



Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

Review

Patient blood management: The best approach to transfusion medicine risk management

Matteo Bolcato^a, Marianna Russo^{a,*}, Kevin Trentino^b, James Isbister^c, Daniele Rodriguez^a, Anna Aprile^a

^a Department of Molecular Medicine, Legal Medicine, University of Padua, Padua, Italy

^b Faculty of Health and Medical Sciences, The University of Western Australia, Perth, Western Australia, Australia

^c School of Medicine, The University of Sydney, Sydney, Australia

ARTICLE INFO

Keywords:

Patient blood management
Clinical risk management
Medical liability
Blood transfusion
Transfusion hazards

ABSTRACT

In advanced health systems it is increasingly important to offer effective medical services that have high quality and safety standards. We present an overview of the direct hazards and the indirect hazards associated with blood transfusions. Our aim is to focus on the potential medico-legal impacts of these hazards in the context of clinical risk management, incorporating the accumulating evidence from Patient Blood Management programs. The direct or deterministic hazards of transfusion refer to scenarios where the mechanisms for post transfusion damage are clearly traceable to the blood transfused in a 1:1 cause and effect manner. The indirect hazards can be defined as probabilistic and are associated with transfusion through epidemiological studies. The implementation of Patient Blood Management programs demonstrates that the use of a blood transfusion is not always necessary or unavoidable but can be considered modifiable. Review of the literature confirms that transfusion should not be the default option to manage anemia or blood loss. Instead, accumulating evidence demonstrates that a patient-centred, proactive approach to managing a patient's own blood is the new standard of care. It thus follows, an adverse transfusion event, where the transfusion was avoidable through the application of patient blood management, may constitute a profile for medical professional medical negligence.

In an effort to maximise patient safety, transfusion medicine practice culture needs to shift towards a patient blood management approach, with hospitals implementing it as an important tool to minimize the risks of allogeneic blood transfusion.

1. Introduction

It is an increasingly important and pressing quality and safety requirement to deliver care that meets the high level standards expected from modern health systems. For this reason, health care providers need to implement strategies and pathways to bring healthcare in line with current scientific evidence. Clinical risk management (CRM) is a necessary organizational approach aimed at improving the quality and safety of health services by identifying medical activities that can expose patients to unnecessary and unacceptable risk. Once identified, controls should be implemented to eliminate the risks or, if this is not possible to implement widespread controls to minimize the risk and/or its impact on patient outcomes.

Through the consideration of the various aspects of legal medicine (patients' rights, ethics, legal research, quality assurance, risk

management, negligence, etc.) and the review of case studies of professional responsibility and legal actions, it is possible to identify potentially high-risk medical practices, improve information and knowledge on adverse events and report medical professional liability profiles before they materialize [1]. By analysing these unacceptable events and working to prevent them, patient safety can be significantly improved [2].

This analytical and organizational approach must include all the elements of risk in every medical intervention, including the transfusion of blood components. It is our aim to analyse current and commonly reported transfusion hazards, both direct and indirect. We discuss the medical-legal impact of these hazards in the context of clinical risk management, incorporating the accumulation of evidence from Patient Blood Management programs.

* Corresponding author at: Legal Medicine, Department of Molecular Medicine, University of Padua, Via Falloppio 50, 35121, Padua, Italy.

E-mail addresses: matteo.bolcato@unipd.it (M. Bolcato), mariannarusso.medleg@gmail.com (M. Russo), Kevin.Trentino@uwa.edu.au (K. Trentino), James.Isbister@sydney.edu.au (J. Isbister), danielec.rodriguez@gmail.com (D. Rodriguez), anna.aprile@unipd.it (A. Aprile).

<https://doi.org/10.1016/j.transci.2020.102779>

Received 9 February 2020; Received in revised form 24 March 2020; Accepted 5 April 2020

1473-0502/ © 2020 Elsevier Ltd. All rights reserved.

2. The hazards of blood component transfusions

Blood transfusions have been a commonly used procedure for the treatment of anemia during the last century and is one of the most frequently performed medical therapies in the world. However, transfusion cannot be regarded as safe and free from risk for the patient, in particular for the pediatric population [3,4]. Indeed, allogeneic blood transfusion is potentially associated with the greatest range of hazards of any single medical intervention. In this review we aim to give an overview of the main hazards associated with transfusions. Firstly, the direct or deterministic hazards, where the mechanisms for post-transfusion damage are clearly traceable to the blood transfused in a cause and effect manner, commonly referred to as the 1:1 hazards and documented in hemovigilance programs. Secondly, are the hazards that are responsible for indirect damage and defined as probabilistic, identified as associated with transfusion through epidemiological studies. In these circumstances the transfusion is a risk factor for an adverse outcome and not necessarily a specifically definable disease state.

2.1. Direct/deterministic transfusion hazards

2.1.1. Infectious hazards (Table 1)

In high income countries the risk of contracting a serious infection (HIV / Hepatitis B and C) following the transfusion of blood is considered small [5]. However, there are previously unknown hazards in the infectious field, and despite testing, diseases transmitted by transfusion remain a potential hazard to patients. Of particular interest are the hazards of bacterial contamination, in particular for platelet concentrates [6]. Moreover, taking on ever greater importance, also due to global climate changes, are emerging pathogens [7] such as Dengue, West Nile virus, Zika virus [8], Chikungunya [9], Ebola [10], and Hepatitis E virus [11], prion transmission [12], and protozoa [13].

Past tragedies associated with the transmission of HIV from blood transfusions have focused the attention on the infectious risk of transfusions. However, in reality the more frequent hazards in high income countries are non-infectious.

