Economic considerations on transfusion medicine and patient blood management

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In times of escalating health-care cost, it is of great importance to carefully assess the cost-effectiveness and appropriateness of the most resource-consuming health interventions. A long-standing and common clinical practice that has been underestimated in cost and overestimated in effectiveness is the transfusion of allogeneic blood products. Studies show that this intervention comes with largely underestimated service cost and unacceptably high utilisation variability for matched patients, thus adding billions of unnecessary dollars to the health-care expenditure each year. Moreover, a large and increasing body of literature points to a dose-dependent increase of morbidity and mortality and adverse long-term outcomes associated with transfusion whereas published evidence for benefit is extremely limited. This means that...
transfusion may be a generator for increased hospital stay and possible re-admissions, resulting in additional billions in unnecessary expenditure for the health system. In contrast to this, there are evidence-based and cost-effective treatment options available to pre-empt and reduce allogeneic transfusions. The patient-specific rather than a product-centred application of these multiple modalities is termed patient blood management (PBM). From a health-economic perspective, the expeditious implementation of PBM programmes is clearly indicated. Both patients and payers could benefit from this concept that has recently been endorsed through the World Health Assembly resolution WHA63.12.

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Introduction and background

In most countries of the developed world, the growth of health-care expenditure is constantly outpacing that of the gross domestic product (GDP). From 1970 to 2010, the health spending to GDP ratio has grown from 6.0% to 11.6% in Germany, from 4.5% to 9.6% in the United Kingdom and from 5.4% to 11.6% in France. Numbers are similar for many other member countries of the Organisation for Economic Co-operation and Development (OECD). In the United States, the ratio has even reached a level of 17.9% compared to 7.1% and the Center for Medicare and Medicaid Services (CMS) estimates it will reach 19.6% by 2021. Many experts agree that this development is unsustainable. Various reasons for this growth have been identified and measures have been proposed to stop further escalation and contain the burden of health-care costs. One part of the action plan is a thorough examination of the appropriateness of health interventions and another is the rigorous assessment or, in the case of long-standing clinical standard interventions, the re-assessment of their cost-effectiveness. Compelling evidence shows that transfusion of the various allogeneic blood components is one of the widely used procedures that is overdue for such health-economic analyses and therefore may soon come to the end of its life cycle, at least in many elective surgical settings.

The true cost of administering blood transfusion

The transfusion of allogeneic blood products, particularly of red blood cells (RBCs), is one of the most prevalent interventions in clinical practice. The World Health Organization (WHO) Global Database on Blood Safety reports that 92 million units of blood were donated in 2011. Approximately half of this volume was collected, processed and paid for in high-income countries with the largest proportion in the European Union, followed by the United States. Although sometimes referred to as a gift coming from non-remunerated donors, the testing and processing of these huge quantities carries significant cost and, in some countries, also yields a profit margin for blood services and related industries. This is why allogeneic blood components come with a price tag and health-care providers or government institutions have to pay the bill. In the USA, the mean hospital acquisition cost for RBCs in 2009 was $223.09 (2008 dollars) and in Australia it is currently priced at AUD$339 (2010 dollars). In Europe prices are lower, possibly because of lower labour cost rates, subsidisations and unpaid volunteers working in various blood services. A much larger cost compared to product acquisition cost is that for the numerous hospital resources that are necessary to run a transfusion medicine department, to phlebotomise, schedule, test and prepare patients eligible for transfusions, to administer blood components to the recipient, to monitor the entire transfusion event, to treat reactions and to document and file all mandated information. Clerical routines and paperwork, cold-chain logistics, information technology (IT) support, human resource management, accounting, purchasing, risk management, cleaning, waste management, maintenance, training and education, quality management and general administration are also necessary to enable hospital transfusion services. Accordingly, a reasonable share of direct and indirect overhead costs has to be allocated to fully assess the cost of transfusion. Activity-based costing (ABC) is an appropriate methodology to capture the cost of complex processes,
especially when they are spread across many cost centres as in the field of inpatient blood transfusions.\textsuperscript{7,8} For this reason ABC was used to capture the total cost of transfusion in four hospitals in the USA and Europe. Study results showed that the mean total cost of administering a single unit of RBCs to surgical patients was between $726 and $1183 in the USA and between $522 and $611 in Europe (2007 dollars).\textsuperscript{9} The total number of RBC units transfused in the USA in 2009 was 14.9 million.\textsuperscript{4} The multiplication of this number with the mean activity-based transfusion cost captured in the two US centres of the study indicates that total annual RBC transfusion costs are somewhere around $14 billion.

