NATIONAL GUIDELINES ON CLINICAL TRANSFUSION

HEALTH SCIENCES AUTHORITY

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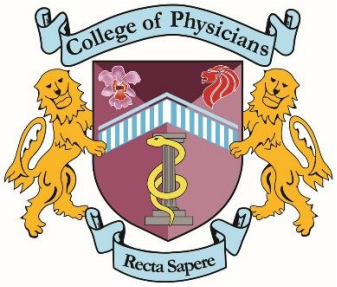
National Guidelines on Clinical Transfusion Endorsed by:

Academy of Medicine, Singapore

College of Anaesthesiologists, Singapore

College of Obstetricians and Gynaecologists, Singapore

College of Paediatrics and Child Health, Singapore



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Introduction

1. Guideline objectives and target groups

Transfusion of blood and blood components (i.e., red cells, platelets, frozen plasma and cryoprecipitate) is one of the most common medical procedures performed worldwide. However, the decision to transfuse is one of the more complex medical decisions and should be carefully considered, balancing the benefits and risks on a background of accumulating medical evidence and available therapies. Well-designed clinical trials have established the safety, and in some cases superiority, of restrictive red cell transfusion practices in general and specific settings. Recent data have also supported the reevaluation of neonatal platelet transfusion triggers. These examples highlight a shift in transfusion practice towards one in which specific scenarios define transfusion triggers.

The development of more sophisticated donor testing, pretransfusion testing, recipient identification and improvements in blood component characteristics (e.g., leucoreduction and irradiation) have resulted in improved blood safety profiles. However, the intense focus on product safety has not been matched with a similar focus on improving transfusion decisions at the bedside.[1] This has led to the concept of "Patient Blood Management", an evidence-based approach aimed at improving clinical outcomes by avoiding unnecessary patient exposure to blood components. This approach minimises the need for transfusion in many patients by the implementation of pre-emptive measures, weeks to days before elective surgeries, or the adoption of more effective alternatives in patients with reversible causes of anaemia such as iron deficiency. There are also robust data to support the use of adjuncts such as tranexamic acid in reducing bleeding and risk of death in major obstetric and trauma related haemorrhage.

This guideline replaces the Clinical Blood Transfusion guideline published in 2011, incorporating up-to-date medical evidence.[2] It has been expanded to include dedicated chapters on paediatric and obstetric transfusion and Patient Blood Management.

The aim of this guideline is to steer the clinician into evidence-based, clinically appropriate and timely use of blood components by maximising its life-saving potential and availability to those who need it most, while minimising unnecessary transfusion and its associated risks in those who are not likely to benefit. Although the administration of blood components is restricted to hospitals and ambulatory care centers, primary care physicians should also find this guideline useful in determining thresholds for transfusion, assessing patients for urgent referrals to hospitals, and identifying the large numbers of patients who would benefit from Patient Blood Management.

2. Scope of guidelines

Recommendations are broad and most are applicable across all patient groups; specific populations (e.g., obstetrics and paediatrics) are considered in separate chapters.

The practical aspects and actual administration of blood components are beyond the scope of this guideline and each institution should have its own policy of checking blood and patient identifiers to ensure safety, as well as the required patient monitoring when administering blood components. Blood derived components such as human albumin, immunoglobulins and factor concentrates are also not covered in this guideline.

3. Methodology

This guideline was developed by a workgroup appointed by Blood Services Group, Health Sciences Authority (HSA). The workgroup comprised experts in their individual fields including haematologists, anaesthetists, surgeons, obstetricians, neonatologists and paediatricians. Endorsements of these guidelines were received from the following Chapters and Colleges of the Academy of Medicine, Singapore: Chapter of Haematologists (College of Physicians), College of Anaesthesiologists, College of Obstetricians & Gynaecologists, College of Paediatrics & Child Health and College of Surgeons.

The workgroup formulated this clinical practice guideline by a comprehensive review of published literature. In assessing the evidence, different study designs were considered including randomised controlled trials (RCTs), cohort studies, case control studies, uncontrolled clinical trials and expert opinions. Best practice guidelines in transfusion medicine were also included. The workgroup then convened to develop recommendations; these considered the methodological quality of the evidence, benefit and risk to the target population and costs. The working group employed the GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group method of grading quality of evidence and strength of recommendations (Table 1).[3,4] The recommendations are adapted to the local situation in Singapore, whenever applicable.

Grade of recommendation	Benefits versus risk and burdens	Methodological quality of supporting evidence	Implications
Strong recommendation; high-quality evidence	*Benefits clearly outweigh risk and burdens, or vice versa*	*RCTs without important limitations or overwhelming evidence from observational studies*	*Strong recommendation, can apply to most patients in most circumstances without reservation*
Strong recommendation; moderate-quality evidence	*Benefits clearly outweigh risk and burdens, or vice versa*	*RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies*	*Strong recommendation, can apply to most patients in most circumstances without reservation*
Strong recommendation; low-quality evidence	*Benefits clearly outweigh risk and burdens, or vice versa*	*Observational studies, case series, or expert opinion*	*Strong recommendation but may change when higher quality evidence becomes available*
Conditional recommendation; high-quality evidence	*Benefits closely balanced with risks and burden*	*RCTs without important limitations or overwhelming evidence from observational studies*	*Weak recommendation, best action may differ depending on circumstances or patients' or societal values*

Conditional recommendation; moderate-quality evidence	*Benefits closely balanced with risks and burden*	*RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies*	*Weak recommendation, best action may differ depending on circumstances or patients' or societal values*
Conditional recommendation; low-quality quality evidence	*Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced*	*Observational studies, case series, or expert opinion*	*Very weak recommendation, other alternatives may be equally reasonable*

Table 1. Grade Working Group grading of quality of evidence and strength of recommendations

4. How to use these guidelines

These guidelines are meant to guide clinical decision making and are not intended to replace medical judgement when managing patients. These guidelines should never be relied on as a substitute for proper assessment with respect to the particular circumstances of each case and the needs of each patient. Furthermore, evidence-based clinical practice guidelines are constantly evolving. Hence users should consider emerging evidence and data that may supersede these guidelines.

References

1. World Health Organization. The urgent need to implement patient blood management. *https://apps.who.int/iris/bitstream/handle/10665/346655/9789240035744-eng.pdf (last accessed May 2022)* (2021).
2. Ministry of Health, Singapore. Clinical Blood Transfusion. HSA-MOH Clinical Practice Guidelines 1/2011 *https://www.moh.gov.sg/docs/librariesprovider4/guidelines/cpg_clinical_blood-transfusion.pdf (last accessed May 2022)* (2011).
3. Guyatt, G.H., Oxman, A.D., Vist, G.E. *et al.* GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *British Medical Journal* **336**, 924–6 (2008).
4. Society of Infectious Diseases (Singapore), College of Family Physicians, Singapore and Chapter of Infectious Disease Physicians. Handbook on Adult Vaccination in Singapore 2020. http://www.sids.org.sg/s/SIDS-Adult-Vaccine-Handbook-2020.pdf (last accessed May 2022) (2020).

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Content Page

1 Patient Blood Management

i. Pillars of Patient Blood Management

Key Points

- **All patients (both surgical and non-surgical) should be managed by the three pillars of Patient Blood Management to reduce transfusion requirement and optimise clinical outcomes. *(Strong recommendation; low-quality of evidence)***

Patient Blood Management

- Blood transfusion while beneficial when used according to the proper indications, comes with potential risks and side effects despite best efforts in ensuring blood and transfusion safety.
- The need to minimise unnecessary exposure to potential transfusion risks, increasing demand and limited blood supply has led to the development of the concept of patient blood management (PBM).
- PBM is a patient-centred, systematic and evidence-based approach to optimising care and clinical outcomes of all patients who may need transfusion. It aims to reduce unnecessary transfusions and minimise omission of potentially beneficial transfusions.[1]
- The effective implementation of PBM requires close collaboration and coordination among multidisciplinary healthcare professionals. It can also be further enhanced through patient education and empowerment with shared decision-making.[1]
- There are three main pillars which have been identified in PBM and can be applied to both surgical and non-surgical patients:
    1. Optimising of red cell mass and haematopoiesis
    2. Minimising bleeding and blood loss
    3. Optimising physiological tolerance of anaemia

The following table illustrates how the three pillars of PBM can be applied preoperatively, intraoperatively and postoperatively for surgical patients.

	1st pillar: Optimising red cell mass and haematopoiesis	2nd pillar: Minimising bleeding and blood loss	3rd pillar: Optimising physiological tolerance of anaemia
Preoperative	• A detailed medical history focusing on family and past history of anaemia. • Screen for anaemia early. Investigate and treat the underlying cause of anaemia (e.g., iron deficiency) before surgery. • Consider postponement of non-urgent surgeries till underlying cause	• Take a detailed history of patient's bleeding risk and personal and family history of bleeding disorders. • Patient's current medications should be reviewed. Any antiplatelet agents or anticoagulants should be noted. The patient should be counselled on whether and when to	• Patient should be assessed for physiological tolerance of anaemia including history of ischaemic heart, cerebrovascular and chronic kidney diseases.

	of anaemia is treated and Haemoglobin (Hb) is optimised.	stop the relevant medications prior to procedure, bearing in mind the patient's renal function.	
Intraoperative	• Time surgery with haematological optimisation.	• Meticulous surgical and anaesthetic techniques to minimise blood loss. • Where feasible, minimally invasive and laparoscopic procedures should be planned to minimise blood loss. • Consider early use of antifibrinolytics if indicated. • Consider the use of cell salvage options. • Use point of care testing devices to aid transfusion decisions.	• Optimise cardiac output and oxygenation.
Postoperative	• Assess and if necessary, investigate and treat the underlying cause of anaemia.	• Close monitoring of vital signs and laboratory parameters to detect post-operative bleeding in patients after major surgery, with view for early re-exploration to stem blood loss if indicated.	• Maintain evidence-based restrictive transfusion strategies during the post-operative period in stable patients. • Optimising patient's ventilation and oxygenation to maintain adequate cardiac output and perfusion.