2.1.2. Non-infectious hazards (Table 2)

These can be classified according to the chronology of the event and divided into immediate or delayed adverse events. The former are in turn are mechanistically divided into immunological or non-immunological. Examples of immunological reactions are represented by acute haemolytic reaction, non-haemolytic febrile reaction, allergic reactions, anaphylactic shock and acute lung injury related to transfusions (TRALI). Immediate non-immunological mechanism reactions include transfusion-related circulatory overload (TACO), post-transfusion hypo and hypertension, non-immunological hemolysis, calcium and potassium ionic imbalances, hypothermia and others [14–16].

The transfusion-related reactions defined as delayed generally occur in the hours or days following the administration of a blood component and can also be divided into those determined by immunological or non-immunological mechanisms. Transfusion associated graft versus host disease, post-transfusion purpura, and induction of erythrocyte and HLA alloantibodies are examples. Non-immunological mechanisms include iron overload, especially in frequently transfused patients.

Of the deterministic hazards those that appear, from an

epidemiological and clinical risk management perspective that are worthy of particular attention are transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), and transfusion error in which an incorrect blood component is administered to the patient, creating an acute hemolytic incompatibility. These three possibilities, together with the bacterial contamination of the blood component represent the main causes of death and serious complication of transfusion [14,17]. Clinicians need to understand and avoid underestimating these transfusion hazards. For several reasons these hazards are of particular relevance in the medical-legal context.

Transfusion-associated circulatory overload (TACO) is now one of the commonest dangers of transfusion [18–21]. It has been reported in over 1 case per 100 transfused units. TACO is characterized by a cardiogenic pulmonary edema with consequent acute respiratory distress and failure. TACO occurs more frequently in patients who have comorbidities, such as cardiac compromise, fluid overload, coronary artery disease or acute renal failure. TACO is an immediate transfusion reaction that may be overlooked, or attributed to other causes, because the development or exacerbation of respiratory symptoms often occurs within 6–12 hours after the transfusion. In such cases, the cause of death may be attributed to the patient's comorbidities. These aspects are particularly relevant in forensic pathology and medicolegal cases where it becomes necessary, at autopsy, to establish the cause of death. Given the possible repercussions in the field of professional liability it is important for clinicians to be aware of TACO, its frequency and potential lethality.

Transfusion Related Lung Injury (TRALI) is a potential transfusion hazard occurring with significant frequency and increasing general awareness of this hazard. The incidence of TRALI is estimated to be one case every 10,000 transfused units although it is widely recognized this condition is underestimated. TRALI is an acute pulmonary lesion, characterized by non-cardiogenic pulmonary edema occurring within 6 h after transfusion, presenting with acute hypoxemia and bilateral pulmonary infiltrations [22–24].

Of significance from the epidemiological, clinical, medico-legal and public health management perspectives, are haemolytic reactions due to the administration of incompatible ABO blood components. These may be a result of human error in blood sampling, in the identification of the patient, or of the unit to be transfused. Particularly insightful are data collected by the Serious Hazards of Transfusion (SHOT) group. These reports underline the danger and not insignificant frequency of erroneous transfusions and near misses. These events are consistently recorded in annual surveys, despite the creation and application of standardized procedures for the identification and correct management of the units of blood components [15,16]. These data can be partly explained by the fact that the transfusion error is a risk that does not belong only to hospital management, but is shared by human error, which is difficult to control and eliminate.

These events are particularly dangerous as they can lead to the occurrence of an acute or delayed haemolytic reaction. An anamnestic immune response can occur up to 21 days after transfusion. Delayed haemolytic transfusion reactions may not be related to the earlier blood transfusion, resulting in an incorrect cause attributed to hemolysis and the possibility of inappropriate therapy.

Complement-binding antibodies can mediate acute intravascular haemolysis, with acute renal failure and mortality between 8 and 44%

Table 1
Infectious hazards.

Viral	HIV, HBV, HCV, CMV, EBV, Hepatitis A (HAV), Hepatitis E (HEV), Human Herpes virus, WNV, Parvovirus, Chikungunya, Dengue fever virus (DFV), Human papilloma virus (HPV), SARS virus, Simian foamy virus (SFV), Human T cell lymphotropic virus (HTLV)
Bacterial	<i>S. epidermidis</i> , <i>Micrococcus</i> , <i>Sarcina</i> , <i>Diphtheroids</i> . <i>Pseudomonas</i> , <i>Bacillus</i> , <i>Yersinia enterocolitica</i> , <i>Streptococcus viridans</i> , <i>Bacteroides</i> , <i>Staphylococcus aureus</i> , <i>Campylobacter</i> . <i>Treponema pallidum</i> .
Protozoan	<i>Plasmodium malariae</i> , <i>Babesia</i> sp., <i>Plasmodium</i> sp., <i>Leishmania</i> sp., <i>Trypanosoma</i> Cr.
Prion	Creutzfeldt-Jakob disease and variant of Creutzfeldt-Jakob disease

Table 2
Non-infectious hazards.

Transfusion Reactions (Immunological)	Immediate	<ul style="list-style-type: none"> ● Acute hemolytic reaction ● Febrile non-hemolytic reaction ● Anaphylactic shock ● Transfusion-related acute lung injury (TRALI)
	Delayed	<ul style="list-style-type: none"> ● Transfusion-associated dyspnea (TAD) ● Delayed haemolytic reaction ● Transfusion associated graft-versus-host disease (TAGVHD) ● Transfusion associated microchimerism (increased risk in trauma) ● Post transfusion purpura ● Alloimmunization and HLA ● Transfusion-related immunomodulation (TRIM)
Transfusion Complications (Non-immunological)	Immediate	<ul style="list-style-type: none"> ● Transfusion-related circulatory overload (TACO) ● Hypotension - Hypertension ● Non-immunological hemolysis ● Hypocalcemia, Hyperkalemia ● Hypothermia
	Delayed	<ul style="list-style-type: none"> ● Martial overload / hemochromatosis (iron overload, especially in frequently transfused patients)
Human Error		<ul style="list-style-type: none"> ● ABO incompatibility ● Wrong name on tube ● Wrong product transfused ● Other

[25].

