blood transfusions during hospital stay	NA; mean preoperative and lowest CPB Hct values were 40.4% and 27.8%, respectively	After adjustment for the other explanatory variables, preoperative Hct and lowest Hct on CPB were independent risk factors for major morbidity
Outpatient populations			
Chen and colleagues[81]	160 080 post-menopausal women	5.5% (Hb <120 g litre^{-1})	Significantly higher risk of fracture after adjustment for multiple covariates (HR 1.07)
Deal and colleagues[106]	436 community-dwelling women aged 70–80 yr old	8.8% at baseline (WHO criteria)	After adjustment for patient characteristics and disease covariates, anaemia was associated with poorer baseline performance and faster rate of decline on tests of verbal recall
Jorgensen and colleagues[98]	5286 55-to-74-yr-old residents of Tromsø, Norway	3.4% (WHO criteria)	Anaemic men had a 2.15 higher risk of non-vertebral fractures while anaemic women had no increased fracture risk
Lipinski and colleagues[116]	1799 patients referred for routine exercise treadmill testing	9% (Hb <130 g litre^{-1})	Anaemic patients had significantly higher mortality ($P<0.05$) and cardiovascular events ($P<0.01$)
Savica and colleagues[102]	196 subjects who developed Parkinson's disease and 196 matched controls	43.9% in cases and 27.6% in controls (WHO criteria)	Anaemia was more common in medical history of patients with Parkinson's disease (OR 2, $P<0.01$)
Zoppini and colleagues[97]	1153 type 2 diabetic outpatients	18.4% (WHO criteria)	After adjustment for other factors, anaemia was associated with all-cause (HR 2.11, $P<0.01$) and cardiovascular mortality (HR 2.23, $P=0.02$)
Chronic kidney diseases			
De Nicola and colleagues[82]	668 stage 3–5 chronic kidney disease patients	41.3% (Hb 110–135 g litre^{-1} in males; Hb 110–120 g litre^{-1} in females)	Anaemia was a marker of end-stage renal disease (HR 1.81) and death (HR 1.87)
Sasatomi and colleagues[112]	166 patients with diabetic nephrosclerosis	21% (Hct $\leq 40\%$)	Anaemia was significantly associated with renal prognosis and survival
Voormolen and colleagues[89]	472 predialysis patients	45% (Hb ≤ 110 g litre^{-1}); mean Hb 112 g litre^{-1}	Anaemia was associated with higher adjusted risk of mortality (HR 1.92) and all-cause hospitalization
Cerebrovascular accidents			
Del Fabbro and colleagues[84]	890 first-time stroke patients	17% (WHO criteria)	After adjustment for other factors, higher Hb level was independently associated with decreased 1-yr mortality (HR 0.98, $P<0.05$)
Diedler and colleagues[91]	196 patients with supratentorial, non-traumatic ICH	NA; mean admission Hb: 137 g litre^{-1}; mean Hb during hospital stay: 126 g litre^{-1}; mean nadir Hb: 119 g litre^{-1}	In multivariate logistic regression analysis, Hb was an independent predictor for poor functional outcome at 3 months (OR 0.73, $P<0.01$)