Adapted from A Shander et al[2]

Application of the three pillars of PBM to stable medical patients:

- Red cell transfusion should not be used as a means to treat iron deficiency anaemia in a haemodynamically stable patient.
- Transfusions should be guided by Red Cell Transfusion and patient's physiological status.
- Excessive and unnecessary phlebotomy should be avoided to prevent iatrogenic anaemia.[3]
- Apart from actively bleeding patients, red cell units should only be transfused one at a time with a reassessment of the patient (including a consideration to recheck the Hb) after each unit before deciding on further transfusion.

ii. Perioperative anaemia management

Key Points

- **All surgical disciplines are recommended to adopt a perioperative care pathway that includes a mandatory screening for anaemia in cases with estimated blood loss of more than 500ml, at least 14 to 45 days prior to surgery. This allows sufficient time for investigation and treatment of the underlying cause of anaemia before the surgery. *(Strong recommendation; low-quality evidence)***
- **In the case of anaemia in a preoperative patient, non-urgent surgical procedures should be postponed till underlying cause of the anaemia is investigated and treated, and the haemoglobin optimised. *(Strong recommendation; low-quality evidence)***
- **All surgical patients with iron deficiency anaemia should be treated with iron replacement. *(Strong recommendation; moderate-quality evidence)***
- **Patients who cannot tolerate oral iron, do not respond to oral iron or do not have sufficient time to respond to oral iron (surgery in less than 6 weeks) should be considered for intravenous (IV) iron therapy. *(Strong recommendation; moderate-quality evidence)***
- **Postoperative transfusion is generally not indicated in stable and asymptomatic patients if Hb is more than 8g/dL. *(Strong recommendation; moderate-quality evidence)***
- **Red cell transfusion should not be used as a means for rapid correction of anaemia without consideration for the underlying cause of the anaemia. *(Strong recommendation; low-quality evidence)***

Perioperative Anaemia

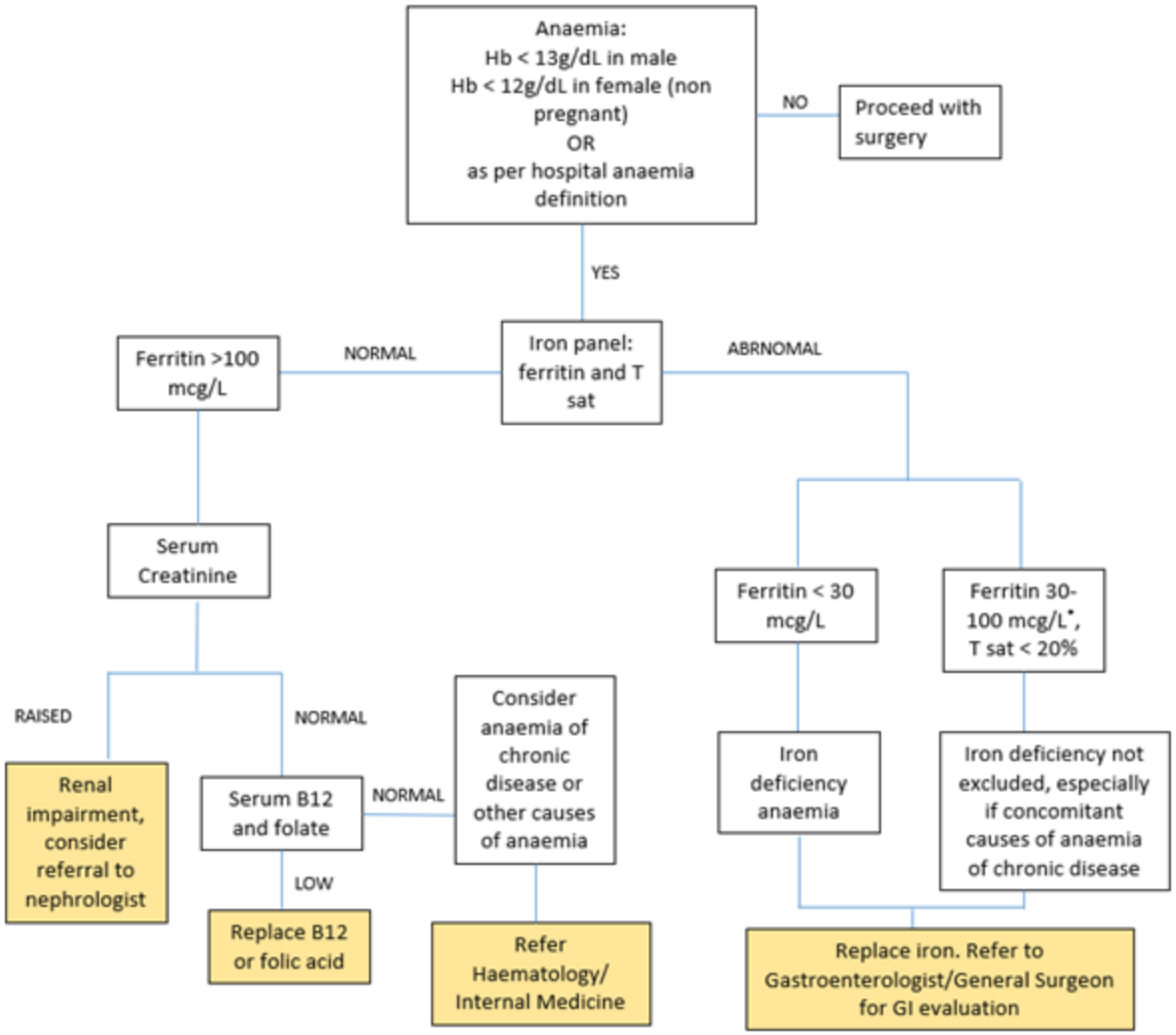
- Surgical patients with anaemia have been found to have a higher risk of morbidity, mortality and higher need for allogenic red cell transfusion.[4,5]
- Perioperative anaemia, in particular preoperative anaemia due to iron deficiency, is a potentially treatable condition. Transfusion has also been found to be associated with poor surgical outcomes.
- As far as possible, patient's underlying cause of anaemia should be investigated and treated prior to surgery.

Investigating preoperative anaemia

- All patients planned for elective surgery with expected blood loss of more than 500ml and > 10% chance of receiving allogenic red cell transfusion should be assessed for presence of anaemia.[3,6]
- By the World Health Organization (WHO) criteria, anaemia is defined as Hb < 13g/dL in adult men and Hb < 12g/dL in adult women.
- Laboratory investigations should be carried out once decision is made for surgery where possible (e.g., in the surgical outpatient clinic) as waiting for preoperative evaluation clinic (PEC) assessment may delay potential treatment for anaemia. Alternatively, an early assessment at the PEC could be scheduled.
- If anaemia is detected, the cause should be investigated and treated prior to surgery.
- Red cell transfusion should not be used as the default method to rapidly correct anaemia prior to surgery without considering the underlying cause of anaemia, as it has not been shown to ameliorate the poor surgical outcomes associated with anaemia.
- Important points to consider:
    - Iron deficiency is a possible cause for the anaemia when ferritin is less than 30 mcg/L.

- Iron deficiency anaemia is usually associated with low Mean Corpuscular Volume (MCV) and Mean Corpuscular Haemoglobin (MCH) while anaemia due to vitamin B12 or folate deficiency is usually associated with a raised MCV.
- A combination of iron deficiency with B12 or folate deficiency may result in a misleadingly normal MCV.
- Consider possibility of thalassaemia in patients with low MCV and MCH but no iron deficiency.
- Anaemia may be multifactorial especially in elderly patients or patients with multiple comorbidities.

Suggested Flowchart for Pre-operative Anaemia Investigation



T sat: Transferrin Saturation, GI: Gastrointestinal

* Ferritin is an acute phase reactant; a higher cut-off of <300mcg/L should be considered for iron deficiency in malignancy or other conditions (such as chronic kidney disease, inflammatory bowel disease or other inflammatory conditions and chronic heart failure). In inflammatory conditions, iron deficiency can be diagnosed with ferritin < 100 mcg/L OR T sat < 20%[7]

Flowchart adapted from Munoz et al[8]

Management of Preoperative Iron Deficiency Anaemia

The choice of iron therapy should depend on patient's Hb level, time to surgery and tolerance and compliance to iron therapy.

Oral iron replacement

- When there is sufficient interval prior to surgery (6-8 weeks), oral iron should be first line for iron replacement.[8]
- While traditionally daily oral iron replacement has been used in iron deficiency, providing lower doses of elemental iron at 40-80mg as a single dose (instead of twice daily dosing) on alternate days (instead of daily) has been shown to maximise fractional absorption of iron, and can be considered for better tolerance.[9,10]
- Different iron formulations have different amounts of elemental iron. Check package insert or with pharmacist prior to prescribing.
- Ferric formulations of iron may be associated with less gastrointestinal side effects than ferrous formulations but may be less well absorbed than ferrous formulations.
- Hb should be measured 4 weeks after trial of oral iron.
- A total duration of 3 to 6 months of iron therapy should be prescribed beyond normalisation of Hb level to adequately replace iron stores.
- Patients with functional iron deficiency, chronic illness and ongoing bleeding may not respond well to oral iron. IV iron may be considered in these patients.