2.2. Probabilistic hazards (Table 3)

The probabilistic adverse outcomes associated with transfusion have been consistently identified through large epidemiological studies [26]. The majority of studies investigating the relationship between transfusion and patient outcomes have demonstrated that transfusion is independently associated with increased mortality and morbidity. This relationship is dose-dependent [27], with a number of studies showing that even transfusing a single unit of blood is associated with worse patient outcome [28–31].

The increased mortality and morbidity observed in these large epidemiological studies are statistical outcomes; they indicate an increase in various adverse events commonly reported to be associated with the administration of blood components.

For decades allogeneic blood transfusion has been known to have a significant impact on the patient's immune system [32]. Transfusion immunomodulation is clinically relevant as it is associated with increased cancer recurrence rates and post-operative infections. One systematic review and meta-analysis of randomized controlled trials found that even when leukocyte-reduced blood is transfused patients assigned to liberal transfusion strategies had a higher risk of health-care associated infections [33]. This suggests transfusion-related immunomodulation persists despite reduction of leukocytes. Although it is difficult to give an exact standardized measure of the adverse patient outcomes attributable to transfusion-related immunomodulation it is nonetheless worthy of consideration [34,35].

Table 3
Probabilistic Transfusion Risks.

Mortality
Morbidity
Multisystem organ failure
Stroke
Renal impairment/failure
Immunomodulation
Cancer recurrence
Development of Non-Hodgkin lymphoma
Venous arterial thromboembolism
Vasospasm
Bleeding requiring reoperation
Increased hospital length of stay
Increased ICU length of stay
Increased admission to ICU

After a review of the literature Farmer et al reported that the use of blood products is associated with increased pulmonary, cardiovascular, neurological, renal, and oncological complications [27]. Many of these studies highlight a dose-dependent increase in adverse outcomes associated with red cell transfusion. An increase in venous and arterial thromboembolism and vasospasm with the occurrence of stroke and acute coronary syndrome is reported. These complications can be identified from the epidemiological studies that demonstrate transfused patients have increased hospital and intensive care unit length of stay, and duration of mechanical ventilation. Contrary to what can be thought, the administration of blood components can increase the risk of bleeding [36,37].

3. The medico-legal aspects

Patient safety is directly related to the attention health professionals and institutions give to prevent exposure to adverse events. This is based on the Hippocratic maxim "*primum non nocere*", which focuses on choosing therapies that expose patients to as few hazards as possible.

In legal medicine, particularly when evaluating the professional liability of health providers, any known risks of medical interventions or procedures that materialize are defined as adverse events [38,39]. Not all adverse events are considered medical errors; only adverse events potentially foreseeable, preventable or can be minimised are to be considered negligence (Fig. 1).

These errors can be attributable to the individual health worker, to the medical team, or to the hospital administration or system problems. The administrative or organisational and system deficiencies resulting in an adverse event can give rise to disputes of a medical-legal nature both in criminal and civil claims for compensation for the damage caused to the patient.

An example of an error by the individual health care professional may be represented by damage caused to nerves as a result of surgical error. A surgeon is expected to be aware of nerves located near the site of surgery and put adequate precautions in place to ensure they will not be damaged.

If the nerve was not directly related to the planned surgery but in close proximity to the site of intervention and could be safeguarded with adequate precaution, the damage would be due to the negligence of the individual operator.

A useful example to understand the organizational liability of hospital authorities can be represented by the otherwise avoidable hospital-wide spread of a known infection due to lack of standardized infection monitoring and control procedures.