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Table 2 *Continued*

Study	Population	Anaemia prevalence (and definition)	Findings on anaemia
Tanne and colleagues[92]	859 patients with acute stroke (ischaemic or haemorrhagic)	19% (WHO criteria)	After adjustment for baseline characteristics, anaemia at admission was associated with increased risk of all-cause death at 1 month (OR 1.9) and 1 yr (1.72), increased disability (OR 2.09), and nursing facility care (OR 1.83). Extremely high Hb level was also associated with increased mortality
Chronic heart diseases			
Dimopoulos and colleagues[99]	830 non-cyanotic adults with congenital heart disease	13.1% (WHO criteria)	Anaemic patients had three-fold higher mortality risk after propensity score adjustment for clinical variables
Hamaguchi and colleagues[109]	1960 patients hospitalized with worsening HF	57% (WHO criteria)	After multivariable adjustment, low Hb was associated with increased risk of all-cause death, cardiac death, and rehospitalization
Kimura and colleagues[86]	711 hospitalized patients with CHF	44.7% (Hb <120 g litre^{-1} at the time of hospitalization)	In multivariate analysis, anaemia was a predictor of mortality (HR 1.62, $P<0.01$)
Peterson and colleagues[104]	2478 patients with primary discharge diagnosis of HF	45% at the time of index hospitalization and 35% during follow-up (WHO criteria)	Persistently low Hb (HR 1.65) and progressively declining Hb (HR 1.54) were associated with increased mortality risk
Saraiva and colleagues[85]	391 patients admitted to a single advanced heart failure care unit	43.2% (WHO criteria)	In multivariate analysis, anaemia was an independent predictor of mortality at 1 yr ($P=0.035$), with an inverse relationship between Hb levels and mortality
von Haehling and colleagues[100]	627 patients admitted with acute HF	29% (WHO criteria)	Patients with moderate or severe anaemia (Hb <12 in men or <110 g litre^{-1} in women) had increased 12-month mortality (HR 1.5, $P=0.01$) after adjusting for other factors
von Haehling and colleagues[114]	2069 70-yr-old or older patients with HF	10% (WHO criteria)	After multivariable adjustment, Hb was an independent predictor of combined primary outcome of mortality and cardiovascular hospital admissions (HR 0.94 per 10 g litre^{-1} decrease, $P=0.017$)
Vrtovec and colleagues[103]	65 patients who had left ventricular assist device for at least 6 months	46% (Hb <120 g litre^{-1})	Long-term survival was two times higher in non-anaemic patients
Ischaemic heart diseases			
Greenberg and colleagues[95]	1042 patients with STEMI who underwent PCI	20% (Hct $<36\%$ for women and $<39\%$ for men)	In multivariate analysis, anaemia was associated with an OR of 3.5 ($P<0.01$) for 1 month mortality
Hasin and colleagues[107]	1065 patients with acute MI	34.7% at discharge, 19.5% persistent at follow-up, and 5.2% new-onset at follow-up (WHO criteria)	Marked increase in mortality and heart failure in patients with persistent (HR 1.8) and new-onset anaemia (HR 1.9)
Kruk and colleagues[101]	1880 patients with STEMI treated with primary PCI	21.1% (Hct $<36\%$ in women and Hct $<39\%$ in men)	In multivariable analysis including important baseline risk factors, anaemia was independently associated with in-hospital death (HR 2.67)
Kurek and colleagues[94]	1497 patients with acute MI treated with PCI	16.6% (WHO criteria)	Multivariate analysis identified anaemia as an independent predictor of any-cause death (HR 1.46, $P<0.05$)
Orthopaedic procedures			
Mantilla and colleagues[83]	391 hip or knee arthroplasty patients who experienced death/MI and 391 matched control	39% of cases and 32% of controls (WHO criteria)	Anaemia was not a significant independent risk factor for death/MI in the 30 day post-surgery period (OR 0.81, $P=0.286$)
So-Osman and colleagues[88]	603 patients undergoing total hip and knee arthroplasty	16.3% (no definition specified)	No correlation between postoperative Hb or acute postoperative Hb decline and quality of life

Continued

Table 2 *Continued*

Study	Population	Anaemia prevalence (and definition)	Findings on anaemia
Critically ill patients			
Sakr and colleagues[87]	5925 patients admitted to a surgical ICU	18.7% (Hb <70 g litre^{-1}) and 29.5% (Hb 70–90 g litre^{-1} at admission); mean Hb 99 g litre^{-1}	After multivariate adjustment, higher Hb level (RR 0.97 per 10 g litre^{-1}, $P<0.001$) and blood transfusions (RR 0.96, $P=0.031$) were independently associated with a lower risk of in-hospital death
Others			
Gheith and colleagues[113]	832 renal transplant recipients	53.7% (WHO criteria)	Anaemia at 6 months was associated with poor graft outcome but not patient survival
Nathavitharana and colleagues[115]	1491 non-surgical inpatient admissions	33.3% (WHO criteria)	Anaemia was independently associated with increased length of hospital stay ($P<0.01$), mortality ($P<0.01$), and unplanned hospital readmission ($P<0.01$)
Reade and colleagues[93]	1893 patients with community-acquired pneumonia	33.9% and 62.1% (Hb ≤130 g litre^{-1} at admission and during hospital stay, respectively)	Development of moderate-to-severe anaemia (Hb ≤100 g litre^{-1}) was independently associated with increased 90-day mortality (OR 1.59, $P=0.01$)
Shema-Didi and colleagues[90]	19 271 patients with normal kidney activity admitted to hospital	27.6% (WHO criteria)	Anaemia at admission was associated with occurrence of acute kidney injury after controlling for potential confounders (OR 1.5).
Toor and colleagues[110]	101 patients with advanced peripheral vascular disease undergoing percutaneous transluminal angioplasty	65% (WHO criteria)	Pre-procedural Hb (OR 4.17 comparing lowest tertile with highest tertile, $P<0.01$) was an independent predictor of adverse peripheral vascular outcome
Weber and colleagues[111]	5873 general surgery procedures	27.6% (Hb <120 g litre^{-1} before surgery)	After adjustment for important patients and procedure characteristics, anaemia or allogeneic blood transfusion were not associated with surgical site infections