**The cost of transfusion variability**

In micro-economic analyses, particularly in the field of quality management, the huge variability in resource utilisation of standardised service and production processes is clearly an indicator for the squandering of resources. The transfusion rate in Denmark is at 60.2 units per 1000 population, in Germany 57.3, in the UK 36.1 and in France 35.4. These countries have similar demographics, similar health systems and a similar distribution of disposable income. However, the range of per capita transfusion variability is almost 1:2.\textsuperscript{10–12} When benchmarking blood utilisation between hospitals, even in matched patient groups, the variability ranges are far greater.

The first inter-centre benchmark studies on transfusion were conducted around 1990. Surgenor et al. studied the transfusion behaviour in patients undergoing total knee and hip replacement surgery in 151 US hospitals. The investigators observed a significant variability in the number of patients transfused, although not in the mean number of RBC units transfused per transfused patient.\textsuperscript{13,14} In 1994 the European Commission sponsored the Sanguis Study (The Sanguis Study Group 1994) to examine transfusion rates in six standardised surgical interventions across 43 teaching hospitals. Transfusion rates for coronary artery bypass graft operations were between 0% and 96% and for total hip replacement between 0% and 100%.\textsuperscript{14} A study conducted in five hospitals in Massachusetts compared transfusion practices in 384 orthopaedic Medicare patients. Both transfusion rates and the mean number of units administered per patient differed significantly but could not be explained by different patient characteristics. The authors concluded that nearly half of all transfusions could potentially have been avoided.\textsuperscript{15} A multicentre cohort study in Canada of 5298 intensive care patients admitted to six tertiary-level intensive care units (ICUs) found significant institutional variation in transfusion practice even after multivariate analysis.\textsuperscript{16}

The first Austrian benchmark study on blood use in elective surgery found for matched patients an inter-centre variability of transfusion rates within a range of 1:5 (16–85%) for total hip and 1:7 (12–87%) for total knee replacements. The second Austrian benchmark study showed an overall reduction of blood utilisation compared to the first study. Twelve out of the 15 randomly selected centres were able to reduce their transfusion rate, some by well over 50%.\textsuperscript{17,18} A study to determine international patterns of blood transfusion in patients with acute coronary syndrome found after adjustment a significant variation in transfusion practice between US patients and non-US patients.\textsuperscript{19} A study of 48,086 surgical patients admitted over an 18-month period at a tertiary-care academic medical centre found significant variation in transfusion practice between individual clinicians.\textsuperscript{20} Mean transfusion trigger ranges varied by about 20 g l\textsuperscript{−1} among surgeons, anaesthesiologists and surgical services. Transfusion rates for individual surgeons ranged from 28.3% to 55.4% for primary coronary artery bypass graft surgery, from 10.8% to 35.9% for Whipple resections and from 30.6% to 58.8% for lumbar fusion surgery.

Benchmarking studies of transfusion rates provide a good indication of the potential to significantly reduce blood product utilisation. In Western Australia, within 4 years from implementation of a state-wide patient blood management (PBM) programme, the transfusion rate dropped from 31.66 to 27.54 per 1000 population (Farmer SL et al., Drivers for change: Western Australia Patient Blood Management Program (WA PBMP), World Health Assembly (WHA) and Advisory, Best Practice & Research Clinical Anaesthesiology 2013 Mar; 27(1): 43–58). This represents the lowest transfusion rate of all highly developed health systems around the world, setting a new benchmark for other states and countries. If the same ratio was achieved in the USA, approximately 6.3 million RBC transfusions with an activity-based cost volume of approximately $6 billion would be avoided each year.\textsuperscript{4,9,21} However, the avoidable activity-based cost portion may represent just the tip of the iceberg.
A much bigger health and health-economic issue exists if the cost of adverse outcomes associated with transfusions in millions of patients is included in the equation.

