Clinical focus

Clinical transfusion practice update: haemovigilance, complications, patient blood management and national standards

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Summary

- Blood transfusion is not without risk. Although the risks of HIV and hepatitis transmission have diminished, haemovigilance programs highlight that other significant transfusion hazards remain. Sepsis from bacterial contamination is the most common residual infectious hazard in developed countries, and events due to clerical error are problematic. Unnecessary transfusions should be avoided.
- New national guidelines on patient blood management (PBM) emphasise holistic approaches, including strategies to reduce transfusion requirements. Perioperative PBM should incorporate preoperative haemoglobin and medication optimisation, intraoperative blood conservation, and consideration of restrictive postoperative transfusion and cell-salvage techniques.
- When massive transfusion is required, hospitals should implement massive transfusion protocols. These protocols reduce mortality, improve communication and facilitate adequate provision of blood products. They should include multidisciplinary team involvement and guidelines for use of blood components and adjunctive agents.
- Although fresh frozen plasma to red blood cell and platelet to red blood cell ratios of $\geq 1:2$ appear to reduce mortality in trauma patients who receive massive transfusion, there is insufficient evidence to recommend specific ratios. Systematic reviews have found no significant benefit of recombinant activated factor VII in critical bleeding, and an increase in thromboembolic events; specialist haematology advice is therefore recommended when considering use of this agent.
- The National Safety and Quality Health Service Standards address use of blood and blood products, and provide important transfusion principles for adoption by all clinicians.
- Storage of red cells in additive solution results in changes, known as the "storage lesion", and studies to determine the clinical effect of the age of blood at transfusion are ongoing.

Blood transfusion is often lifesaving but not without risk, and many aspects of transfusion practice lack a sound evidence base when compared with other areas of medicine. While historically the focus has been on prevention of transfusion-transmitted infection, other major hazards have been highlighted through haemovigilance programs. In addition, blood is a scarce resource that is donated by volunteers. Australian governments spend over $900 million annually on provision of blood products, with additional costs incurred for transfusion-related hospital activities, such as laboratory testing and blood administration and monitoring.[1] With an ageing population, demand for this resource may increase. These factors support the need to promote safe and evidence-based clinical transfusion practice.

In this article, we review developments in transfusion practice, policy and research that are relevant to a broad audience of health practitioners: recently developed national guidelines for patient blood management (PBM);[2,3] blood management principles in the National Safety and Quality Health Service (NSQHS) Standards;[4] and new transfusion research, such as trials assessing the clinical effects and logistical implications of the duration of blood storage.[5,6] Other developments, such as development of molecular phenotyping methods, investigation of optimal transfusion triggers, and advances in production and safety of blood products, are beyond the scope of this article.

Haemovigilance

Haemovigilance may be defined as "A set of surveillance procedures covering the whole transfusion chain (from the collection of blood and its components to the follow-up of recipients), intended to collect and assess information on unexpected or undesirable effects resulting from the therapeutic use of labile blood products, and to prevent their occurrence or recurrence".[7] Since establishment of the first national haemovigilance system in France in 1994, such systems have identified issues requiring attention and helped improve blood product safety and transfusion processes.

Australian surveillance systems have been established at a jurisdictional level, and these report to a national haemovigilance framework (http://www.blood.gov.au/haemovigilance-reporting). Participation in these systems is voluntary, but NSQHS Standards mandate that hospitals have systems in place for recognising and reporting transfusion-related incidents and adverse events. Although these and other initiatives contribute to safer transfusion, avoidance of unnecessary transfusion is essential to ensuring safe transfusion practice.

Infectious hazards of transfusion

Doctors and patients are often greatly concerned about transfusion-transmitted viruses such as HIV and hepatitis. In Australia, the estimated risks of HIV, hepatitis B and hepatitis C transmission are extremely low, owing to donor

screening and serological and nucleic acid testing. Estimates of infectious and non-infectious hazards are reported periodically by the Australian Red Cross Blood Service (http://www.transfusion.com.au/adverse_events/risks/estimates).