of a volunteer blood donor, creating the world's first transfusion service.[120] Transfusion-transmitted infections came to attention as early as the 1940s.[121] Over the decades that followed, developed countries invested virtually unlimited resources to screen for and identify the responsible infectious agents early enough and, as such, improve the safety of blood supply. While these efforts have been highly effective in achieving their goal (albeit with a hefty price tag that might undermine the cost-effectiveness),[122] emergence of new infectious agents such as human immunodeficiency virus[123] and variant Creutzfeldt–Jakob disease[124] has challenged the possibility of creating a blood supply that is absolutely free of risk of transmitting infectious agents.[125 126] Nonetheless, the risk of transfusion-transmitted infections has diminished to the point that for the first time in its 14 yr history, the UK's Serious Hazards of Transfusion (SHOT) haemovigilance initiative had no confirmed case of transfusion-transmitted infection in its 2010 report. However, non-infectious risks and complications of blood transfusion have taken the lead (Table 3).[127]

The 2010 SHOT data (Table 3) indicate that 505 serious complications and events resulting in (or contributing to) 4.5 deaths and 35 major morbidities were reported per 1 million units of blood component issued. In the same period, 345 critical transfusion errors that could have resulted in transfusion of wrong blood components occurred per 1 million units of blood component issued.[127] Not all events are reported under this and similar programmes, and some complications of transfusion (e.g. transfusion-related acute lung injury [TRALI]) are known to be vastly under-diagnosed and under-reported.[128 129] Still, these numbers provide an overall picture of the prevalence of major known immediate complications and risks of blood transfusions and their consequences.

What is missed in these and similar types of data is another important risk of transfusion that could potentially be affecting significantly higher number of patients. With a few exceptions, it is easy to establish the causal link of the complications listed in Table 3 with transfusions. There are, however, other risks of allogeneic blood that are much more enigmatic as they are not as obviously linked to transfusions and can be attributed to other events or the recipients' co-morbidities. Data supporting these types of risks come from a multitude of studies linking allogeneic blood transfusions with worse outcomes in various patient populations.[130]

The Transfusion Requirements in Critical Care (TRICC) trial was a turning point in transfusion medicine as it showed that a restrictive transfusion strategy was at least equally effective as a more liberal-transfusion strategy in critically ill anaemic patients.[131] This finding was confirmed by a

Table 3 Serious complications of transfusions and related events in 2010 reported under the SHOT initiative in the UK. Reports were submitted by 94.7% of National Health System (NHS) hospitals or trusts; 2 898 425 units of blood components (including 2 180 781 units of RBC) were issued in the UK during the same period. Numbers in parentheses indicate the percentage of transfusion-related deaths or major morbidities for each type of reported complication or event.[127] *Incidences in which the patient was transfused correctly despite one or more serious errors that could have potentially resulted in transfusion of incorrect blood component in other circumstances

Reported complications and events	Number of reported events	Reported numbers per million blood component units issued	Deaths with transfusion as a causal or contributory factor	Major morbidities attributed to transfusion
Incorrect blood component transfused	200	69	0	2 (1%)
Inappropriate, unnecessary, and under/delayed transfusions	110	38	2 (1.8%)	4 (3.6%)
Handling and storage errors	239	82	0	0
Failure to give anti-D immunoglobulin	241	83	0	1 (0.4%)
Acute transfusion reactions	510	176	3 (0.6%)	57 (11.2%)
Haemolytic transfusion reactions	58	20	1 (1.7%)	2 (3.4%)
Transfusion-related acute lung injury (TRALI)	15	5	1 (6.7%)	13 (86.7%)
Transfusion-associated circulatory overload (TACO)	40	14	6 (15%)	15 (37.5%)
Transfusion-associated dyspnoea	35	12	0	6 (17.1%)
Post-transfusion purpura	1	0	0	0
Transfusion-associated graft-*vs*-host disease	0	0	0	0
Transfusion-transmitted infection	0	0	0	0
Complications from transfusion of autologous blood	15	5	0	1 (6.7%)
Total reported serious incidences	1464	505	13 (0.9%)	101 (6.9%)
Near-miss events	863	298	—	—
Right blood right patient incidences*	137	47	—	—