**The cost of adverse transfusion outcomes**

A large number of observational\textsuperscript{22–28} and randomised controlled trials (RCTs) have linked transfusion of RBCs with increased morbidity and mortality\textsuperscript{34} whereas evidence for benefit is scant.\textsuperscript{35} Adverse outcomes associated with transfusion include nosocomial infections, myocardial infarction, cardiac arrest, atrial fibrillation, vasospasm, thrombotic events, renal failure, stroke, re-bleeding, delayed wound healing, transfusion-related acute lung injury, systemic inflammatory response syndrome, acute respiratory distress syndrome, multi-organ failure, cancer recurrence and death. A large number of these studies show a dose–response relationship with each additional unit of blood transfused increasing the risk.\textsuperscript{36}

Applying the Bradford Hill Criteria or ‘causality criteria’ to the large body of observational literature strongly suggests a causal link between transfusion and adverse outcomes. Sir Austin Bradford Hill and Sir Richard Doll in their historic endeavour established the causal relationship between tobacco smoking and the development of lung cancer using this methodology.\textsuperscript{37} While RCTs are usually too small to identify safety issues, a recent systematic review and meta-analysis of RCTs showed that when compared with restrictive transfusion triggers, a liberal transfusion threshold increased infection (19\% higher) and in-hospital mortality (23\% higher).\textsuperscript{38} This is level-1 evidence in line with the observational literature showing a detrimental impact of transfusion. In addition, a vast number of research papers describing biochemical, biophysical, immunological and physiological mechanisms add substantially to the understanding of the possible aetiology of adverse transfusion outcomes.\textsuperscript{39–49} Against this backdrop, the health-economic implications become obvious. Dose-dependent transfusion complications would leverage resource consumption due to prolonged hospital and ICU stay, prolonged mechanical ventilation time, admissions and re-admissions to the ICU and hospital re-admission. What this may mean in macro-economic terms was alluded to by a large retrospective cohort study of the American College of Medical Quality with the 2004 Nationwide Inpatient Sample (NIS) database that included 8,004,571 discharges from 1004 hospitals in 37 states in the year 2007. Based on these data, the authors estimated that from 38.66 million discharges in the USA, 2.33 million were transfused. After controlling for confounders such as age, gender, co-morbidities, admission type and diagnosis-related group, they were able to show that for transfused admissions the odds ratio for death was 1.7 (\( P < 0.0001 \)) and for infection 1.9 (\( P < 0.0001 \)). Charges per transfused admission were $17,194 higher (\( P < 0.0001 \)) than in the non-transfused.\textsuperscript{50} When multiplied with 2.33 million patients and when charges are adjusted to 2013 dollars, the total volume of transfusion-related charges is estimated to be $64 billion just for the USA. Of course given other possible unidentified confounders, one could argue how much of this cost volume is attributable to transfusion, but the absolute number remains high in the context of the overwhelming, mostly unidirectional evidence available in the literature.

**The cost-effectiveness of PBM programmes**

PBM modalities are evidence-based interventions to pre-empt transfusions through identifying and, where possible, correcting the causes of anaemia, minimising blood loss and bleeding and harnessing the physiological tolerance of anaemia.\textsuperscript{51,52} This concept significantly reduces serious complications, morbidity and mortality when compared to transfusion therapies and therefore reduces resource-consuming hospital length of stay (LOS) and hospital and ICU re-admissions. Early on, Helm and colleagues applied PBM modalities in open-heart surgery to reduce transfusion.\textsuperscript{53} After a 3-month period with 100 consecutive coronary artery bypass graft surgeries without transfusions, they compared outcomes with transfused patients matched by diagnosis-related group (DRG). Costs were $387,070 less in the 100 non-transfused patients. This saving was mainly due to reduced LOS. Moskowitz et al. compared outcomes between a cohort of 586 coronary artery bypass graft surgery patients in an institution with an implemented PBM programme and a propensity score-matched cohort of 586 patients from other institutions not having a PBM programme. In the PBM cohort the transfusion rate was four times lower (10.6\% vs. 42.5\%, \( P < 0.0001 \)), the mortality rate was more than three times lower (0.8\%
vs. 2.5%, $P < 0.02$) and the rate of serious complications, including pneumonia, sternal wound infection and sepsis, was significantly lower.\textsuperscript{54} Compelling cost-effectiveness data on PBM or blood conservation in elective surgical procedures have been published in Canada. The government of Ontario initially invested CAN$21 million to develop a blood conservation programme in 23 hospitals. After 12 months, a 24% reduction in blood use was achieved in total knee arthroplasties, 14% in abdominal aortic aneurysm repairs and 23% in coronary artery bypass graft surgeries. Postoperative infection rates were significantly lower in the non-transfused and LOS was significantly reduced. The annual cost of the programme was $1,800,000 with estimated annual savings of $8,640,000.\textsuperscript{55} Kotzé et al. retrospectively audited 717 primary hip and knee arthroplasties in a general hospital in the UK as a control group. Then in a study group of the same procedures the investigators prospectively implemented PBM algorithms. They found a reduction in the transfusion rate from 23% to 8% and a drop in LOS from 6 to 5 days for total hip replacement and from 6 to 4 days in total knee replacements. The 90-day re-admission rate dropped from 14% to 8%. The overall net savings for this cohort were estimated to be £160,000.\textsuperscript{56,57} These and other studies show that PBM offers improved outcomes for less cost. In contrast to transfusion, PBM reduces LOS, costly complications such as nosocomial infections and re-admissions.