Sepsis from bacterial contamination is the most common residual infectious hazard of transfusion in developed countries, and may cause significant morbidity or mortality. Measures introduced in Australia and elsewhere to minimise bacterial contamination include diversion pouches used during donor blood collection, and routine pre-release bacterial screening of platelets. Since Australia introduced pre-release bacterial screening in early 2008, septic transfusion reactions have greatly declined.[8] When clinically significant organisms were identified, transfusion was often prevented through early notification to hospitals, and, when products had been transfused, early intervention (eg, antibiotic treatment in at-risk patients) was often possible.

Vigilance for emerging infectious diseases (EID) is required, since some EID have the potential for rapid geographical spread (including by transfusion) and severe clinical consequences. For example, variant Creutzfeldt–Jakob disease (vCJD) in the United Kingdom and West Nile virus (WNV) in the Americas pose threats to the blood supplies in these countries and internationally.[9,10] Epidemiological monitoring and prompt action — such as deferral of donors from high-risk countries to reduce transfusion-transmitted vCJD, and rapid implementation of screening tests for WNV in North America — have largely contained these threats. Other transfusion-transmitted infectious diseases of concern include dengue and chikungunya viruses, malaria, babesiosis, and *Trypanosoma cruzi* infection.[9] Ongoing active surveillance and cooperation between the medical community, public health and regulatory authorities and blood services are needed for prevention and management strategies to be effective. Pathogen reduction methods for blood products may help to reduce transmission of EID by transfusion, but these techniques are not effective for all EID and their efficacy and safety have not been fully determined.

Non-infectious hazards of transfusion

Haemovigilance programs highlight events relating to clinical procedures and clerical tasks as ongoing major problem areas. These include "wrong blood in tube" events (where blood is taken from the correct patient but labelled with another patient's details, or taken from an incorrect patient) and "incorrect blood component transfused" events (where a transfusion is administered to the wrong patient, or where the transfusion does not meet a patient's special needs), typically because of failure to adhere to patient identification procedures. Doctors are overrepresented as contributors to these events. Examples from the Victorian Serious Transfusion Incidents Reporting program show that although these tasks may seem tedious and unimportant, they are key elements in ensuring patient safety.[11] A recent survey of interns' transfusion knowledge showed significant shortfalls in knowledge of clinical transfusion practice, even though most interns reported that they had been offered specific transfusion education in medical school.[12] These findings highlight the need for improved education and practical transfusion training for medical staff. Several educational programs are available, including the online BloodSafe program (https://www.bloodsafelearning.org.au), which has modules for all members of multidisciplinary transfusion teams.

Haemovigilance has also identified transfusion-associated cardiac overload and transfusion-related acute lung injury (TRALI) as common causes of serious morbidity and mortality due to transfusion. In the UK, measures to reduce TRALI, including preferential use of plasma from male donors, have resulted in encouraging trends that show reduction of this complication.[13] This is due to the lower incidence of anti-HLA antibodies, which have been implicated in the pathogenesis of TRALI, in males. The combination of immunosuppressive and proinflammatory effects of transfusion is collectively referred to as transfusion-related immunomodulation (TRIM). The exact mechanism of TRIM is unknown and multiple theories have been proposed since an association between improved renal allograft survival and transfusion was noted in the early 1970s. The immunosuppressive effect of allogeneic red blood cell (RBC) transfusion was subsequently confirmed by animal and observational clinical studies.[14,15] TRIM has been linked to cancer recurrence, postoperative bacterial infection and multiorgan failure. However, data are conflicting and further in-vitro and clinical studies to elucidate the effects of TRIM are needed.

Patient blood management

Transfusion medicine has moved from an emphasis on product safety to the concept of PBM, focusing on holistic patient management, including methods to minimise transfusion requirements and therefore decrease the risk of transfusion-related adverse events. Interest in the implementation of PBM strategies has been increasing internationally. National PBM guidelines for Australian clinicians are in development and, when complete, they will comprise six modules for different clinical settings: critical bleeding and massive transfusion; perioperative care; acute and chronic medical conditions; critical care; obstetrics; and paediatrics. The first four have been published, and the first two are briefly reviewed here.