Intravenous (IV) iron replacement

- IV iron should be considered in the following situations:
    - Patients who are not responding to oral iron or unable to tolerate side effects of oral iron.
    - Patients with surgical or physiological iron malabsorption e.g., coeliac disease, inflammatory bowel disease.
    - Patients with significant anaemia secondary to severe or ongoing blood loss, as an initial treatment measure before transitioning to oral iron to allow for a faster increase in Hb. The underlying cause of the blood loss should also be treated.
    - Preoperative patients with iron deficiency who may not have sufficient time to respond to oral iron treatment (surgery less than 6 weeks away).
    - To support the use of Erythropoiesis Stimulating Agents (ESAs).

- Patients should be counselled on potential side effects of IV iron replacement. These may include:
    - Risk of anaphylaxis. The risk of anaphylaxis is low.[4] However, patients should still receive IV iron in a monitored setting with availability of resuscitation equipment and trained medical personnel. Vital signs should be monitored regularly during IV iron infusion and up to 30 minutes after completion of infusion.
    - Risk of hypophosphatemia. Phosphate levels need not be routinely monitored unless patient has symptoms of hypophosphatemia, receives multiple doses of IV iron or is on long term IV iron therapy.
    - Skin discolouration at injection site due to extravasation.

Management of Vitamin B12 and folate deficiency

- Folate deficiency can be treated with folic acid 5mg/day.

- If there is concomitant Vitamin B12 and folate deficiency, replace Vitamin B12 first before replacing folate, as folic acid replacement alone may precipitate subacute combined degeneration of the cord.
- Patients with Vitamin B12 deficiency should be worked up for presence of pernicious anaemia.

Management of Anaemia of Chronic Disease with Erythropoiesis Stimulating Agents

- Erythropoiesis Stimulating Agents (ESAs) are approved for use in certain types of chronic anaemia and can be considered for patients who meet indications for ESA therapy.
- Patients should also receive adequate iron supplementation alongside ESA therapy to optimise Hb increment.
- ESAs should be prescribed by clinicians familiar with its use or in consultation with a Haematologist. Clinicians should be familiar with the indications, contraindications and potential side effects of ESA therapy and counsel their patients accordingly. Clinicians are recommended to refer to the local prescribing information of the specific ESA formulation for such information.
- Patients must be counselled for and monitored for potential side effects such as thromboembolic risks and the rate of increase of Hb.
- Hb should be closely monitored during ESA therapy, with set target Hb levels which may indicate need to discontinue therapy.
- ESA therapy should not be offered to raise the Hb in patients with anaemia for reasons other than chronic disease or outside its approved indications. It may be considered in the following circumstances (provided no contraindications) whereby the use of ESA in such instances should involve a haematology consult:[11,12]
    - Patient has anaemia and declines blood transfusion due to religious beliefs or other reasons.
    - Difficulty in finding matched red cell units due to rare blood group or multiple red cell alloantibodies.

Management of Postoperative Anaemia

- Anaemia may be present in up to 90% of patients in the immediate postoperative period after major surgery.[13]
- Patients may develop functional iron deficiency post-surgery due to post-surgical inflammatory stress response.
- Oral iron has limited efficacy in the postoperative period due to poor absorption.
- Administration of IV iron has been shown to correct anaemia after major orthopaedic, abdominal and genito-urinary surgery and others.[8]
- Postoperative transfusion is usually not indicated in stable asymptomatic patients if Hb is more than 8g/dL.
- Red cell transfusion should not be used to rapidly correct anaemia so that patient can be discharged early.

iii. Red Cell Conservation Techniques

Key Points

- **Intraoperative cell salvage should be considered for all surgeries where expected blood loss is more than 500ml or more than 10% of patient's total blood volume.** ***(Conditional recommendation; moderate-quality evidence)***

- **Cell salvage can be considered in patients with rare blood types, presence of multiple alloantibodies or in patients who object to receiving allogeneic transfusion, if significant blood loss is expected.** ***(Strong recommendation; low-quality evidence)***

General Information

- Red cell conservation techniques include a range of processes that use patient's own red cells (autologous) in transfusion, hence reducing the need for allogenic blood transfusion.
- It is important to note that while autologous transfusion may reduce transfusion risks such as alloimmunisation and transmission of blood borne infections, it does not mitigate all transfusion related risks.
- Intraoperative cell salvage should be considered on a case-by-case basis where a patient may meet the indications.

Intraoperative Cell Salvage

- Cell salvage involves collection of blood that is found in the body cavity, lost during or immediately post-surgery.
- This blood is filtered and subsequently anticoagulated with heparin or citrate. The blood is then centrifuged, washed and transferred to a separate bag.
- If the patient has been deemed to have lost sufficient blood to warrant a blood transfusion at the end of a surgery, the collected blood is then infused back to the same patient.
- Every surgical unit is recommended to have a protocol for intraoperative cell salvage in place.

Indications:	Considerations:	Contraindications/Concerns:

• When surgical blood loss is expected to exceed 500ml or more than 10% or total blood.[14]
• May also be considered when significant surgical blood loss is expected in following groups of patients:
  ○ In patients who are coagulopathic or anaemic prior to surgery.[14,15]
  ○ In patients who object to receiving allogeneic transfusion.[15]
  ○ In patients with rare blood groups or multiple alloantibodies for whom it is difficult to find a matched donor.[15]
  ○ In surgeries where tourniquets cannot
	• Patients with previous heparin-induced thrombocytopaenia should not use heparin containing anticoagulant solutions. Acid-citrate dextrose solution should be used instead.[15]
	• There is a potential risk for metallosis, though rare, at a rate of 5%, when cell salvage is performed in presence of metal implants.[14] Hence cell salvage should not be used where metal implants may be in situ until the surgical field is irrigated and metal fragments removed.[14]
	• Cell salvage should be ceased if there is a risk of contamination by substances not compatible with intravenous use such as iodine, topical antibiotics, joint cement
		• Cell salvage is currently not recommended when bowel contents or infected material is present in the surgical field.[15,17] There are a few other situations when use of cell salvage may be a concern. In all these instances risks and benefits of cell salvage should be discussed with the patient.
		• Malignancy
		  ○ A theoretical concern of metastases of malignant cells in cancer surgery exists. However, it has been estimated that only 0.000001 to 0.01% of circulating tumour cells have the potential to form metastatic lesions.[18,19]
		  ○ There are published reports on the use of

be applied such as spine surgeries.[15]	and topical clotting agents.[15,16]	cell salvage in cancer surgeries without association of early metastasis.[15] ○ Aspiration of blood for salvage should be avoided around the tumour site, and the salvaged blood should be reinfused through a leucocyte depletion filter.[15] • Presence of Haemoglobinopathy or Cold Agglutinin Disease ○ Intraoperative cell salvage for patients with underlying Haemoglobinopathy and Cold Agglutinin Disease should be discussed in conjunction with a Haematologist.[17]

iv. Non-Transfusion Interventions

Key Points

- **Anaesthetic and surgical techniques such as maintaining optimal physiology during surgery, use of minimally invasive techniques and rapid control of bleeding can contribute to optimal coagulation and reduced blood loss. Such techniques should be considered and individually tailored for all patients.** ***(Strong recommendation; high-quality evidence)***
- **Tranexamic acid should be considered in surgeries with anticipated substantial blood loss, if there is no contraindication.** ***(Strong recommendation; high-quality evidence)***
- **Timely use of point of care testing with Viscoelastic Haemostatic Assays (VHA) may reduce the amount of blood products required.** ***(Conditional recommendation; moderate-quality evidence)***

Anaesthetic and Surgical Considerations[11,16,20,21]

Maintenance of balanced physiology	Avoidance of hypothermia, acidosis and hypocalcaemia is vital to optimal clot formation
Patient positioning	Patient positioning intraoperatively can be manipulated to reduce venous and arterial pressure on surgical field and hence reduce blood loss.
Rapid Control of Bleeding	Control of bleeding via vessel ligation, pressure, diathermy and use of topical vasoconstrictors and haemostatic agents should be done proactively.

Use of tourniquets	Careful and appropriate use of tourniquets with close monitoring to avoid ischaemic complications.
Regional Anaesthesia	Central neuraxial blockade has been shown to reduce perioperative blood loss.
Minimally Invasive Surgical Techniques	Techniques such as laparoscopic surgery, endovascular techniques and robotics assisted surgery reduce blood loss when compared to open invasive procedures.

Antifibrinolytic Agents

- Aminocaproic acid and tranexamic acid (TXA) are antifibrinolytic drugs that work by preventing breakdown of blood clots. Of the two, TXA has been more commonly used.
- The CRASH-2 trial studied the efficacy of TXA in trauma patients and found that early treatment with TXA safely reduced the risk of death in bleeding trauma patients.[22]
- Studies have also shown TXA to be beneficial in reducing bleeding in major surgery.[23,24] TXA is currently recommended in prophylactic treatment of bleeding in major surgery in international anaesthesia guidelines.[25,26]

Point of care testing

- Point of care testing with VHA such as thromboelastography (TEG) and rotational thromboelastrometry (ROTEM) have been found to be associated with reduced transfusion requirements in cardiac and liver surgeries.[27-29]
- They hold an advantage over conventional coagulation assays by having a quicker turnaround time and requiring smaller sample volumes. They may help to guide usage of blood components or other agents for haemostasis in massively bleeding patients.