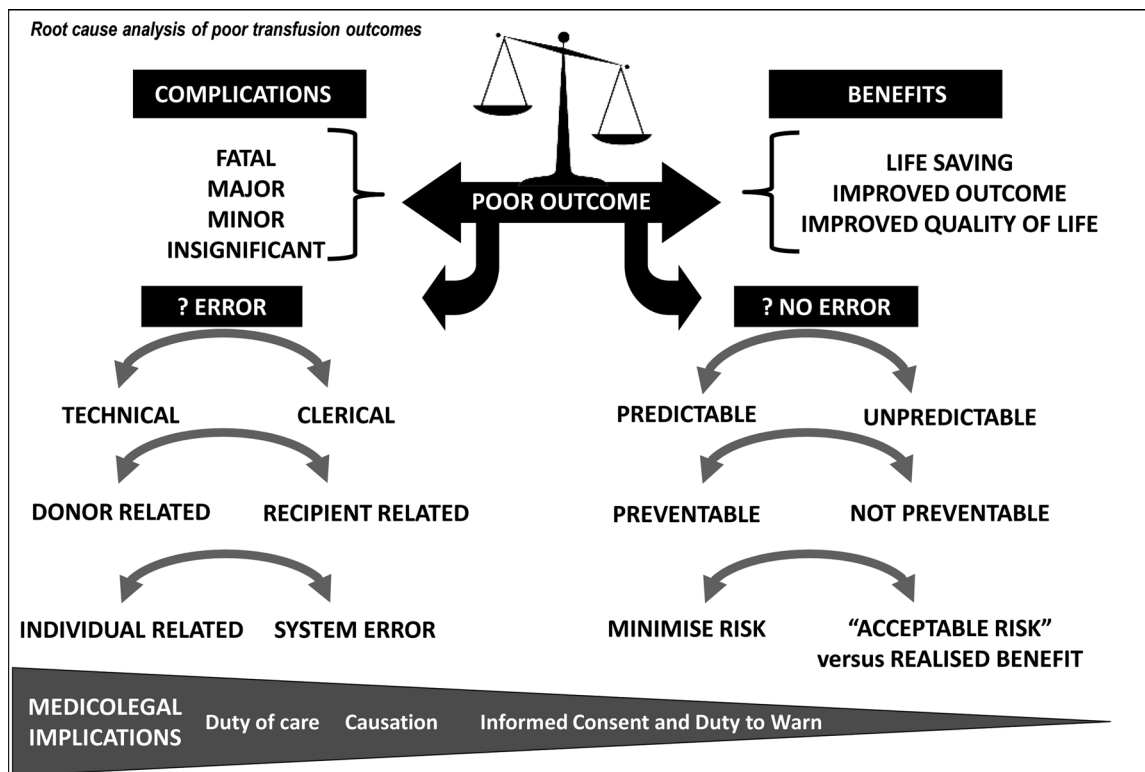


Fig. 1. Root cause analysis of poor transfusion outcome.

These concepts also apply to the field of transfusion medicine. Over the years transfusion medicine has focused more on blood product safety through investments in research and development in order to improve the collection, storage, cataloguing, transportation and administration of blood [40–44]. While these activities have contributed to improving the safety of the product it is not possible to eliminate all risks as blood is a biological product and the processes of collection, storage, cataloguing, transportation and administration is influenced by numerous factors, many including human involvement.

Patient-focused strategies include interventions that may reduce or even eliminate the need for a transfusion and the associated risks. The evolution and application of patient blood management is resulting in the necessary paradigm shift back to addressing the patients' diagnosis and clinical problem, rather than transfusion medicine being product-focused. Patient blood management (PBM) can be regarded as a *sine qua non* as it shifts the attention in transfusion medicine back to the patient and management of the patient's own blood where it should always have been [45]. PBM is an evidence-based, patient-specific medical and surgical concept that employs a multidisciplinary multi-modal team approach to optimizing the patient's red cell mass, minimizing blood loss and exploiting and optimizing the patient's physiological tolerance of anaemia.

The implementation of PBM programs has repeatedly demonstrated that transfusions can generally be predicted and avoided or minimised in many clinical scenarios. The First Austrian Benchmark Study in elective orthopaedic and cardiac surgery demonstrated that the level of anaemia prior to surgery, the volume of perioperative blood loss, and the transfusion trigger used predicted 97.4% of all transfusions [46].

This predictability makes possible the modification of the risk factors for transfusion. Anaemia, transfusion, and bleeding can be managed [47] through PBM which "pre-empts and significantly reduces transfusions by addressing modifiable risk factors that may result in transfusion well before a transfusion may even be considered" [48].

In some clinical scenarios, the use of medical and surgical techniques and devices with associated haemorrhage is a necessity. In such

circumstances the application of the three pillars principle of PBM can minimise the use of a blood transfusion when it cannot be avoided.

A randomized controlled trial by Froessler and colleagues [49] highlighted the impact of applying the first pillar of PBM. The trial compared transfusion rates in patients with iron deficiency anaemia treated with intravenous (IV) iron with usual care for major abdominal surgery. Only the treatment with intravenous iron resulted in a 60% reduction in transfusion. Though terminated early, the authors also found that patients receiving IV iron had higher haemoglobin levels four weeks after surgery and shorter hospital length of stay. Regarding strategies from the second pillar of PBM, two systematic reviews and meta-analyses [50,51] pooled data from randomised controlled trials on the use of intraoperative cell salvage and report that the use of cell salvage reduced the rate of exposure to RBC transfusion by 38% (RR 0.62; 95% CI 0.55 to 0.70) [50] and 39% (RR 0.61; 95% CI 0.57 to 0.65) [51]. Globally a systematic review and meta-analysis of PBM programs [52] found that implementation of PBM significantly reduced transfusion rates by 39% (RR 0.61, 95% CI 0.55–0.68, $P < 0.001$), and mortality rate by 11% (RR 0.89, 95% CI 0.80–0.98, $P = 0.02$).

The accumulation of evidence in the literature demonstrates transfusion does not need to be the default option to manage anaemia or blood loss. Continuing to consider blood transfusion as a default therapy will mean transfusion safety efforts will continue to focus on blood product safety. However, accumulating evidence now demonstrates that a patient-centred and proactive approach to managing a patients' own blood is possible, necessary and should be a standard of care.

Anaemia and bleeding are to some extent foreseeable perioperative elements and through the application of PBM it is possible to reduce, and in many cases eliminate transfusions and safeguard the patient from avoidable transfusion related hazards. The implementation of PBM in a systematic and patient-centered manner becomes a fundamental tool for controlling and managing clinical risk in order to increase the quality of care provided and patient safety [36].

It is reasonable to state that the administration of blood components

is generally predictable and known to be associated with numerous hazards, both direct and indirect. For this reason, patient exposure to allogeneic blood should be avoided or minimized as far as possible. There is now good evidence that restrictive transfusion thresholds should be applied, in agreement with the current indications from based on clinical practice guidelines [53]. As a corollary and not its primary aim, implementing PBM programs results in reduced patient exposure to the unnecessary risks of allogeneic blood products and fulfills stewardship of donor blood responsibilities and ensuring a valuable community and costly resource is available. This can be accomplished by appropriately managing a patient's own blood, proactively diagnosing and managing the possible and probable indications for blood transfusion.