subsequent Cochrane systematic review of 17 trials (including the TRICC trial) on a total of 3746 patients which concluded that restrictive transfusion strategies are associated with reduced transfusion rates and volumes while not worsening patient outcomes (including mortality, cardiac events, stroke, pneumonia, and thromboembolism) and reducing infection rates.[132] The data from TRICC become more intriguing when viewed from a complication perspective: The patients in the liberal-transfusion arm of the study were all transfused and received on average 3 more units of RBC transfusions compared with the restrictive transfusion arm who had a transfusion rate of 66%. Despite comparable baseline characteristics and severity of illness, patients who were transfused liberally suffered more in-hospital deaths (23.3% *vs* 18.7%), higher adjusted multiple organ dysfunction score (11.8 *vs* 10.7), and more complications [combined cardiac complications (21.0% *vs* 13.2%), myocardial infarctions (2.9% *vs* 0.7%), and pulmonary oedema (10.7% *vs* 5.3%)] during intensive care unit (ICU) stay.[131] Two groups of patients, those with acute coronary syndromes and those with traumatic brain injury, might not follow this pattern.[133 134] Indeed, a recently completed pilot trial in high-risk cardiac surgery suggests that these patients might have more favourable outcome with a higher transfusion threshold.[135]

The observation that allogeneic blood transfusions are associated with worse patient outcomes (e.g. higher mortality and morbidity rates) is a common finding in studies comparing cohorts of transfused patients with non-transfused (or less-transfused) patients across various patient populations (Table 4).[136–154] The frequency of unfavourable outcomes associated with allogeneic blood transfusions observed in these studies is clearly much higher than expected from the effects of traditional transfusion complications alone given their relative low frequency (Table 3). Similar to the case of anaemia, the studies have evaluated widely different patient populations, and they have linked RBC transfusions with many negative outcomes including renal, cardiac, and neurological events, infections, lung injury, increased length of stay, increased risk of cancer occurrence or recurrence, and death. On the other hand, transfusion is often associated with other co-morbidities, and factors such as older age can confound the relationship. However, allogeneic blood transfusion usually emerges as an independent risk factor after adjustment for other potential factors.[136 137 140–153] Risks of allogeneic blood transfusion should be viewed in the context of the assertion that efficacy of RBC transfusions in improving patient outcomes is largely unestablished. Using evidence

Table 4 Recent studies evaluating the clinical outcomes of allogeneic RBC transfusions various patient populations. The non-systematic search included PubMed-indexed English-language manuscripts published between August 2009 and August 2011. ARDS, acute respiratory distress syndrome; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; Hb, haemoglobin; Hct, haematocrit; HR, hazard ratio; ICU, intensive care unit; LOS, length of stay; OR, odds ratio; PRBC, packed red blood cell; SAH, subarachnoid haemorrhage