Critical bleeding and massive transfusion[2]

Recent publications on transfusion in trauma patients in military settings have triggered increased interest in the management of massive transfusion (MT) and led to advances in various aspects of MT in trauma patients. However, controversies remain and data in other areas of MT, such as obstetric practice, are lacking. The first module of the national PBM guidelines outlines the limited available evidence and recommendations for critical bleeding and MT.

Coagulopathy

Early coagulopathy in trauma patients is associated with increased mortality.[2] Tissue injury and hypoperfusion, through hyperfibrinolysis and tissue factor activation, are associated with early (preresuscitation) acute trauma coagulopathy.[16] In addition, haemodilution and consumptive coagulopathy in MT, as well as decreased clotting factor function due to hypothermia and acidosis, play a role in

acute trauma coagulopathy. Monitoring the results of coagulation studies, and correction of hypothermia and acidosis, are therefore important in resuscitation of trauma patients.[2] Interest in point-of-care thromboelastography devices, such as the TEG (Haemonetics Corporation) and ROTEM (Tem International GmbH), for the management of MT has increased. However, their use has not been standardised in this setting,[17] and data that clarify whether their use reduces morbidity or mortality in patients with MT are needed.[18]

Blood component ratios

Initial observational studies in military settings have suggested that a fresh frozen plasma (FFP) to RBC ratio of 1 : 1 is associated with decreased mortality.[19] This has led to a number of studies assessing the potential benefits of higher FFP : RBC ratios in civilian MT settings. Several studies have reported advantages of higher FFP : RBC ratios.[2] However, a recent systematic review found insufficient evidence to recommend fixed ratios for MT in trauma patients.[20] This is likely, at least in part, to be due to lack of randomised controlled trials (RCTs), patient heterogeneity, and survivor bias, where only those who survive long enough receive FFP. Two RCTs addressing this question are currently underway.[16] Although FFP : RBC and platelet : RBC ratios of $\geq$ 1 : 2 appear to reduce mortality rates in trauma patients, there is currently insufficient evidence to recommend specific ratios.[2]

Tranexamic acid

The Clinical Randomization of an Antifibrinolytic in Significant Haemorrhage (CRASH-2) trial assessed the effect of tranexamic acid (TXA) in bleeding trauma patients and showed reduced all-cause mortality and death due to bleeding.[21] However, these benefits were only seen with early administration (within 3 hours of injury), and increased bleeding rates were seen when TXA was administered later.[22] The impact of TXA in advanced trauma centres is still uncertain as most of the CRASH-2 study sites were in developing countries. Nevertheless, TXA is inexpensive and early administration was not associated with increased adverse events. It is therefore potentially useful in high-resource settings if administered early, although further research is needed to investigate the clinical utility of this agent in other MT contexts.

Recombinant activated factor VII

Initial interest in off-label use of recombinant activated factor VII (rFVIIa) in MT has led to its use in various critical bleeding settings. However, recent systematic reviews have concluded that use of this agent appears to have no significant benefit, with an increased risk of arterial thromboembolism.[23-25] It should therefore only be considered when conventional measures, including surgical haemostasis and component therapy, have failed to control critical bleeding and when survival is considered a credible outcome.[2] Specialist haematology advice is recommended.

Massive transfusion protocols

Use of a massive transfusion protocol (MTP) improves outcomes. It results in a significant reduction in mortality without increased use of blood components.[26] MTPs facilitate communication between clinical stakeholders and the transfusion laboratory. Good communication streamlines timely processing of patient samples, enables laboratory staff to prepare products such as FFP (which needs to be thawed) and supports provision of sufficient product to enable use of higher FFP : RBC and platelet : RBC ratios, and access to specialist haematology advice can optimise management of bleeding patients.