Not proactively practicing PBM may inevitably expose patients to additional and potentially avoidable hazards and clinicians and the health system to potential litigation in the event of an adverse clinical outcome. A systematic review and meta-analysis of preoperative anaemia and outcomes reported that anaemic patients had a three times higher probability of death, four times higher probability of acute kidney injury and twice the likelihood of infection compared to patients not anaemic at the time of admission [54].

Elective patients who are treated according to the three pillars of PBM would ensure hematological optimization before surgery and minimize intraoperative blood loss. With this approach, the patient's hemoglobin is less likely to fall to a level at which the red cell transfusion would be considered appropriate.

Where opportunities to optimize the patient's blood before surgery are missed, relevant good practice strategies could still be applied in the management of postoperative anaemia after major surgery [55]. This approach has made major surgery possible without the use of transfusions with similar or better results for patients [56,57], by avoiding exposure to the hazards associated with transfusion.

The concepts and practice of PBM being confirmed as achieving optimal outcomes for patients, especially in the perioperative setting, it is reasonable to communicate these concepts into the fields of professional conduct assessment and the medical-legal setting. With this medicolegal awareness, that transfusion hazards are known and most perioperative transfusions can be avoided or minimised through appropriate PBM strategies, it is reasonable to regard PBM as a medicolegal standard of care. It thus follows that, in the absence of PBM strategies, and an adverse outcome ensues for a patient that is causally linked to a transfusion medical professional liability is established.

In specific cases, with knowledge of the hazards of allogeneic blood transfusion and their predictability, avoidance should be a priority. Even if transfusions cannot be avoided and medical or surgical procedures are not completely performed without transfusions, adoption of PBM strategies can contribute to the reduction of clinical risk. Studies demonstrate that the risks associated with transfusions are dose-dependent [33,58,59]. It thus follows that administering fewer transfusions will reduce the risk of the risk of direct adverse events and is also likely to decrease the mortality and morbidity independently associated with transfusion as demonstrated by epidemiological studies.

On the contrary, a medico-legal dispute for medical liability may develop following the occurrence of direct transfusion-related adverse events due to avoidable transfusions through PBM strategies.

These direct risks are clearly identified by a definitive medico-legal evaluation as would be the case in criminal law where the determination of the causal link requires a high level of scientific and well-reasoned credibility and certainty. According to the current scientific evidence, as in criminal law, correlation cannot attribute causation to the indirect or statistical risks of transfusion as the probability of causation is based in large part on epidemiological studies [26]. It flows that from the point of view of litigation for medical professional liability is thus in the field of civil law, where the causal assessment is normally obtainable with different rigor, ie balance of probabilities.

Medico-legal disputes will be realized in a particular way in

countries where the action of the European Court of Human Rights is present. The Court has already executed numerous judgments regarding situations in which the health of patients is endangered or compromised due to the failure to provide adequate organizational measures to prevent and reduce adverse events.

It is true that other medical activities forming part of the toolbox of PBM strategies may present risks. Some obviously present no risk and are simply good patient care, such as the use of micro-sampling, meticulous surgical technique and point of care technology. Other strategies, such as intravenous iron administration, the use of erythropoiesis-stimulating agents, and fibrinogen concentrate replacement therapy, do involve some risk. However, these risks are generally not comparable when balanced against the risks of transfusing labile blood components. All such risks must be known, identified and minimized through adequate training of the clinical staff in order to guarantee the maximum quality and safety for the patient [60,61]. It would be inappropriate to avoid or delay implementation of a PBM program out of fear of the risks associated with specific PBM strategies.

The considerations of a medical-legal nature must be known by the health authorities since, in addition to the costs associated with not implementing PBM programs, there could be added costs linked to the medico-legal litigation linked to an outdated and disorganized transfusion medicine practices. The resulting liability could affect individual physicians who have not followed the current evidence-based PBM guidelines, as well as the health executives who have an organizational responsibility to introduce procedures and systems for the establishing and monitoring of PBM within the hospitals.

PBM programs are particularly important considering that implementation of blood-saving programs has proved cost-effective when implemented as part of a coordinated quality and safety program [62–64]. For a PBM program to have maximum impact and effectiveness it must have executive-sponsorship and be supported by hospital administration through the coordination, education and training of all clinical staff.

Not only does a PBM program appropriately manage a patient's blood but identifies the probability of a patient requiring allogeneic blood transfusion and the known risks. An evidence-based PBM program with individualised patient clinical pathways better patient outcome are achieved and the risks of allogeneic blood transfusion minimized or eliminated. The program should also consider patient preferences, by providing education so patients can confirm and document their consent to their blood management treatment options in a reasoned and informed manner. By updating and training health-care personnel, a "culture" of Patient Blood Management is created, in which allogeneic transfusion, like any other tissue transplant, is the last resort, not the first reflective and default action [65].

4. Conclusions

PBM programs are a pivotal quality and safety patient management tool for improving clinical outcomes. Local health and hospital authorities with support from high level government responsible for providing resources are central to promoting effective and sustainable implementation of PBM programs. Accreditation and related regulatory measures are also integral to ensuring maximum patient safety. The PBM approach enables a change in transfusion medicine practice culture and as a corollary is a valuable tool for limiting transfusion risk and minimising potential litigation related preventable poor clinical outcomes.

Declaration of Competing Interest

The authors declare no competing financial interests.