Study	Population	Transfusion rate	Findings on transfusion
Cardiac surgeries			
Bahrainwala and colleagues[138]	617 patients undergoing cardiac surgery with CPB	Not specified	Higher quartile of PRBCs transfused was associated with higher risk of postoperative stroke (OR 1.37)
Ferraris and colleagues[137]	8728 nonvascular cardiac operations	9.8%	After propensity adjustment, transfusion of 1–2 units of PRBC increased the risk of composite morbidity, pulmonary complications, systemic sepsis, wound complications, and postoperative LOS
Koch and colleagues[150]	16847 patients undergoing on-pump CABG, valve or combined procedures	Not specified	RBC transfusion was associated with more risk-adjusted complications including respiratory distress and failure, longer intubation time, ARDS and reintubation
Mohnle and colleagues[144]	945 patients undergoing CABG	20.4%	In multivariate analysis, RBC transfusion was associated with cardiac events (OR 1.39, $P=0.04$) and harvest-site infection. Other possible associations included increased risk of composite morbidity, in-hospital mortality, renal morbidity, pneumonia, and mediastinitis
Salvin and colleagues[141]	802 paediatric patients discharged after cardiac surgery	46.2%	In a multivariable model, both the low transfusion group (HR 0.80, $P=0.02$) and high transfusion group (HR 0.66, $P<0.01$) were associated with increased LOS
van Straten and colleagues[151]	10 435 patients undergoing CABG surgery	23.3%	RBC transfusion was an independent, dose-dependent risk factor for early mortality
Veenith and colleagues[147]	874 80-yr-old or older patients undergoing cardiac surgery	73.4%	Transfusion was independently associated with hospital mortality
Vivacqua and colleagues[136]	566 reoperations after CABG, valve, or combined surgeries	36%	More transfusion was independently associated with increased risk of mortality and major morbidity
Whitson and colleagues[152]	741 patients undergoing CABG, valve procedures, or both	54%	In multivariate analysis, transfusions were independently associated with infection, neurological complications, organ dysfunction, cardiac complications, and death
Malignancies			
Chau and colleagues[143]	520 patients undergoing head and neck surgery for cancer	37.9%	In multivariate analysis, blood transfusion was an independent predictor of recurrence (OR 1.6) and survival (HR 1.5)
Chang and colleagues[154]	77 488 elderly haematologic malignancy cases and 154 509 controls	7.9% of cases and 5.9% of controls	Transfusion was associated with increased risk of lymphoplasmacytic and marginal zone lymphomas
Vascular, orthopaedic, and other surgeries			
Glance and colleagues[139]	10 100 patients undergoing general, vascular, or orthopaedic surgery	21.4%	Intraoperative transfusion was associated with increased risk of death (OR 1.29), pulmonary complications (OR 1.76), sepsis (OR 1.43), thromboembolic complications (OR 1.77), and wound complications (OR 1.87)
Nuis and colleagues[142]	118 patients undergoing transcatheter aortic valve implantation	Not specified	RBC transfusion was independently associated with increased risk of acute kidney injury
O'Keeffe and colleagues[148]	8799 patients undergoing lower extremity revascularization	Ranging from 14.5% to 27.1%	After adjustment for transfusion propensity and patient and procedural risks, transfusion was a significant predictor of mortality (OR 1.92 for 1–2 units and 2.48 for 3 or more units), composite morbidity, sepsis/shock, pulmonary occurrences, and return to the operating theatre
Pedersen and colleagues[149]	28 087 patients undergoing primary total hip replace surgery	32.3%	Transfused patients had higher 90-day mortality (OR 2.2) and pneumonia (OR 2.1) in multivariate analysis
Wu and colleagues[145]	239 286 65-yr-old or older patients who underwent major non-cardiac surgery	9.4%	After propensity-score matching, transfusion was associated with lower 30 day mortality in patients with preoperative Hct <24% or blood loss >500 ml, but associated with higher mortality if Hct 30–35.9% or blood loss <500 ml

Continued

Table 4 *Continued*

Study	Population	Transfusion rate	Findings on transfusion
Other non-surgical populations			
Hearnshaw and colleagues[146]	4441 acute upper gastrointestinal bleeding patients presenting to hospitals	44% (within 12 h of admission)	After adjusting for Rockall score and initial Hb, early transfusion was associated with two-fold increased risk of re-bleeding (OR 2.26) and a 28% increase in mortality (OR 1.28)
Jolicoeur and colleagues[153]	5532 patients with ST-elevation myocardial infarction	3.9%	After adjustment for baseline characteristics, other interventions, and propensity for receiving transfusions, blood transfusion remained a significant risk factor for mortality (HR 2.16)
Juffermans and colleagues[140]	134 patients with sepsis after ICU admission	50%	In an adjusted model, the amount of transfused RBCs was associated with secondary infection (OR 1.18)

from published literature, a panel of clinicians recently rated allogeneic blood transfusions unlikely or uncertain to improve patient outcomes in the vast majority of common hypothetical clinical scenarios in which blood transfusions are commonplace.[130] Credible risks and dubious efficacy do not make a promising combination and fail to justify the widespread utilisation of allogeneic blood transfusions in practice.

Dissecting the causality

Anaemia and allogeneic blood transfusions have been linked to worse clinical outcomes in various patient populations. It remains a challenge to conclude with certainty whether anaemia is an independent risk factor of worse outcomes, is a marker of severity of disease, or both.

Most of the studies establish correlation between anaemia and various unfavourable outcomes (Table 2), but correlation does not necessarily imply causation. Causality can be particularly complicated and difficult to establish in certain populations since anaemia is common in patients suffering from a wide array of chronic illnesses that could negatively affect outcomes. Anaemic cohorts are commonly older, and more frequently afflicted by co-morbidities compared with non-anaemic patients in most of the studies. Frequently, anaemia is caused or contributed to by chronic illnesses. Anaemia of chronic disease (or anaemia of inflammation) results from activation of inflammatory responses during many diseases that affect several aspects of haematopoiesis, namely, hepcidin-induced sequestration of iron and hypoferremia.[155 156] Another example is the vicious triad known as cardio-renal-anaemia syndrome, in which chronic cardiac or renal dysfunction results in dysfunction of the other organ and concurrent development of anaemia, which, in turn, exacerbates both organ failures.[157 158] Although it might not be possible to attribute an unfavourable outcome to an individual factor alone or establish an accurate apportionment among various factors in such cases, accomplicity of anaemia and chronic diseases in worsening the clinical outcomes is usually evident, and anaemia often emerges as an independent risk factor after adjustment for confounders in multivariate analyses.[81 84–87 89–97 99–101 105 106 108–110 114 115]