References

1. World Health Organization. The Urgent Need to Implement Patient Blood Management: Policy Brief. *https://apps.who.int/iris/bitstream/handle/10665/346655/9789240035744-eng.pdf (last accessed May 2022)* (2021).
2. Shander, A., Javidroozi, M., Perelman, S. *et al*. From bloodless surgery to patient blood management. *Mount Sinai Journal of Medicine* **79**, 56–65 (2012).
3. Whitehead, N.S., Williams, L.O., Meleth, S. *et al.* Interventions to prevent iatrogenic anemia: a Laboratory Medicine Best Practices systematic review. *Critical Care* **23**, 278 (2019).
4. Munting, K.E. & Klein, A.A. Optimisation of pre-operative anaemia in patients before elective major surgery - why, who, when and how? *Anaesthesia* **74**, 49–57 (2019).
5. Musallam, K.M., Tamim, H.M., Spahn, D.R. *et al.* Preoperative anaemia and postoperative outcomes in non-cardiac surgery: a retrospective cohort study. *The Lancet* **378**, 1396–1407 (2011).
6. Rössler, J., Schoenrath, F., Seifert, B. *et al.* Iron deficiency is associated with higher mortality in patients undergoing cardiac surgery: a prospective study. *British Journal of Anaesthesia* **124**, 25–34 (2020).
7. Cappellini M.D., Comin-colet J., de Francisco A et al. Iron deficiency across chronic inflammatory conditions: International expert opinion on definition, diagnosis and management. *American Journal of Haematology* **92**, 1068-1078 (2017).
8. Muñoz, M., Acheson, A.G., Auerbach, M. *et al.* International consensus statement on the peri-operative management of anaemia and iron deficiency. *Anaesthesia* **72**, 233–247 (2017).
9. Stoffel, N.U., Cercamondi, C.I., Brittenham, G. *et al.* Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women: two open-label, randomised controlled trials. *The Lancet Haematology* **4**, e524–e533 (2017).
10. Moretti, D., Goede, J.S., Zeder, C. *et al.* Oral iron supplements increase hepcidin and decrease iron absorption from daily or twice-daily doses in iron-depleted young women. *Blood* **126**, 1981–1989 (2015).

11. Thakrar, S.V., Clevenger, B. & Mallett, S. Patient blood management and perioperative anaemia. *British Journal of Anaesthesia Education* **17**, 28–34 (2017).
12. Booth, C., Allard, S. & Robinson, S. Blood transfusion. *Medicine (United Kingdom)* **49**, 238–242 (2021).
13. Shander, A., Knight, K., Thurer, R., *et al*. Prevalence and outcomes of anemia in surgery: a systematic review of the literature. *The American Journal of Medicine* **116**, 58–69 (2004).
14. Klein, A.A., Bailey, C.R., Charlton, A.J. *et al.* Association of Anaesthetists guidelines: cell salvage for peri-operative blood conservation 2018. *Anaesthesia* **73**, 1141–1150 (2018).
15. UK Cell Salvage Action Group (UKCSAG). Intraoperative Cell Salvage Education Workbook: Section 7 Indications and Contraindications. (2015).
16. Squire, Y., Laxton, C. Blood conservation techniques. Tutorial 390. https://www.*wfsahq.org/components/com_virtual_library/media/8d6712e97e44cd3c3c2af5cc1cbffc00-atow-390-00-01.pdf.* (*last accessed May 2022*) (2018).
17. National Blood Authority, Australia. Guidance for the provision of Intraoperative Cell Salvage. *https://www.blood.gov.au/system/files/documents/ics-guidance-march-2014_1.pdf (last accessed May 2022)* (2014).
18. Weiss, L. Metastatic Inefficiency. *Advances in Cancer Research* **54**, 159-211 (1990).
19. Esper, S.A. & Waters, J.H. Intra-operative cell salvage: a fresh look at the indications and contraindications. *Blood Transfusion* **9**, 139–47 (2011).
20. Richman, J. M., Rowlingson, A.J., Maine, D.N. *et al.* Does neuraxial anesthesia reduce intraoperative blood loss? A meta-analysis. *Journal of Clinical Anesthesia* **18**, 427–35 (2006).
21. Fung, M.K., Eder, A., Spitalnik, S.L. et al. Technical Manual. AABB. (2017)
22. CRASH-2 collaborators *et al.* The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet* **377**, 1096–101, 1101.e1–2 (2011).
23. Devereaux, P. J., Marcucci, M. Painter, T.W. *et al.* Tranexamic Acid in Patients Undergoing Noncardiac Surgery. *New England Journal of Medicine* **386**, 1986-1997 (2022).
24. Ockerman, A., Vanassche, T., Garip, M. *et al.* Tranexamic acid for the prevention and treatment of bleeding in surgery, trauma and bleeding disorders: a narrative review. *Thrombosis Journal* **19**, 54 (2021).
25. Kozek-Langenecker, S.A., Ahmed, A.B., Afshari, A. *et al.* Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology: First update 2016. *Euroepan Journal of Anaesthesiology* **34**, 332–395 (2017).
26. American Society of Anesthesiologists Task Force on Perioperative Blood Management. Practice guidelines for perioperative blood management: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Management. *Anesthesiology* **122**, 241–75 (2015).
27. Tafur, L.A., Taura, P., Blasi, A. *et al.* Rotation thromboelastometry velocity curve predicts blood loss during liver transplantation. *British Journal of Anaesthesia* **117**, 741–748 (2016).
28. Pustavoitau, A., Lesley, M., Ariyo, P. *et al.* Predictive Modeling of Massive Transfusion Requirements During Liver Transplantation and Its Potential to Reduce Utilization of Blood Bank Resources. *Anesthesia & Analgesia* **124**, 1644–1652 (2017).
29. Karkouti, K., Callum, J., Wijeysundera, D.N. *et al.* Point-of-Care Hemostatic Testing in Cardiac Surgery. *Circulation* **134**, 1152–1162 (2016).

2 Red Cell Transfusion

Key Points

- **Transfusions of red cells are associated with a risk of mild to severe adverse reactions.**
- **Transfusions of red cells should be performed only when there are clear indications and benefits. Transfusion decisions should also take into account the patient's clinical condition and comorbidities, rather than being based only on their haemoglobin values. *(Strong recommendation; low-quality evidence)* The indication should be clearly documented.**
- **In hospitalised patients with anaemia and no active bleeding:**
  - **It is important to evaluate and treat the underlying cause of anaemia whenever possible. *(Strong recommendation; low-quality evidence)***
  - **Transfusions are rarely beneficial when haemoglobin levels exceed 10g/dL in the absence of acute blood loss. *(Strong recommendation; moderate-quality evidence)***
  - **Benefits of transfusion are likely to exceed the risks when haemoglobin levels fall below 7g/dL in most populations. *(Strong recommendation; moderate-quality evidence)***
  - **For haemoglobin levels between 7 to 10g/dL, clinical judgement based on symptoms, comorbid conditions and evidence-based transfusion thresholds should be applied. *(Strong recommendation; low-quality evidence)***
- **Informed consent should be taken from the patient after informing of the risks and benefits and alternatives to allogenic blood transfusion.**
- **Efforts should be made to prevent administrative errors leading to incompatible transfusions which can be potentially life threatening or fatal. *(Strong recommendation; low-quality evidence)* Patient misidentification and incorrect sample labelling are common reasons for the administration of incompatible blood components.**
- **It is imperative that positive patient identification is done at the bedside at the time of collecting the sample for crossmatch and prior to initiating the blood transfusion. *(Strong recommendation; low-quality evidence)***

General Information

- Conventional red blood cell (RBC) concentrates should suffice in most instances.
- Some patients may have additional requirements for leucoreduced, washed and irradiated RBC concentrates and the indications for these are covered in the Modified Blood Components chapter.
- The mean (range) volume of one unit of RBC concentrate is approximately 280 (230-330) ml with mean haematocrit (Hct) of 0.6.
- In the absence of ongoing blood loss or haemolysis, one unit of RBC concentrate should raise the haemoglobin in an adult of 70-80kg, by approximately 1g/dL.[1]

Compatibility

ABO blood group compatibility

In transfusion practice, the ABO blood group (O, A, B and AB) is the most important. From early childhood, normal healthy individuals produce antibodies against the A or B antigens that are not expressed on their red cells.

Blood Group	Antibody present in plasma
A	Intrinsic anti-B antibody
B	Intrinsic anti-A antibody
AB	Neither intrinsic anti-A nor anti-B antibodies
O	Intrinsic anti-A and anti-B antibodies

The antibodies can haemolyse transfused red cells rapidly, thus it is important that ABO compatible red cells are transfused. In an emergency setting, when the patient's ABO group cannot be determined, group O red cells must be selected.