References

- [1] Bolcato M, Fassina G, Rodriguez D, Russo M, Aprile A. The contribution of legal medicine in clinical risk management. *BMC Health Serv Res* 2019;19:85. <https://doi.org/10.1186/s12913-018-3846-7>.
- [2] Oyebo F. Clinical errors and medical negligence. *Med Princ Pract* 2013;22:323–33. <https://doi.org/10.1159/000346296>.
- [3] Oakley FD, Woods M, Arnold S, Young PP. Transfusion reactions in pediatric compared with adult patients: a look at rate, reaction type, and associated products. *Transfusion* 2015;55:563–70. <https://doi.org/10.1111/trf.12827>.
- [4] Vossoughi S, Perez G, Whitaker BI, Fung MK, Stotler B. Analysis of pediatric adverse reactions to transfusions. *Transfusion* 2018;58:60–9. <https://doi.org/10.1111/trf.14359>.
- [5] Carson JL, Triulzi DJ, Ness PM. Indications for and adverse effects of red-cell transfusion. *N Engl J Med* 2017;377:1261–72. <https://doi.org/10.1056/NEJMr1612789>.
- [6] Spindler-Raffel E, Benjamin RJ, McDonald CP, Ramirez-Arcos S, Aplin K, et al. Enlargement of the WHO international repository for platelet transfusion-relevant bacteria reference strains. *Vox Sang* 2017;112:713–22. <https://doi.org/10.1111/vox.12548>.
- [7] Blajchman MA, Vamvakas EC. The continuing risk of transfusion-transmitted infections. *N Engl J Med* 2006;355:1303–5. <https://doi.org/10.1056/NEJMp068178>.
- [8] Franchini M, Velati C. Blood safety and zoonotic emerging pathogens: Now it's the turn of Zika virus!. *Blood Transfus* 2016;14:93–4. <https://doi.org/10.2450/2015.0187-15>.
- [9] Petersen LR, Stramer SL, Powers AM. Chikungunya virus: possible impact on transfusion medicine. *Transfus Med Rev* 2010;24:15–21. <https://doi.org/10.1016/j.tmr.2009.09.002>.
- [10] Koepsell SA, Winkler AM, Roback JD. The role of the laboratory and transfusion service in the management of ebola virus disease. *Transfus Med Rev* 2017;31:149–53. <https://doi.org/10.1016/j.tmr.2016.11.002>.
- [11] Hoofnagle JH, Nelson KE, Purcell RH. Hepatitis E. *N Engl J Med* 2012;27:1237–44.
- [12] Seed CR, Hewitt PE, Dodd RY, Houston F, Cervenakova L. Creutzfeldt-Jakob disease and blood transfusion safety. *Vox Sang* 2018;113:220–31. <https://doi.org/10.1111/vox.12631>.
- [13] Mortimer PP. Making blood safer. *BMJ* 2002;325:400–1. <https://doi.org/10.1136/bmj.325.7361.400>.
- [14] Bolton-Maggs PHB, Cohen H. Serious Hazards of Transfusion (SHOT) haemovigilance and progress is improving transfusion safety. *Br J Haematol* 2013;163:303–14. <https://doi.org/10.1111/bjh.12547>.
- [15] Bolton-Maggs PHB. SHOT conference report 2016: serious hazards of transfusion – human factors continue to cause most transfusion-related incidents. *Transfus Med* 2016;26:401–5. <https://doi.org/10.1111/tme.12380>.
- [16] Bolton-Maggs PHB. Conference report: International Haemovigilance Seminar and the SHOT Annual Symposium, 10–12 July 2018. *Transfus Med* 2019;29:247–52. <https://doi.org/10.1111/tme.12569>.
- [17] Vamvakas EC, Blajchman MA. Blood still kills: six strategies to further reduce allogeneic blood transfusion-related mortality. *Transfus Med Rev* 2010;24:77–124. <https://doi.org/10.1016/j.tmr.2009.11.001>.
- [18] Roubinain NH, Hendrickson JE, Triulzi DJ, Gottschall JL, Chowdhury D, Kor DJ, et al. Incidence and clinical characteristics of transfusion-associated circulatory overload using an active surveillance algorithm. *Vox Sang* 2017;112:56–63. <https://doi.org/10.1111/vox.12466>.
- [19] Gosmann F, Nørgaard A, Rasmussen MB, Rahbek C, Seeberg J, Møller T. Transfusion-associated circulatory overload in adult, medical emergency patients with perspectives on early warning practice: A single-centre, clinical study. *Blood Transfus* 2018;16:137–44. <https://doi.org/10.2450/2017.0228-16>.
- [20] Li G, Rachmale S, Kojicic M, Shahjehan K, Malinchoc M, Kor DJ, et al. Incidence and transfusion risk factors for transfusion-associated circulatory overload among medical intensive care unit patients. *Transfusion* 2011;51:338. <https://doi.org/10.1111/j.1537-2995.2010.02816.x>.
- [21] Klanderman RB, Bosboom JJ, Migdady Y, Veelo DP, Geerts BF, Murphy MF, et al. Transfusion-associated circulatory overload—a systematic review of diagnostic biomarkers. *Transfusion* 2019;59:795–805. <https://doi.org/10.1111/trf.15068>.
- [22] Shander A, Popovsky MA. Understanding the consequences of transfusion-related acute lung injury. *Chest* 2005;128:598S–604S. https://doi.org/10.1378/chest.128.5_suppl.2.598S.
- [23] Vlaar APJ, Binnekade JM, Prins D, Van Stein D, Hofstra JJ, Schultz MJ, et al. Risk factors and outcome of transfusion-related acute lung injury in the critically ill: a nested case-control study. *Crit Care Med* 2010;38:771–8. <https://doi.org/10.1097/CCM.0b013e3181cc4d4b>.
- [24] Benson AB, Moss M, Silliman CC. Transfusion-related acute lung injury (TRALI): a clinical review with emphasis on the critically ill. *Br J Haematol* 2009;147:431–43.
- [25] Davenport RD, Bluth MH. Hemolytic transfusion reactions. In: Simon T, McCullough J, Snyder EL, Solheim BG, Strauss RG, editors. *Ross. Princ. Transfus. Med.* 5th ed. West Sussex, UK: Wiley-Blackwell; 2016. p. 642–51.
- [26] Isbister JP, Shander A, Spahn DR, Erhard J, Farmer SL, Hofmann A. Adverse blood transfusion outcomes: establishing causation. *Transfus Med* 2011;25:89–101. <https://doi.org/10.1016/j.tmr.2010.11.001>.
- [27] Farmer S, Hofmann A, J. I. Transfusion and patient outcomes. In: Gombotz H, Zacharowski K, Spahn DR, editors. *Patient Blood Manag.* Stuttgart: Thieme; 2016. p. 19–28.
- [28] Bernard AC, Davenport DL, Chang PK, Vaughan TB, Zwischenberger JB. Intraoperative transfusion of 1 U to 2 U packed red blood cells is associated with increased 30-day mortality, surgical-site infection, pneumonia, and sepsis in general surgery patients. *J Am Coll Surg* 2009;208:931–7. <https://doi.org/10.1016/j.jamcollsurg.2008.11.019>.