Another factor complicating the relationship between anaemia and unfavourable clinical outcomes is the treatments used for anaemia. For example, erythropoiesis-stimulating agents (ESAs) have been the focus of heated debate, as they are highly effective in increasing Hb level in various patient populations. However, treatment with these agents comes with risks of its own and has been linked to increased risk of mortality and cardiovascular events, particularly when the ESA dose is increased or continued in order to achieve a predetermined relatively high Hb target.[159 160] Thus, whether the outcomes seen in anaemic patients are related to anaemia or treatment with ESAs is unclear.[161] Allogeneic blood transfusion is the other common treatment used in management of anaemic patients, with its own plethora of complications.

Similar to the case of unfavourable outcomes of anaemic patients, transfused cohorts often have a heavier burden of illness, and it can be challenging to delineate with certainty whether unfavourable outcomes are due to the existing conditions and co-morbidities that biased the patients to receive more transfusions or due to the transfusion itself. Nonetheless, even when patients who are transfused are in worse condition to begin with, part of the reason they were transfused was likely to be the expectation that transfusions would improve their condition. As can be seen from the multitude of studies (Table 4), allogeneic blood transfusions appear to do little to improve patient condition, undermining the clinical effectiveness of transfusions.

Clinical trials in which patients are randomized to various transfusion strategies provide some protection against this possible bias of sicker patients being more likely to get transfused, but these trials ultimately focus on comparison of various transfusion strategies (such as various Hb-based transfusion triggers),[162] and not directly on the outcomes of transfusion. Given ethical and methodological complexities, a trial randomizing patients to transfusion *vs* no transfusion might not be feasible.

Compared with the limited evidence from randomized controlled trials, the wealth of data from observational

studies on allogeneic blood transfusion is staggering. Transfusion practices show well-documented significant variations across providers and institutions. Maddux and colleagues[163] reported the rate of intraoperative RBC transfusion in isolated coronary artery bypass graft (CABG) surgeries to range from 0% to 85.7% across 144 institutions in the USA. Bennett-Guerrero and colleagues[164] studied 82 446 on-pump CABG operations from 408 sites in the USA and reported the RBC transfusion rates from 7.8% to 92.8%; these variations occurred independent of case mix. Data from 18 Austrian public hospitals indicated intra- and postoperative blood transfusions occurring in 16–85% of total hip replacement, 12–87% of total knee replacement, and 37–63% of CABG surgeries; the number of RBC units given in transfused patients also varied significantly.[165] Similarly, an audit of 223 hospitals in the UK reported that perioperative transfusion rates ranged from 0% to 100% in patients undergoing elective primary unilateral hip replacement surgery.[166] The hugely variable transfusion rate in more-or-less similar procedures and patient populations occurring at hospitals with presumably high standards of care begs the question that what the role of blood transfusion in patient care is and what goal it is achieving. Clearly, the possible explanation that sicker patients are transfused more frequently cannot explain by itself these variations, and other factors (such as various transfusion thresholds) are at play.[166] In other words, physicians' attitudes towards transfusion are likely to be as important (if not more important) than the patients' condition in determining who receives blood, to the point of creating a *de facto* quasi-randomized process. We believe that this would add to the credibility of the observational data on clinical outcomes of transfusion.

It is often overlooked that some of the most influential discoveries in medicine were derived from observation in contexts where human experimentation would have been unethical (e.g. the relationship between smoking and lung cancer).[167] Data from observational studies can be viewed in the light of Bradford Hill's nine criteria to establish causation based on association: strength of association, consistency, specificity, temporal relationship, biological gradient (dose-dependence), plausibility, coherence, analogy, and availability of experimental evidence.[167] Although Bradford Hill is famously quoted as saying that 'None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required *sine qua non*',[168] data from studies on association of adverse outcomes with allogeneic blood transfusions fit all of these criteria, and therefore, a strong case for causality exists.[167]