Patient ABO Blood Group	Compatible Donor RBC concentrates
A	A, O
B	B, O
AB	AB, A, B, O
O	O

RhD blood group compatibility

- RhD negative red cells should be given to all RhD negative individuals, whenever feasible.
- In cases of unknown RhD blood group, RhD negative red cells should be issued to Indian, Caucasian, African or Middle Eastern female patients of current or future childbearing age (below 50 years of age) if RhD negative RBC concentrates are available, because these groups have higher chances of being RhD negative and may be at higher risk of haemolytic disease of fetus and newborn from anti-D development. In other racial groups, RhD positive red cells may be issued for emergency transfusion if their RhD blood group is unknown.
- RhD negative patients who have been or will be transfused with RhD positive blood components should be informed and counseled regarding the implications of possible alloimmunisation.
- Where there has been inadvertent transfusion of RhD positive red cells to non-alloimmunised RhD negative females with current or future child-bearing potential, anti-D immunoglobulin should be given. (Dose for intramuscular (IM) administration: usually 125 IU will clear 1 ml of RhD positive red cells. Reference to dosing in the product information of the anti-D immunoglobulin preparation is also recommended.)[2]
- If more than 15ml of RhD positive red cells have been transfused, Intravenous (IV) anti-D immunoglobulin may be more practical if this is available (dose for IV administration: 100 IU will clear 1 ml of RhD positive red cells).[2] Otherwise, larger IM anti-D immunoglobulin preparations (1500 IU) may also be considered. IM-only preparations of anti-D immunoglobulins must NOT be given IV.

- Where more than 1 unit of RhD positive blood has been transfused, a haematology consult should be sought for consideration of exchange transfusion.

Dose and Administration

- Transfusion should be completed within 4 hours of the RBC concentrate leaving controlled temperature storage.
- A single unit of RBC concentrate can be safely transfused to most patients over 90-120 minutes.
- During major haemorrhage, very rapid transfusion (each unit over 5-10 minutes) may be required.
- In the absence of ongoing blood loss, single unit red cell transfusions are recommended to minimise risks of transfusion. Further units should not be prescribed without monitoring the patient's haemoglobin and re-assessing the patient's condition.
- The risk of transfusion-associated circulatory overload (TACO) is reduced by careful pre-transfusion clinical assessment of fluid balance. Risk factors for TACO include age over 60 years, female gender, pre-existing cardiac or renal dysfunction and a higher total volume of blood components administered.[3] Evidence based transfusion practice, reduction of infusion rates and prophylactic volume reduction with diuretics may all limit the incidence of TACO.[3]

Indications

Management of transfusion needs during acute blood loss

The management of massive transfusion is covered in the Massive Transfusion Protocol guideline.

- In the acutely haemorrhaging patient, transfusion considerations are based on estimated percentage of blood volume lost, the rate of ongoing blood loss, the haemoglobin level prior to bleeding, evidence of end organ dysfunction and the risk of coronary artery disease, rather than haemoglobin thresholds.
- Symptoms of anaemia that are firm indications for transfusion, include chest pain, congestive heart failure, unexplained hypotension and tachycardia attributable to anaemia.
- While anaemic younger patients rely on their organ reserve to compensate for the lack of oxygen, anaemic older patients may be unable to augment cardiac output to compensate for anaemia due to a greater degree of diffuse vascular disease and the presence of additional comorbid illnesses.
- The source of bleeding should be identified early and appropriate action should be taken immediately, including endoscopic or surgical control of bleeding.
- Excessive transfusion should be avoided in normotensive patients with acute variceal bleeding, as aggressive volume expansion is associated with a higher rebleeding risk.[4,5]

Management of transfusion needs in patients without active and acute haemorrhage

General principles

- The cause of anaemia should be established before red cell transfusion.
- Where appropriate, specific pharmacological agents should be used to correct the anaemia.
- The risks of transfusions should always be weighed against the perceived benefits.
- Transfusions are rarely beneficial when haemoglobin level exceeds 10g/dL in the absence of acute blood loss.
- Benefits of transfusion are likely to exceed the risks when haemoglobin concentrations fall below 7.0g/dL in most populations.
- For haemoglobin concentrations between 7.0 to 10.0g/dL, clinical judgement based on symptoms, comorbid conditions and evidence-based transfusion thresholds should be applied.

Specific scenarios

These recommendations should be used in conjunction with the HSA guideline "Recommended red cell transfusion triggers for the non-haemorrhagic patients with chronic anaemia" (Annex 1). Transfusion triggers based on haemoglobin levels should always be evaluated in the context of a multiplicity of factors including clinical signs and symptoms of anaemia and cardiopulmonary reserve.

Some scenarios are tabulated below where evidence from studies is available.

Clinical situation	Hb transfusion trigger (g/dL)
Asymptomatic general medical patient	Hb less than 7g/dL[6-8] *(Strong recommendation; moderate-quality evidence)*
Critically ill patients e.g., Intensive Care Unit (ICU) setting	Hb less than 7g/dL[6,7,9,10] *(Strong recommendation; high-quality evidence)* Transfusion triggers should not exceed 9g/dL in most critically ill patients.[9] *(Strong recommendation; moderate-quality evidence)*
Haemodynamically stable postoperative patients	Hb less than 8g/dL[6,8,11,12] *(Strong recommendation; moderate-quality evidence)* In post-operative surgical patients with Hb between 8 and 10 g/dL who are haemodynamically unstable, transfusion of a single unit of red cells followed by reassessment of clinical efficacy, is appropriate.[7] *(Strong recommendation; moderate-quality evidence)*
Haemodynamically stable patients with pre-existing cardiovascular disease	Hb less than 8g/dL[6,8,10,11] *(Strong recommendation; moderate-quality evidence)* Transfusion may also be considered for patients with a Hb between 8 and 10 g/dL who are haemodynamically unstable.[6,12] *(Strong recommendation; moderate-quality evidence)*
Acute Coronary Syndrome	Hb less than 8 g/dL[7,13-16] *(Conditional recommendation; moderate-quality evidence)* The optimal transfusion strategy is still under investigation. Ducrocq et al. reported that a restrictive transfusion strategy (triggered by haemoglobin < 8 g/dL) was non-inferior compared to a liberal transfusion strategy (triggered by haemoglobin < 10 g/dL) with regards to the rate of major cardiovascular events, however the authors concluded that in view of the study design, non-inferiority could not be completely eliminated.[13] In the 3504 patient MINT study, a liberal strategy (transfusion threshold: Hb < 10g/dL) did not significantly reduce the composite primary outcome of death or recurrent myocardial infarction at 30 days, compared to restrictive transfusion strategy (transfusion threshold: Hb < 7-8g/dL). However, these results should be interpreted with caution

	and more studies are needed to inform these findings as the liberal arm had more favourable outcomes for individual endpoints such as cardiac death and for certain subgroup of patients. [14] At Hb concentrations between 8 and 10 g/dL, transfusion decisions should be individualised and a decision to transfuse should be based on consideration of symptoms and benefits versus risks. Patients with symptoms of anaemia or haemodynamic instability may require transfusion to ameliorate symptoms.[7,9] *(Strong recommendation; low-quality evidence)*
Heart failure	No specific Hb level. Patients are at increased risk of TACO; transfuse only if necessary and monitor fluid status.[7] *(Strong recommendation; low-quality evidence)* If red cell transfusion is indicated, this should be carried out one unit at a time followed by reassessment of clinical response and fluid status after each unit. Patients with iron deficiency should have iron replacement therapy.[7] *(Strong recommendation; high-quality evidence)*
Cancer	No specific Hb level. Transfusion should be based on the need to alleviate symptoms.[7] *(Strong recommendation; low-quality evidence)*

Management of chronically transfused patients

- All chronically transfused patients should receive leucoreduced red cells.
- Patients who are likely to need chronic transfusions, should be considered for extended red cell antigen phenotyping that includes C, c, E, e, K, Jk^a, Jk^b, Fy^a, Fy^b, S and s before initiating transfusion therapy, whenever feasible.
- If the patient has already been transfused, phenotyping should be performed at least 3 months from the last red cell transfusion to ensure accuracy or have their blood group antigens determined by molecular methods if this is available.
- All patients with transfusion dependent or non-transfusion dependent thalassaemia should receive leucodepleted ABO, Rh (D, C, c, E, e) and Kell matched red cells to reduce red cell alloimmunisation risk. [17–19] Kidd (Jka, Jkb) matched red cells are also recommended in Singapore as alloantibodies to the Kidd blood group antigens are some of the commonest red cell alloantibodies among the patients here.[20]
- All patients with Sickle Cell Disease should receive red cells from donors unlikely to have haemoglobin S (e.g., donor of Chinese ethnicity), that are leucoreduced and ABO, Rh (D, C, c, E, e) and Kell matched to reduce alloimmunisation risk.[17]
- For patients with non-transfusion dependent thalassaemias, there is concern about risk of worsening iron overload and alloimmunisation. Transfusion therapies should be individualised based on their symptoms and other comorbidities from chronic anaemia and ineffective erythropoiesis e.g., pulmonary hypertension and symptomatic extramedullary haematopoietic pseudotumours.[7,18]
- In patients with transfusion dependent thalassaemia (i.e. thalassaemia major), the recommended treatment is lifelong transfusions (usually every 2 to 6 weeks) to maintain a pre-transfusion

haemoglobin level above 9 to 10.5g/dL.[7,19] Patients should also be monitored for iron overload and started on appropriate iron chelation.

- Transfusion of patients with haemoglobinopathies should be managed in conjunction with a haematologist.
- In patients with myelodysplastic syndrome (MDS) who are regularly and chronically transfused, there is no evidence to guide haemoglobin transfusion thresholds.[7] Transfusion triggers and frequency should be adjusted to patient's symptoms and functional status and response to previous transfusions. Like patients with thalassaemia who are chronically transfused, patients with MDS with a reasonable prognosis should be considered for iron chelation therapy.