- [29] Whitlock EL, Kim H, Auerbach AD. Harms associated with single unit perioperative transfusion: retrospective population based analysis. *BMJ* 2015;350:h3037. <https://doi.org/10.1136/bmj.h3037>.
- [30] Ferraris VA, Davenport DL, Saha SP, Austin PC, Zwischenberger JB. Surgical outcomes and transfusion of minimal amounts of blood in the operating room. *Arch Surg* 2012;147:49–55. <https://doi.org/10.1001/archsurg.2011.790>.
- [31] Ferraris VA, Davenport DL, Saha SP, Bernard A, Austin PC, Zwischenberger JB. Intraoperative transfusion of small amounts of blood heralds worse postoperative outcome in patients having noncardiac thoracic operations. *Ann Thorac Surg* 2011;91:1674–80. <https://doi.org/10.1016/j.athoracsur.2011.01.025>.
- [32] Refaai MA, Blumberg N. Transfusion immunomodulation from a clinical perspective: an update. *Expert Rev Hematol* 2013;6:653–63. <https://doi.org/10.1586/17474086.2013.850026>.
- [33] Rohde JM, Dimcheff DE, Blumberg N, Saint S, Langa KM, Kuhn L, et al. Health care-associated infection after red blood cell transfusion: a systematic review and meta-analysis. *JAMA - J Am Med Assoc* 2014;311:1317–26. <https://doi.org/10.1001/jama.2014.2726>.
- [34] Vamvakas EC, Bordin JO, Blajchman MA. Immunomodulatory and pro-inflammatory effects of allogeneic blood transfusion. In: Simon TL, McCullough J, Snyder EL, Solheim BG, Strauss RG, editors. *Ross. Princ. Transfus. Med.* West Sussex, UK: Wiley-Blackwell; 2016. p. 695–710.
- [35] Johnson DJ, Scott AV, Barodka VM, Park S, Wasey JO, Ness PM, et al. Morbidity and mortality after high-dose transfusion. *Anesthesiology* 2016;124:387–95. <https://doi.org/10.1097/ALN.0000000000000945>.
- [36] Farmer SI, Trentino K, Hofmann A, Semmens Jb, Mukhtar Sa, Prosser G, et al. A programmatic approach to patient blood management – reducing transfusions and improving patient outcomes. *Open Anesthesiol J* 2015;9:6–16. <https://doi.org/10.2174/1874321801509010006>.
- [37] Villanueva C, Colomo A, Bosch A, Concepción M, Hernandez-Gea V, et al. Upper GI bleed - transfusion. *N Engl J Med* 2013;368:111–21. <https://doi.org/10.1056/NEJMoa1211801>.
- [38] Beran RG. What is legal medicine - Are legal and forensic medicine the same? *J Forensic Leg Med* 2010;17:137–9. <https://doi.org/10.1016/j.jflm.2009.09.011>.
- [39] Tweedy JT. Healthcare hazard control and safety management. 2nd ed Boca Raton, FL: Taylor & Francis; 2005. <https://doi.org/10.1201/b16667>.
- [40] Ifland L, Bloch EM, Pitman JP. Funding blood safety in the 21st century. *Transfusion* 2018;58:105–12. <https://doi.org/10.1111/trf.14374>.
- [41] Yonemura S, Doane S, Keil S, Goodrich R, Pidcocke H, Cardoso M. Improving the safety of whole blood-derived transfusion products with a riboflavin-based pathogen reduction technology. *Blood Transfus* 2017;15:357–64. <https://doi.org/10.2450/2017.0320-16>.
- [42] Devine DV, Schubert P. Pathogen inactivation technologies: the advent of pathogen-reduced blood components to reduce blood safety risk. *Hematol Oncol Clin North Am* 2016;30:609–17. <https://doi.org/10.1016/j.hoc.2016.01.005>.
- [43] Stout L, Joseph S. Blood transfusion: patient identification and empowerment. *Br J Nurs* 2016;25:138–43. <https://doi.org/10.12968/bjon.2016.25.3.138>.
- [44] Mora A, Ayala L, Bielza R, Ataúlfo González F, Villegas A. Improving safety in blood transfusion using failure mode and effect analysis. *Transfusion* 2019;59:516–23. <https://doi.org/10.1111/trf.15137>.
- [45] Isbister JP. The three-pillar matrix of patient blood management-an overview. *Best Pract Res Clin Anaesthesiol* 2013;27:69–84. <https://doi.org/10.1016/j.bpa.2013.02.002>.
- [46] Gombotz H, Rehak PH, Shander A, Hofmann A. Blood use in elective surgery: the Austrian benchmark study. *Transfusion* 2007;47:1468–80. <https://doi.org/10.1111/j.1537-2995.2007.01286.x>.
- [47] Ranucci M, Baryshnikova E, Castelvécchio S, Pelissero G. Major bleeding, transfusions, and anemia: the deadly triad of cardiac surgery. *Ann Thorac Surg* 2013;96:478–85. <https://doi.org/10.1016/j.athoracsur.2013.03.015>.
- [48] Hofmann A, Farmer S, Shander A. Five drivers shifting the paradigm from product-focused transfusion practice to patient blood management. *Oncologist* 2011;16:3–11. <https://doi.org/10.1634/theoncologist.2011-s3-3>.
- [49] Froessler B, Palm P, Weber I, Hodyl Na, Singh R, Murphy Em. The important role for intravenous iron in perioperative patient blood management in major abdominal surgery. *Ann Surg* 2016;264:41–6. <https://doi.org/10.1097/SLA.0000000000001646>.
- [50] Carless PA, Henry DA, Moxey AJ, O'Connell D, Brown T, Fergusson DA. Cell salvage for minimising perioperative allogeneic blood transfusion. [Review] [135 refs] [Update of Cochrane Database Syst Rev. 2010;(3):CD001888; PMID: 20238316]. *Cochrane Database Syst Rev* 2010:CD001888. <https://doi.org/10.1002/14651858>.
- [51] Meybohm P, Choroaipoikayil S, Wessels A, Herrmann E, Zacharowski K, Spahn DR. Washed cell salvage in surgical patients: a review and meta-analysis of prospective randomized trials under PRISMA. *Med (United States)* 2016;95:e4490. <https://doi.org/10.1097/MD.0000000000004490>.
- [52] Althoff Fc, Neb H, Herrmann E, Trentino Km, Vernich L, Füllenbach C, et al. Multimodal patient blood management program based on a three-pillar strategy. *Ann Surg* 2019;269:794–804. <https://doi.org/10.1097/sla.0000000000003095>.
- [53] National Blood Authority (Australia). Patient blood management guidelines. 2020 n.d. (Accessed January 17, 2017). <https://www.blood.gov.au/pbm-guidelines>.
- [54] Fowler AJ, Ahmad T, Abbott TEF, Torrance HD, Wouters PF, et al. Association of operative anaemia with postoperative morbidity and mortality: an observational cohort study in low-, middle-, and high-income countries. *Br J Anaesth* 2018;121:1221–35. <https://doi.org/10.1016/j.bja.2018.08.026>.
- [55] Muñoz M, Acheson AG, Bisbe E, Butcher A, Gómez-Ramírez S, et al. An international consensus statement on the management of postoperative anaemia after