A framework for designing and implementing MTPs has been suggested.[27] Key stakeholders include emergency, anaesthetics, critical care, nursing, haematology and transfusion laboratory staff. The protocol should identify guidelines on activation and deactivation of the MTP, roles of all staff, communication between staff, suggested product ratios, laboratory testing, and adjunctive therapies such as TXA and rFVIIa. Key activities for MTP success include staff education, regular audits, and reviews of protocol compliance and patient outcomes. The national PBM guidelines provide an MTP template for local adaptation.[2]

Obstetric haemorrhage

Obstetric haemorrhage differs from other conditions that require MT owing to the frequent early development of disseminated intravascular coagulation. In addition to other measures, fibrinogen levels should be closely monitored and fibrinogen replacement therapy given where indicated. Also, fibrinogen levels are raised in pregnancy, hence significant disseminated intravascular coagulation can be present despite normal fibrinogen levels. Correction of hypofibrinogenaemia with cryoprecipitate or fibrinogen concentrates should be considered for patients with fibrinogen levels of < 2 g/L.[28] Other important measures include primary prevention of bleeding through identification of risk factors, correction of antepartum anaemia and obstetric management.

Perioperative care[3]

Although causality is difficult to determine,[29] various studies have reported increased perioperative morbidity and mortality associated with preoperative anaemia and perioperative transfusion in certain patient groups.[30,31] The perioperative setting provides a great opportunity for implementing PBM strategies to minimise the transfusion requirements, including preoperative, intraoperative and postoperative approaches (Box 1). Institution of a PBM program has been shown to decrease transfusion rates, length of stay and readmission rates without delaying surgery.[32]

Preoperative management

Identification and appropriate management of preoperative anaemia are important components of successful PBM. In practice, however, logistical issues may make implementation difficult, and success is dependent on multidisciplinary team participation to streamline hospital preadmission processes. The team should include surgeons and anaesthetists, and have input from a haematologist. General practitioners are important stakeholders and should be involved in early evaluation of patients (ie, at time of referral for or scheduling of surgery). Guidelines should identify team members responsible for identification, treatment and further investigation of preoperative anaemia. Diagnosis and management of iron deficiency anaemia is critical to the success of preoperative PBM.[33] Medications, especially anticoagulant and antiplatelet

1 Elements of a perioperative patient blood management program[3]

Preoperative management
- Optimisation of haemoglobin status and haematinic status
- Optimisation of haemostasis — consider and address factors which may increase bleeding risk:
  - review bleeding history, and perform relevant laboratory tests for at-risk patients
  - review medications
  - withhold anticoagulation and antiplatelet agents in accordance with advice from a haematologist or the prescribing specialist
- No role for routine preoperative autologous donation

Intraoperative management
- Surgical techniques
  - Position patient to avoid excessive venous pressure at site of surgery
  - Ensure meticulous surgical haemostasis
- Anaesthetic techniques
  - Use deliberate induced hypotension where clinically appropriate
  - Consider using intraoperative cell salvage
  - Consider using acute normovolaemic haemodilution
- Prevention of hypothermia and acidosis
- Administration of tranexamic acid where clinically appropriate

Postoperative management
- Restrictive transfusion strategies where clinically appropriate
- Consider postoperative cell salvage ◆

2 Triggers for transfusion[3]

Haemoglobin level	Suggested strategy
< 80 g/L	• Consider transfusion; lower haemoglobin levels can be tolerated in healthy asymptomatic patients
80–100 g/L	• Transfusion dependent on clinical factors, including symptomatic anaemia, bleeding and comorbidities • Consider single-unit transfusion and reassess
> 100 g/L	• Transfusion not recommended ◆

agents, should be reviewed before surgery, to assess bleeding and thrombosis risk.

Consensus recommendations for warfarin reversal by the Australasian Society of Thrombosis and Haemostasis have recently been updated.[34] For procedures with low risk of bleeding (eg, cataract, dental and dermatological procedures), warfarin can be continued at therapeutic levels. For urgent surgery where warfarin reversal is required, vitamin K and prothrombin complex concentrate can be used.

New oral anticoagulants, such as rivaroxaban and dabigatran, have created new clinical challenges. Laboratory testing for drug presence and effects is not standardised.[35,36] These drugs should be discontinued 24–48 hours before elective surgery (sooner in renal failure), but there are currently no specific reversal agents for use in emergency settings.[35] Clopidogrel has been associated with increased perioperative bleeding and transfusion and should be discontinued, where possible, at least 5 days before surgery.[3] The effect of aspirin is unclear; it may be continued during the perioperative period, except in intraocular surgery and neurosurgery.[3] Platelet support may be needed if timely cessation of antiplatelet agents is not possible. Perioperative management of antiplatelet agents in patients with intracoronary stents should be done in consultation with a cardiologist.[37] Non-steroidal anti-inflammatory drugs increase bleeding in orthopaedic surgery and should be discontinued before surgery. Advice from a haematologist may be helpful for monitoring and managing patients who are taking any of these agents.