References

1. Murphy, Atterbury, Chapman *et al.* The administration of blood and blood components and the management of transfused patients. British Committee for Standards in Haematology, Blood Transfusion Task Force. Royal College of Nursing and the Royal College of Surgeons of England. *Transfusion Medicine* **9**, 227–238 (1999).
2. Qureshi, H., Massey, E., Kirwan, D. *et al.* BCSH guideline for the use of anti-D immunoglobulin for the prevention of haemolytic disease of the fetus and newborn. *Transfusion Medicine* **24**, 8–20 (2014).
3. Roubinian N. & Murphy, E. Transfusion-associated circulatory overload (TACO): prevention, management, and patient outcomes. *International Journal of Clinical Transfusion Medicine* ***3***, 17-28 (2015).
4. Villanueva, C., Colomo, A., Bosch, A. *et al*. Transfusion strategies for acute upper gastrointestinal bleeding. *New England Journal of Medicine* **368**, 11-21 (2013).
5. Laine, L., Barkun, A.N., Saltzman, JR. *et al*. ACG Clinical Guideline: Upper gastrointestinal and ulcer bleeding. *American Journal of Gastroenterology* **116**, 899-917 (2021).
6. Carson, J. L., Grossman, B.J., Kleinman, S. *et al*. Red Blood Cell Transfusion: A Clinical Practice Guideline From the AABB. *Annals of Internal Medicine* **157**, 49-58 (2012).
7. National Blood Authority, Australia. Patient Blood Management Guidelines: Module 3 Medical. *https://www.blood.gov.au/pbm-module-3 (last accessed April 2022)* (2012).
8. Carson, J. L., Guyatt, G., Heddle, N.M. *et al.* Clinical Practice Guidelines from the AABB: Red Blood Cell Transfusion Thresholds and Storage. *Journal of American Medical Association* **316**, 2025-2035 (2016).
9. Retter, A., Wyncoll, D., Pearse, R. *et al.* Guidelines on the management of anaemia and red cell transfusion in adult critically ill patients. *British Journal of Haematology* **160**, 445–464 (2013).
10. Hébert, P.C., Wells, G., Blajchman, M.A. *et al.* A Multicenter, Randomized, Controlled Clinical Trial of Transfusion Requirements in Critical Care. *New England Journal of Medicine* **340**, 409–417 (1999).
11. Carson, J.L., Terrin, M.L., Magaziner, J. *et al.* Transfusion Trigger Trial for Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS). *Transfusion (Paris)* **46**, 2192–2206 (2006).
12. Docherty, A.B., O'Donnell, R., Brunskill, S. *et al.* Effect of restrictive versus liberal transfusion strategies on outcomes in patients with cardiovascular disease in a non-cardiac surgery setting: systematic review and meta-analysis. *Brisith Medical Journal* i1351–i1351 (2016).
13. Ducrocq, G., Gonzalez-Juanatey, J.R., Puymirat, E. *et al.* Effect of a Restrictive vs Liberal Blood Transfusion Strategy on Major Cardiovascular Events Among Patients With Acute Myocardial Infarction and Anemia. *Journal of American Medical Association* **325**, 552-560 (2021).
14. Carson, J.L., Hébert, P.C., Goodman, S.G., *et al.* Restrictive or Liberal Transfusion Strategy in Myocardial Infarction and Anemia. *New England Journal of Medicine* DOI: 10.1056/NEJMoa2307983.
15. Garfinkle, M., Lawler, P.R., Filion, K.B. *et al*. Red blood cell transfusion and mortality among patients hospitalized for acute coronary syndromes: A systematic review. *International Journal of Cardiology* **164**, 151–157 (2013).
16. Carson, J.L., Stanworth, S.J., Dennis, J.A. *et al.* Transfusion thresholds for guiding red blood cell transfusion. *Cochrane Database of Systematic Reviews* **2022** (2021).

17. Trompeter, S., Massey, E. & Robinson, S. Position paper on International Collaboration for Transfusion Medicine (ICTM) Guideline 'Red blood cell specifications for patients with hemoglobinopathies: a systematic review and guideline.' *British Journal of Haematology* **189**, 424–427 (2020).
18. Taher, A.T., Musallam, K.M., Cappellini M.D. Guidelines for the management of non-transfusion-dependent β thalassaemia (NTDT). 3rd ed: Thalassaemia International Federation (2023).
19. Cappellini, M.D., Farmakis, D., Porter, J. *et al*. Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT). 4th ed. Thalassaemia International Federation (2021).
20. Ang, A.L., Lim, C.Y., Ng, W. Non-transfusion dependent thalassemia is independently associated with higher alloimmunization risk than transfusion dependent thalassemia and would benefit the most from extended red cell antigen-matching. *Transfusion* **61**, 2566–2577 (2021)

3 Platelet Transfusion

Key Points

- **If the cause of thrombocytopaenia is unclear, further investigations are required to guide appropriate management including whether platelet transfusions are appropriate. (*Strong recommendation; low-quality evidence)***
- **The therapeutic goal of platelet transfusion is to provide adequate numbers of normally functioning platelets for the prevention (prophylactic transfusion) or cessation of bleeding (therapeutic transfusion).**
  - **Prophylactic platelet transfusion should be given to patients with hypoproliferative thrombocytopaenia from intensive chemotherapy or allogenic haematopoietic stem cell transplant when their platelet count is <10 X 10^9/L. (*Strong recommendation; moderate-quality evidence)***
  - **For the above group of patients with additional bleeding risk factors such as fever or infection, prophylactic platelet transfusions should be considered when their platelet count is <20 X 10^9/L. *(Conditional recommendation; low-quality evidence)***
  - **Higher platelet count targets are recommended for patients with hypoproliferative thrombocytopaenia who are undergoing procedures or surgeries that are likely to cause bleeding. The platelet count thresholds for prophylactic platelet transfusions are dependent on the type of procedure and its associated bleeding risk. *(Strong recommendation; low-quality evidence)***
  - **Therapeutic platelet transfusions should be given to those who have significant thrombocytopaenia and WHO grade 2 or above bleeding. The platelet count thresholds for transfusions are dependent on the severity and site of bleeding. *(Strong recommendation; low-quality evidence)***
- **Not all patients with severe thrombocytopaenia benefit from platelet transfusions.**
  - **Patients with immune thrombocytopaenic purpura (ITP) and post-transfusion purpura (PTP) often do not have adequate or sustained platelet count increment to platelet transfusions.**
  - **Platelet transfusions in heparin induced thrombocytopaenia (HIT) may increase the risk of thrombosis. *(Conditional recommendation; low-quality evidence)***
  - **For patients with thrombotic thrombocytopaenic purpura (TTP) and other thrombotic microangiopathies, platelet transfusions are avoided (unless life-threatening bleeding is present) due to the potential thrombotic complications from platelet transfusions in these conditions. (*Strong recommendation; low-quality evidence)***
- **Use only one adult dose routinely for prophylactic platelet transfusions. *(Strong recommendation; high-quality evidence)***
- **Apply local measures, such as compression, to reduce the risk of bleeding post procedure and consider the use of adjunctive agents such as tranexamic acid. *(Strong recommendation; low-quality evidence)***
- **Screening for HLA class I antibodies should be performed in platelet refractoriness not explained by non-immune conditions such as sepsis, splenomegaly and consumptive coagulopathy. *(Strong recommendation; low-quality evidence)***

General Information

- Platelet therapy may be achieved by infusion of either apheresis platelets from a single donor or whole blood-derived platelet concentrates pooled from 4 donors.
- One unit of pooled platelets derived from a whole blood collection contains at least 2.4×10^{11} platelets suspended in 240 to 350 mL of plasma.
- One unit of apheresis platelets usually contains at least 3.0×10^{11} platelets and is suspended in 250 to 400 ml of plasma.
- Pooled and apheresis platelet units are leucoreduced.
- Some patients may have additional requirements such as irradiated platelets and the indications for these are covered in the Modified Blood Components guideline.

Compatibility

- As ABO antigens are present on platelets, it is preferable to transfuse with ABO identical platelets to maximise the platelet count response. However, ABO matching is not an absolute requirement for platelet transfusion, though ABO blood group compatibility of the plasma used to suspend the platelets should be observed except during emergencies and unavailability of such platelets.

ABO Blood Group Selection for Platelet Transfusion (Adults)				
Recipient ABO Blood Group	Component ABO Group			
	1st Choice	2nd Choice	3rd Choice	4th Choice
AB	AB	A* or B*	O*	
A	A	AB	B*	O*
B	B	AB	A*	0*
O	O	A	B	AB
***Note for Platelet Transfusion: Items highlighted in grey are considered "incompatible" and issued only during emergency situations or shortages.**				

- It is recommended that in Singapore, all RhD negative males and females (including those without childbearing potential) receive anti-D immunoglobulin if they are transfused with RhD positive platelets to prevent RhD alloimmunisation.
  - A full dose of anti-D immunoglobulin (1500 IU) will be sufficient for up to 6 adult therapeutic doses of RhD positive platelets (6 units of apheresis or pooled platelet concentrates) given within one month of the anti-D immunoglobulin dose.
  - Anti-D immunoglobulin can be given either IM or subcutaneous (SC). If the patient's platelet levels are low (< 50 x 10^9/L), anti-D immunoglobulin should be administered by the SC route.