**The cost-effectiveness of single PBM modalities versus transfusion**

Overall, the multimodal PBM approach has been shown to be more cost-effective than the traditional transfusion approach. However, the modalities used in the various programmes described in the literature differ from centre to centre. In the Canadian Ontrac programme, preoperative autologous donation, erythropoietin, cell salvage and education were the main programme elements.\textsuperscript{55} Kotzé et al. followed an algorithm that included the use of oral and intravenous iron, erythropoietin, antifibrinolytic drugs, cell salvage and several other strategies.\textsuperscript{56} Moskowitz et al. reported, for their programme, the use of preoperative haemoglobin optimisation, intra-operative acute normovolaemic haemodilution, endovascular vein harvesting, point-of-care coagulation testing, targeted pharmacotherapy and tolerance of postoperative anaemia.\textsuperscript{54} What still remains unresolved is the question of whether and to what extent each single PBM modality contributes to improved cost-effectiveness. In order to avoid misallocation of resources as seen in traditional transfusion practice, it is important to conduct cost-effectiveness analyses (CEAs) for PBM modalities, at least for those that appear to require a considerable amount of resource consumption such as autologous cell salvage or preoperative anaemia detection, evaluation and management, point-of-care coagulation management and the use of fibrinogen and other factor concentrates.

Two formal conditions should be met to correctly conduct CEAs. First, for each treatment modality, the same costing methodology to capture the resource utilisation must be applied. Second, the outcome of each therapy must be measured by exactly the same outcome parameter. Neither condition is met in the context of transfusion and PBM. As far as costing is concerned, the First Consensus Conference on the Cost of Blood (COBCON I) identified ABC as the appropriate method to capture and determine the cost of blood.\textsuperscript{7,58} This has been used to establish the cost of RBC transfusion in surgical patients.\textsuperscript{9} However, this methodology has not been used to establish the cost of any of the single PBM modalities. In relation to establishing effectiveness parameters there are multiple problems that need to be acknowledged. For instance, various outcome measures of RBC efficacy have been used, some of these being surrogates such as an increase in the haemoglobin concentration or the haematocrit or an improvement in the patient’s symptoms, the latter being a subjective judgement that could be confounded by the volume replacement effect of transfusion. More challenging is to measure transfusion’s ability to increase tissue oxygenation with no direct measures currently available. What studies exist have shown a limited ability of transfused RBCs to improve tissue oxygenation.\textsuperscript{59} None of these measures relate to the quality and effectiveness of the RBCs. Allogeneic RBCs are stored and have undergone biochemical and biophysical changes. Depending on the storage time, a certain percentage of these cells have lesions.\textsuperscript{60} They are allogeneic and so may have negative immunological sequelae. Endogenous RBCs produced with iron and haematinic-induced erythropoiesis are, however, native to the patient, young and fully functional. The two competing strategies also require very different dosing schedules to achieve the same red cell and haemoglobin concentration increases. Therefore, the second CEA criterion is not met, namely using the same outcome parameter to compare competing modalities.
Another option for an effectiveness measure would be the number of quality-adjusted life years (QALYs) gained or disability-adjusted life years (DALYs) averted. However, their use is problematic in transfusion. The question arises of how the causality between the administering of transfusion and QALYs gained can be established. Evidence supporting transfusion improving patients’ health outcomes (quality of life) is minimal.\textsuperscript{35,61} To the contrary, the body of literature predominantly points to the negative effects of transfusion.\textsuperscript{36}

However, some may argue that blood safety measures, such as nucleic acid testing (NAT), have shown a gain in QALYs. In reality, the use of QALY and DALY measures in relation to NAT testing is misleading. NAT testing, like other infectious agent identification tests, is about reducing the pathogenic risk of the blood product, not improving its therapeutic benefit or the underlying disease of the patient. Even if QALY and DALY measures are used, the allocation of funds to blood pathogen safety would represent a grossly disproportionate allocation of resources in comparison with other accepted health resource allocation thresholds.\textsuperscript{6,62–64} The cost per QALY for NAT donor blood testing is between $4.7 million and $11.2 million.\textsuperscript{65} This exceeds the commonly accepted threshold of approximately $50,000 by more than 100 times. It also means that the money used to gain one single QALY from detecting infected donor blood could be used elsewhere in the health system to gain approximately 100 QALYs.