Preoperative autologous blood donation is recommended only for patients with very specific transfusion needs, such as those with rare blood groups or multiple alloantibodies, as it is associated with development of preoperative anaemia, increased overall transfusion rates and high wastage of collected components.[38]

Intraoperative management

Techniques that can be used to minimise intraoperative blood loss are outlined in Box 1. Attention should be paid to institutional and other relevant guidelines, and adequate preoperative planning (to identify anticipated significant blood loss) should be carried out so that appropriate blood conservation methods are used during surgery and trained staff and necessary equipment are available.

Postoperative management

A recent Cochrane review of transfusion triggers concluded that data were inadequate to determine whether lower haemoglobin thresholds had adverse clinical effects and suggested that a restrictive transfusion approach was as safe as a liberal approach.[39] A trial in older patients with cardiovascular disease or risk factors for cardiovascular disease who had had hip surgery showed no difference in mobility or overall mortality outcomes between liberal and restrictive transfusion strategies.[40] Although insufficiently powered to detect cardiac and other morbidity, the low cardiac event rates in both patient groups were reassuring. Transfusion decisions should not be based on haemoglobin triggers alone, but made in conjunction with clinical assessment; restrictive approaches should therefore be considered where clinically appropriate (Box 2). When significant postoperative blood loss is anticipated, postoperative cell-salvage techniques should be considered.

National Safety and Quality Health Service Standards

The NSQHS Standards, which were introduced by the Australian Commission on Safety and Quality in Health Care in 2011, include safety and quality measures for use of blood and blood products.[4] They provide important blood management principles for all clinicians, and compliance with the Standards is required for hospital accreditation. The Standards direct institutions to implement, monitor and improve systems for use of blood, including cellular components, fractionated blood products and recombinant agents.

Transfusion-related clinical governance systems, such as hospital transfusion committees, are important elements of institutional quality improvement. Clinical governance systems for transfusion are now mandated, including establishing local transfusion policy and procedures, monitoring transfusion-related risks, internal and external reporting of adverse events and other quality improvement activities. These systems promote an institutional culture where transfusion safety is viewed as paramount, and they support clinicians and other team members involved in the transfusion process.

The NSQHS Standards recognise the importance of patient involvement in the transfusion process and require informed consent to be obtained and documented. Another component, which is often overlooked, is documentation of patient transfusion history, transfusion indication and out-

come, special product requirements and adverse events. This promotes appropriate clinical decision making, improves future practice through audit and investigation of adverse reactions, highlights special product requirements and assists the transfusion laboratory to comprehensively identify antibodies in previously transfused patients.

Age of blood

Currently, RBCs may be stored at 4°C for up to 42 days before expiry. In-vitro and animal studies have shown that storage in additive solution results in biochemical and structural changes — collectively referred to as the "storage lesion"[41] — but clinical effects of these have not been determined. Results from heterogeneous, mainly retrospective, clinical studies are conflicting. Some show that increases in mortality, length of stay and infection rates are associated with increased duration of RBC storage,[6] and recent meta-analyses favour "fresher" units for some outcomes.[42,43] In contrast, an RCT in premature infants showed no benefit of fresher units over standard issue RBCs.[44]

Understanding possible effects of the storage lesion is important not only due to potential effects on patient outcomes, but also because of implications for inventory management and blood supply planning. Clinical trials are underway internationally to address this question,[6] including an Australasian study in intensive care that is comparing standard issue RBCs with "freshest available" RBCs.[5]

Conclusion

Transfusion safety and appropriateness have improved because of clinical and basic science research, effective PBM programs, adverse event monitoring, and developments in blood product manufacturing. Increasing awareness by governments and health services of the need to mandate key elements of the transfusion process is also contributing to safer clinical practice. Ongoing efforts and collaboration will be required to further improve patient outcomes.

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