The exact pathways through which allogeneic blood transfusions result in adverse outcomes are not fully understood and several phenomena have been suggested.[167] The analogy of allograft can provide a clue: similar to grafts, allogeneic blood transfusions can result in cascades of immunologic and inflammatory reactions.[169] Overt events such as haemolytic reactions are one end of the spectrum, but the other end of the spectrum can be more cryptic in the form of immunomodulation.[170] This has been implicated in the reported association between allogeneic blood transfusions and cancer.[170 171] Another suspect has been the white blood cells present in donated blood.[172] Nowadays, banked blood is widely leucoreduced in many countries and before–after studies are indicative of reduced complications and improvements in outcome, namely, reduced febrile transfusion reactions, alloimmune platelet refractoriness, and infections.[173 174] Another factor suspected to play a role in adverse effects of transfusion is the age of stored allogeneic blood. Several observational studies have reported worse outcomes in patients who received older units of blood (still within current blood banking standards), and randomized trials to further investigate this are underway.[175]

There is no doubt that occurrence of an adverse outcome in a patient is a result of complex interactions among various patient and environment (treatment) factors. Figure 3 depicts a simplified scheme summarizing some of the interactions that exist among anaemia, blood transfusions, and co-morbidities in causal loops that could contribute to unfavourable outcomes. As discussed here, co-morbidities (i.e. chronic illness in Fig. 3), anaemia, and transfusions all can independently worsen the outcome. Chronic illnesses and anaemia can reinforce each other as seen in anaemia of inflammation. Another reinforcing loop can exist between chronic illnesses and allogeneic blood transfusions: some co-morbidities (especially ischaemic heart disease) are commonly considered to reduce tolerance to anaemia and therefore can result in more transfusions, which in turn could increase inflammation and organ injury. Anaemia could also reinforce this interaction by increasing the risk of transfusions. Finally, once an unfavourable outcome occurs, it can further reinforce the whole vicious cycle through increasing the inflammation and chronic illness burden, exacerbating anaemia, and increasing the risk of getting transfused (e.g. when an anaemic patient recovering from an elective surgery experiences a new myocardial infarction resulting in prolonged hospitalization and ICU stay, followed by more diagnostic blood loss, etc.).

An example of these interactions can be seen in the study by Kao and colleagues,[176] in which the impact of renal insufficiency, anaemia, and transfusions on in-hospital mortality was examined in 596 456 patients admitted for heart failure. Renal insufficiency and anaemia were present in 27.4% and 27.1% of the patients; both were independently associated with increased mortality (adjusted OR 2.54 and 1.12, respectively). RBC transfusions were given to 6.2% of the patients, and it was the strongest single predictor of mortality (OR 3.81). In this population, all three components (anaemia, renal insufficiency, and transfusion) were independently associated with mortality, and transfusion reinforced the detrimental effects of the other two.[176]

Breaking the vicious cycle

As discussed here, anaemia and transfusions can independently and synergistically contribute to poor outcomes and can potentially form reinforcing loops. How can this vicious