Against the background of the current literature on transfusion cost and outcomes, excluding extreme settings such as critical bleeding and bone marrow failure, it appears to be difficult to establish meaningful cost-effectiveness ratios for RBC transfusion. Efforts should rather be put into CEAs that compare various PBM modalities with each other, not with transfusion.

Some modalities may not need to go through formal CEAs. Tolerance of lower anaemia thresholds significantly reduces the number of RBC transfusions with marginal cost attached. Other strategies with minimal cost have also been shown to significantly reduce RBC transfusion. Berger et al. demonstrated a significant 25% reduction in RBC transfusion in haematology patients with the introduction of a single unit policy.\textsuperscript{66} Reductions in phlebotomy volumes are associated with significant reductions in transfusion in patients in the ICU.\textsuperscript{67} A systematic review and meta-analysis of RCTs showed that maintaining normothermia compared with mild hypothermia significantly reduced the relative risk of transfusion by 22%.\textsuperscript{68} Each unit of RBCs avoided reduces the dose-dependent adverse outcomes associated with transfusion and their attendant costs.

CEA in transfusion clearly has dubious applicability and there is work to be done in this area in relation to PBM modalities. However, PBM is essentially, as described elsewhere in this theme issue (Isbister JP, The 3 Pillar Matrix of Patient Blood Management – An Overview, Best Practice & Research Clinical Anaesthesiology (2013)), the application of good clinical medicine and thus inherently represents better cost-effectiveness.

**Summary**

The escalating health-care cost needs to be controlled. One of the measures is the rigorous re-evaluation of the cost-effectiveness of resource-intensive therapies. One-sixth of the world’s donor blood is consumed in the USA, causing activity-based RBC transfusion costs of approximately $14 billion annually. A multiple of this amount is likely if the cost of adverse transfusion outcomes is added. The enormous transfusion variability between countries, institutions and physicians demonstrates that the potential for reducing the number of transfusions is in millions of units translating into billions of dollars. This staggering resource consumption of transfusion with its limited evidence for benefit and a strong dose-dependent association with adverse outcomes stands in contrast to the overall improved patient outcomes and cost savings of the PBM approach. PBM pre-empts transfusions through identifying and correcting anaemia, minimising blood loss and bleeding and harnessing the physiological tolerance of anaemia. It is in the interest of patients, health-care providers and payers to implement PBM. This concept has been endorsed by the World Health Assembly’s resolution 63.12. Worldwide, health authorities and administrators are now urged to implement this new standard of care. Data show that PBM programmes generate quick returns of investment. It is a rare win–win opportunity where patients get more and payers spend less. Once this message gets through, it might be ignored or contradicted, but it cannot be refuted. In the light and spirit of *primum non nocere* it is also an ethical obligation to replace the current transfusion-reliant practice with PBM.
**Practice points**

- Activity-based cost analyses have shown that allogeneic red blood cell transfusions are more costly than previously estimated.
- RBC transfusions are associated with increased hospital length of stay and re-admissions and the evidence from the literature suggests a dose-dependent causal relationship between transfusion and outcomes.
- Patient blood management is good clinical practice, leading to improved outcomes while reducing cost.
- Clinicians, hospital administrators and authorities can significantly benefit from PBM and need to be informed accordingly.
- The concept of patient blood management with its three pillars has been adopted by the World Health Assembly’s 63rd session (WHA) and public authorities are urged to support the establishing of PBM as a new standard of care.

**Research agenda**

- Activity-based costing studies for single PBM modalities must be conducted.
- In addition to RBCs, activity-based costing studies for the transfusion of other allogeneic blood components must be conducted.
- Costing of the short-, mid- and long-term adverse outcomes of transfusion must be undertaken to capture the full cost scope of transfusion.
- Cost-effectiveness studies looking at QALY gained or DALY averted through single PBM modalities must be designed and conducted.
- Meaningful secondary ‘end’ points for such cost-effectiveness studies must be defined.

**Statement of conflict of interest**

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AS: Consultant for Bayer, Luitpold, Masimo, Novartis, Novo Nordisk, OrthoBiotech, and Zymogenetics; has received research and grant support from Bayer, Novartis, Novo Nordisk, OrthoBiotec, Pfizer, and ZymoGenetics; and has been a speaker with honorarium for Bayer, Novartis, OrthoBioetech, Zymogenetics, and Masimo. He is a founding member of SABM where he currently serves as the President Elect.

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