Dose and Administration

- Use only one adult dose (one unit) routinely for prophylactic platelet transfusions.
- Transfusion of one therapeutic dose (1 unit of apheresis or pooled platelets) will increase the platelet count of a 70kg adult by 20 – 40 x 10^9/L if there are no other concomitant factors.
- Platelets are usually administered over 30-60 minutes. For patients at risk for fluid overload, use slower rates.

Indications

- Prophylactic platelets transfusion should be given to patients with significant hypoproliferative thrombocytopaenia to prevent spontaneous bleeding or bleeding from procedures or surgeries.
- The platelet count thresholds for prophylactic transfusions in hypoproliferative thrombocytopaenia are stated below.

Platelet count thresholds for prophylactic platelet transfusions in hypoproliferative thrombocytopaenia

To prevent spontaneous bleeding from thrombocytopaenia	Platelet count threshold for transfusion
Hypoproliferative thrombocytopaenia from intensive chemotherapy or haematopoietic stem cell transplant[1–4] Chronic bone marrow failure undergoing treatment[1,5]	Less than 10 x 10^9/L (*Strong recommendation; moderate-quality evidence)*
Above groups of patients with additional risk factors for bleeding such as fever and infection[1,6–9]	Consider increasing to less than 20 x 10^9/L *(Conditional recommendation; low-quality evidence)*
Chronic bone marrow failure which is not likely to recover (e.g., not receiving treatment)	Consider not prophylactically transfusing platelets in patients without bleeding. [1,5,6] (*Conditional recommendation; moderate-quality evidence)* For patients with history of persistent WHO grade ≥ 2 bleeding, consider individualising prophylactic platelet transfusions according to bleeding severity.[1] *(Conditional recommendation; low-quality evidence)*

Pre-procedure to prevent bleeding expected to occur during surgery/invasive procedure	Transfusion indicated (Threshold)
• Central venous catheter (CVC) insertion excluding peripherally inserted central catheter (PICC)[1,10]	20 x 10^9/L

	(Strong recommendation; moderate-quality evidence)
• Lumbar puncture[11]	50 x 10^9/L *(Conditional recommendation; low-quality evidence)*
• Percutaneous liver biopsy[1]	50 x 10^9/L (*Conditional recommendation; moderate-quality evidence)*
• Major surgery[1]	50 x 10^9/L (*Strong recommendation; low-quality evidence)*
• Spinal and epidural anaesthesia, insertion and removal[1,12]	80 x 10^9/L *(Conditional recommendation; low-quality evidence)*
• Neurosurgery or ophthalmic surgery involving the posterior segment of the eye[1]	100 x 10^9/L *(Strong recommendation; low-quality evidence)*
• Bone marrow aspirate or trephine biopsies[1] *(Strong recommendation; moderate-quality evidence)* • PICC insertion, Traction removal of CVCs [1] *(Conditional recommendation; low-quality evidence)* • Cataract surgery[1] *(Conditional recommendation; low-quality evidence)*	Not indicated

- Therapeutic platelets transfusions should be given to bleeding patients with significant thrombocytopaenia.
- The platelet count thresholds for therapeutic platelet transfusions, based on the severity and sites of bleeding are stated below.

Therapeutic use (WHO grade ≥ 2 bleeding)[1]	Transfusion indicated (Threshold)
• Severe bleeding	50 x 10^9/L *(Strong recommendation; low-quality evidence)*
• Multiple trauma • Brain or eye injury • Spontaneous intracerebral haemorrhage	100 x 10^9/L *(Conditional recommendation; low-quality evidence)*
• Bleeding but not severe (WHO grade 2 bleeding)	30 x 10^9/L *(Conditional recommendation; low-quality evidence)*

Platelet transfusions in other clinical conditions are stated below.

Specific Clinical Conditions
Dengue • Platelet transfusion is indicated in patients with bleeding. • Prophylactic platelet transfusion in adult patients with significant thrombocytopaenia (<20 x 10^9/L) from non-severe dengue is not recommended as it is not associated with additional benefits and may carry increased risk of adverse events. [13] *(Strong recommendation; moderate-quality evidence)*
Immune thrombocytopaenia (ITP) • Do not use prophylactic platelet transfusions in patients with ITP as there is usually no significant platelet increase after platelet transfusions.[14] *(Strong recommendation; low-quality evidence)* • Only use platelet transfusions prior to a procedure or surgery when other treatment has failed and/or if the intervention is urgent. The usual target platelet counts may not be achievable.[1] *(Strong recommendation; low-quality evidence)* • Give therapeutic platelet transfusions to treat severe bleeding.[1] *(Strong recommendation; low-quality evidence)* • Consider co-administration of IVIG.[1] *(Conditional recommendation; low-quality evidence)*
Heparin-induced thrombocytopaenia (HIT) • Do not use prophylactic transfusions in view of potential risk of thrombosis.[15–17] *(Conditional recommendation; low-quality evidence)*
Thrombotic thrombocytopaenia purpura (TTP)/Thrombotic microangiopathy • Give therapeutic platelet transfusions only in the event of life-threatening bleeding.[18] *(Strong recommendation; low-quality evidence)*
Post-transfusion purpura (PTP) • Give therapeutic platelet transfusions only in the event of life-threatening bleeding.[1,19] *(Strong recommendation; low-quality evidence)* • Intravenous immunoglobulin is the treatment of choice.[1,19] *(Strong recommendation; low-quality evidence)*
Congenital (inherited) platelet function defect • Recombinant FVIIa should be considered for first line treatment and prophylaxis for bleeding in Glanzmann Thrombasthenia.[20] (*Conditional recommendation; moderate-quality evidence)* • Tranexamic acid and desmopressin may be considered for other congenital platelet function disorders.[20] *(Conditional recommendation; moderate-quality evidence)* • Platelet transfusion can be considered only if pharmaceutical treatment is contraindicated, ineffective or if there is high risk of bleeding.[20] (*Conditional recommendation; low-quality evidence)*
Acquired platelet function defect <u>Uraemia</u> • Platelet transfusion should be avoided in renal failure as the transfused platelets acquire a dysfunction similar to the patient's own platelets.[1] *(Strong recommendation; moderate-quality evidence)* • Ensure potential risk factors for bleeding are corrected prior to procedures or surgeries (e.g., treat anaemia with erythropoietin and iron) and reduce uraemia with dialysis.[1] *(Strong recommendation; moderate-quality evidence)* • If renal biopsy is urgent, consider desmopressin pre-procedure, if time allows.[1] *(Conditional recommendation; moderate-quality evidence)*

Antiplatelet agents

- Platelet transfusions to reverse the antiplatelet effect are usually not indicated as any transfused platelets would acquire the same platelet function defect that the patient has.[1] (*Conditional recommendation; low-quality evidence)*
- In the event of bleeding in patients on antiplatelet agents, consider using general haemostatic measures and tranexamic acid.[1] *(Strong recommendation; moderate-quality evidence)*
- Platelet transfusion can be considered as an additional measure for critical bleeding.[1] *(Conditional recommendation; low-quality evidence)*

Contraindications to platelet transfusion

- In TTP and other thrombotic microangiopathies, platelet transfusions are avoided unless life-threatening bleeding is present.[1,21] *(Strong recommendation; low-quality evidence)*

Platelet refractoriness[1,22,23]

- Platelet refractoriness in patients with hypoproliferative thrombocytopaenia presents as a post transfusion platelet increment that is less than expected.
- It is usually defined in clinical studies as a 10-minute to 1-hour post transfusion corrected count increment (CCI) of less than 5 x 10^9/L on two consecutive occasions, using fresh ABO identical platelets (72 hours or less from collection). As the CCI calculation requires knowledge of the transfused platelet content, which is usually not available, it may be more practical to use an absolute platelet count increment of less than 10 X 10^9/L at between 1 and 24 hours after the platelet transfusion as a simple measure of poor response.
- Platelet refractoriness is more commonly caused by non-immunological factors (e.g., consumptive coagulopathy, sepsis, splenomegaly, chemotherapy, antifungal medication). These causes should be excluded before investigating for alloimmune causes due to class I Human Leucocyte Antigen (HLA) antibodies.
- Patients with hypoproliferative thrombocytopaenia who are refractory to platelet transfusions that cannot be attributed to non-immunological causes alone and have class I HLA antibodies, should receive class I HLA A and B compatible irradiated platelets. ABO identical platelets should also be concomitantly used when available, to maximise platelet count increments.

Adverse effects of platelet transfusion

- The most common adverse reactions following platelet transfusions include allergic, febrile and anaphylactic reactions, transfusion associated circulatory overload (TACO) and transfusion related acute lung injury (TRALI).