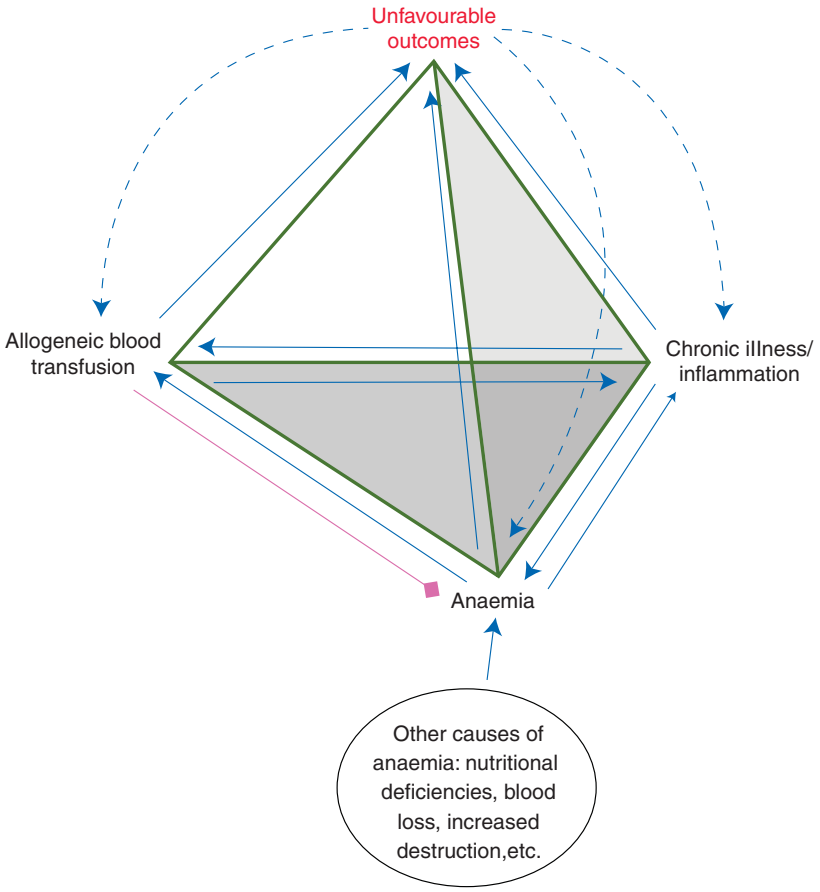

Fig 3 Causal pyramid depicting the theoretical relationship of anaemia and its accomplices in causing unfavourable outcomes. Positive causal links are denoted by solid arrows and indicate that the first node (or increase in its severity or dose in the case of transfusions) would cause the second node (or increase in its severity or dose in the case of transfusions). A negative causal link denoted by dashed arrow exists between transfusion and anaemia as the former is expected to reduce the severity of the latter (albeit temporarily), but the effectiveness of this measure in terms of improving oxygen delivery and consumption is debated. Unfavourable outcomes can include occurrence of new morbid events or exacerbation of pre-existing ones, which could lead to increased chronic illness/inflammation burden and further reinforce the loop.

cycle be broken? Anaemia should never be regarded as an innocent bystander.[177] Patients at risk, particularly those undergoing elective surgery, should be screened for anaemia as early as possible, preferably 4 weeks ahead of surgery. If present, diagnostic work-up to uncover the aetiology of anaemia must be performed and appropriate treatment provided.[117 178] Rather than allowing an anaemic patient to go into the operating theatre and be transfused to rectify the Hb value, anaemia must be viewed as a contraindication for the elective procedure (particularly if high blood loss is anticipated), and the procedure should be rescheduled to manage anaemia first.[117] Current guidelines should be followed for allogeneic blood transfusions,[179–181] and each unit of blood should be given only when clear indication exists. The ultimate goal of transfusion must remain avoiding organ ischaemia and treating the clinical condition, and not treating a laboratory value (i.e. attaining a specific Hb value). This is often in contrast with routine clinical practices. In a study of randomly selected hospitalized patients in Northern Ireland, Barr and colleagues[182] reported that 23% of transfusions were inappropriate and among the patients who were appropriately transfused, 19% were over transfused. Clearly, much room for improvement exists.

Many strategies to improve outcome while reducing allogeneic blood transfusions are available. These strategies rely on approaches to optimize haematopoiesis, minimize blood loss, and use and manipulate physiological responses to anaemia while treating this condition with minimal or no use of allogeneic blood transfusion. The concept encompassing these interventions is collectively known as patient blood management.[183–185] Emerging evidence supports the efficacy of these strategies in managing various patients, including those known to be exposed to a high risk of blood loss, anaemia, and transfusion.[69 186–188] Using these strategies, it is possible to detect and treat anaemia in a timely manner and mitigate the risk of allogeneic blood

transfusions and their associated negative outcomes. Untreated anaemia and inappropriate transfusions are both deleterious to patients in addition to being significant burdens to the healthcare system. Therefore, clinicians should remain vigilant and apply evidence-based best clinical practices to save patients from the long list of adverse outcomes associated with allogeneic transfusion.

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Conflict of interest

A.S. has been a consultant for Bayer, Luitpold, Masimo, Novartis, Novo Nordisk, OrthoBiotech, and Zymogenetics and has received research and grant support from Bayer, Novartis, Novo Nordisk, OrthoBiotech, Pfizer, and ZymoGenetics; and has been a speaker with honorarium for Bayer, Novartis, OrthoBioetch, Zymogenetics, Masimo. He is a founding member of the Society for the Advancement of Blood Management where he currently serves as the President Elect. S.O. is a founding member of the Society for the Advancement of Blood Management where she currently serves as a member of the Board of Directors. G.M.T.H. has received research funding from Forest Laboratories Inc. to assess the impact of nebivolol on cerebral perfusion. G.M.T.H has received peer-reviewed funding from a Bristol-Myers Squibb-CAS Career Scientist Award; a University of Toronto, Department of Anesthesia Merit Award; and IARS-SCA New Investigator and Mid-Career Grants.

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