- major surgical procedures. *Anaesthesia* 2018. <https://doi.org/10.1111/anae.14358>.
- [56] Pattakos G, Koch CG, Brizzio ME, Batizy LH, Sabik JF, Blackstone EH, et al. Outcome of patients who refuse transfusion after cardiac surgery: a natural experiment with severe blood conservation. *Arch Intern Med* 2012;172:1154–60. <https://doi.org/10.1001/archinternmed.2012.2449>.
- [57] Frank SM, Wick EC, Dezern AE, Ness PM, Wasey JO, Pippa AC, et al. Risk-adjusted clinical outcomes in patients enrolled in a bloodless program. *Transfusion* 2014;54:2668–77. <https://doi.org/10.1111/trf.12752>.
- [58] Rawl J. The silent risks of blood transfusion. *Curr Opin Anaesthesiol* 2008;21:664–8. <https://doi.org/10.1097/ACO.0b013e32830f1fd1>.
- [59] Claridge JA, Sawyer RG, Schulman AM, McLemore EC, Young JS. Blood transfusions correlate with infections in trauma patients in a dose-dependent manner. *Am Surg* 2002;68(566):572.
- [60] Park S, Greenberg P, Yucel A, Farmer C, O'Neill F, et al. Clinical effectiveness and safety of erythropoietin-stimulating agents for the treatment of low- and intermediate-1 – risk myelodysplastic syndrome: a systematic literature review. *Br J Haematol* 2019;184:134–60. <https://doi.org/10.1111/bjh.15707>.
- [61] Lim W, Afif W, Knowles S, Lim G, Lin Y, Mothersill C, et al. Canadian expert consensus: management of hypersensitivity reactions to intravenous iron in adults. *Vox Sang* 2019;114:363–73. <https://doi.org/10.1111/vox.12773>.
- [62] Ferraris VA, Ferraris SP, Saha SP, Hessel EA, Haan CK, Royston BD, et al. Perioperative blood transfusion and blood conservation in cardiac surgery: the society of thoracic surgeons and the society of cardiovascular anesthesiologists clinical practice guideline. *Ann Thorac Surg* 2007;83:S27–86. <https://doi.org/10.1016/j.athoracsur.2007.02.099>.
- [63] Martyn V, Farmer SL, Wren MN, Towler SCB, Betta JA, Shander A, et al. The theory and practice of bloodless surgery. *Transfus Apher Sci* 2002;27:29–43. [https://doi.org/10.1016/S1473-0502\(02\)00024-1](https://doi.org/10.1016/S1473-0502(02)00024-1).
- [64] Goodnough LT, Shander A. Blood management. *Arch Pathol Lab Med* 2007;131:695–701.
- [65] Franchini M, Marano G, Veropalumbo E, Masiello F, Pati I, Candura F, et al. Patient Blood Management: a revolutionary approach to transfusion medicine. *Blood Transfus* 2019;17:191–5. <https://doi.org/10.2450/2019.0109-19>.