References

1. Estcourt, L. J., Birchall, J., Allard, S., *et al.* Guidelines for the use of platelet transfusions. *British Journal of Haematology* **176**, 365–394 (2017).
2. Wandt, H., Shaefer-Eckart, K., Wendelin, K., *et al.* Therapeutic platelet transfusion versus routine prophylactic transfusion in patients with haematological malignancies: an open-label, multicentre, randomised study. *Lancet* **380**, 1309–16 (2012).
3. Crighton, G. L., Estcourt, L., Wood, E., *et al.* A therapeutic-only versus prophylactic platelet transfusion strategy for preventing bleeding in patients with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation. *Cochrane Database of Systemic Reviews* CD010981 (2015)
4. Stanworth, S. J., Estcourt,L., Powter, G., *et al.* A no-prophylaxis platelet-transfusion strategy for hematologic cancers. *New England Journal of Medicine* **368**, 1771–80 (2013).
5. Killick, S. B., Bown, N., Cavenagh, J., *et al.* Guidelines for the diagnosis and management of adult myelodysplastic syndromes. *British Journal of Haematology* **164**, 503–525 (2014).
6. Estcourt, L. J., Birchall, J., Lowe, D. *et al.* Platelet transfusions in haematology patients: are we using them appropriately? *Vox Sanguinis* **103**, 284–293 (2012).
7. Lawrence, J. B., Yomtovian, RA., Hammons, T. *et al.* Lowering the prophylactic platelet transfusion threshold: a prospective analysis. *Leukemia and Lymphoma* **41**, 67–76 (2001).
8. Friedmann, A. M., Sengul, H., Lehmann, H. *et al*. Do basic laboratory tests or clinical observations predict bleeding in thrombocytopaenic oncology patients? A re-evaluation of prophylactic platelet transfusions. *Transfusion Medicine Reviews* **16**, 34–45 (2002).
9. Webert, K., Cook, R. J., Sigouin, C. S. *et* al. The risk of bleeding in thrombocytopaenic patients with acute myeloid leukemia. *Haematologica* **91**, 1530–7 (2006).
10. Zeidler, K., Arn, K., Senn, O. *et al*. Optimal preprocedural platelet transfusion threshold for central venous catheter insertions in patients with thrombocytopaenia. *Transfusion (Paris)* **51**, 2269–76 (2011).
11. Kaufman, R. M., Djulbegovic, B., Gernsheimer, T. *et al.* Platelet Transfusion: A Clinical Practice Guideline From the AABB. *Annals of Internal Medicine* **162**, 205–213 (2015).
12. van Veen, J. J., Nokes, T. J., Makris, M. The risk of spinal haematoma following neuraxial anaesthesia or lumbar puncture in thrombocytopaenic individuals. *British Journal of Haematology* **148**, 15–25 (2010).
13. Lye, D. C., Archuleta, S., Syed-Omar, SF., *et al.* Prophylactic platelet transfusion plus supportive care versus supportive care alone in adults with dengue and thrombocytopaenia: a multicentre, open-label, randomised, superiority trial. *The Lancet* **389**, 1611–1618 (2017).
14. Provan, D., Arnold, D., Bussel, J. *et al.* International consensus report on the investigation and management of primary immune thrombocytopaenia. *Blood* **115**, 168–186 (2010).
15. Hopkins, C. K. & Goldfinger, D. Platelet transfusions in heparin-induced thrombocytopaenia: a report of four cases and review of the literature. *Transfusion (Paris)* **48**, 2128–2132 (2008).
16. Linkins, L.-A., Dans, A., Moores, L. *et al.* Treatment and Prevention of Heparin-Induced Thrombocytopaenia. *Chest* **141**, e495S-e530S (2012).
17. Warkentin, T. E. How I Diagnose and Manage HIT. *Hematology* **2011**, 143–149 (2011).
18. Scully, M., Benjamin, S., Liesner, R. *et al.* Guidelines on the diagnosis and management of thrombotic thrombocytopaenic purpura and other thrombotic microangiopathies. *British Journal of Haematology* **158**, 323–335 (2012).
19. Conti, F. M., Yokohama, APH., Dezan, M. *et al.* Diagnosis and Management of POST-Transfusion Purpura - Case Report. *Blood* **122**, 4834–4834 (2013).
20. Bolton-Maggs, P. H. B, Chalmers, E., Collins, P. *et al.* A review of inherited platelet disorders with guidelines for their management on behalf of the UKHCDO. *British Journal of Haematology* **135**, 603–633 (2006).
21. Peigne, V., Perez, P., Rigon, M.R. *et al.* Causes and risk factors of death in patients with thrombotic microangiopathies. *Intensive Care Med* **38**, 1810–7 (2012).

22. Hod, E. & Schwartz, J. Platelet transfusion refractoriness. *British Journal of Haematology* **142**, 348–360 (2008).
23. Stanworth, S. J., Navarrete, C., Estcourt, L. *et al*. Platelet refractoriness - practical approaches and ongoing dilemmas in patient management. *British Journal of Haematology* **171**, 297–305 (2015).

4 Frozen Plasma Transfusion

Key Points

- **Frozen plasma (FP) transfusions should be limited to specific indications where it may have therapeutic roles (see table below) to minimise unnecessary exposure of patients to the multiple risks associated with FP.**
- **Abnormal standard coagulation tests (prothrombin time [PT]/activated partial thromboplastin time [APTT]) are poor predictors of bleeding risks prior to invasive procedures in patients without a history of bleeding symptoms. *(Strong recommendation; low-quality evidence)***
- **FP should not be prophylactically transfused before invasive procedures to correct abnormal results on coagulation screening in non-bleeding patients without investigating the underlying cause. *(Strong recommendation; low-quality evidence)***
- **The impact of commonly used doses of FP to correct coagulation results are very limited particularly when the PT ratio or International Normalised Ratio (INR) are only mildly deranged. *(Strong recommendation; low-quality evidence)***

General Information

- Frozen Plasma (FP) is prepared from whole blood that has been stored at room temperature of 20-24°C by separating and freezing the plasma at ≤ -18°C within 24 hours of phlebotomy. This is the most common type of plasma preparation available in Singapore.
- Plasma may be stored for as long as one year at -18°C or colder. The volume of a typical unit of FP is 200 to 250 ml.
- Once thawed, FP must be stored at 4 ± 2°C in an approved temperature-controlled blood storage refrigerator before administration to a patient.[1]
- Transfusion of FP should be completed within 24 hours of thawing (if stored at 4 ± 2°C in an approved temperature-controlled blood storage) and within 4 hours of issue (if out of a controlled temperature environment).[1-3]

Compatibility

ABO blood group compatibility

- Plasma of donors with identical ABO blood group to the recipient should be used as the first choice.[1,3]
- Group O plasma should only be given to group O patients as group O plasma contains anti-A and anti-B antibodies.[1]

Recipients	1st Choice	2nd Choice	3rd Choice
O	O	A or B	AB
A	A	AB	-
B	B	AB	-
AB	AB	-	-

RhD blood group compatibility

- Frozen plasma of any RhD group may be transfused. If RhD positive plasma is given to an RhD negative individual, no anti-D prophylaxis is required.[1,3]

Dose and Administration

- The appropriate dose of plasma depends on the clinical indication and is typically 12-15 mL/kg. [4]
- For management of major bleeding, the recommended dose for plasma is 15 to 20 ml/kg.[4,5]
- The recommended infusion time is typically 10-20 mL/kg/hour, though more rapid transfusion may be appropriate in major bleeding.[4]

Indications

	Clinical Indications	Remarks
1.	**Prophylactically before major procedure/ surgery or therapeutically in severe bleeding** • Inherited single coagulation factor deficiency if virally inactivated specific coagulation factors are not available *(Strong recommendation; low-quality evidence)* • Multiple coagulation factor deficiencies *(Strong recommendation; low-quality evidence)* • Disseminated intravascular coagulation (DIC)[6,7] *(Strong recommendation; low-quality evidence)*	Plasma is indicated for severe bleeding or major surgery in Factor V deficient patients as there are no virally inactivated Factor V concentrates or recombinant Factor V. [1,3,8] Plasma is indicated for severe bleeding or high-risk surgery in combined Factor V and VIII deficient patients.[1,8] Plasma is indicated in bleeding patients with DIC and prolonged PT and aPTT.[6]
2.	**Therapeutic Plasma Exchange**[9–11] Indications include: • Thrombotic Thrombocytopaenic Purpura (TTP) *(Strong recommendation; moderate-quality evidence)* • Acute liver failure *(Strong recommendation; high-quality evidence)* • Diffuse alveolar haemorrhage or other bleeding associated with vasculitis (*Strong recommendation; low-quality evidence)* • Plasma exchange in conjunction with immunosuppressive regimens for removal of HLA and ABO antibodies in the setting of haemopoietic stem cell transplantation and solid organ transplantation, typically kidney, liver and heart[10,11] *(Strong recommendation; moderate-quality evidence)*	As replacement fluid in therapeutic plasma exchange.[9–11]
3.	Reversal agent for warfarin effects in patients with severe bleeding only if 4-Factor Prothrombin	Many hospitals in Singapore have 4-Factor PCC.

	complex concentrate (PCC) is unavailable or contraindicated[1,12] (*Conditional recommendation; low-quality evidence)*	
4.	Management of massive bleeding *(Strong recommendation; high-quality evidence)*	Refer to Massive Transfusion Protocol

Situations when Frozen Plasma (FP) transfusion is generally NOT recommended

		Remarks
1.	Before an invasive procedure, prophylactic transfusion of frozen plasma for blind correction of abnormal standard coagulation test results without first considering the likely causes for the abnormal results, is not recommended. [3,13]	Abnormal standard coagulation tests (prothrombin time [PT]/activated partial thromboplastin time [APTT]) are poor predictors of bleeding risks prior to invasive procedures in patients without a history of bleeding symptoms.[1,3,14] Not all bleeding disorders which are associated with abnormal PT/APTT can be adequately treated by FP transfusion.
2.	Prophylactic transfusion of plasma in liver disease is generally not recommended in the following situations:[1,3,16] • for correction of abnormal coagulation tests in non-bleeding patients prior to interventions • in low bleeding risk procedures, such as paracentesis, thoracocentesis, endoscopic variceal ligation, transjugular liver biopsy and dental extractions.	PT and APTT do not reflect the true haemostatic status of patients with advanced liver disease as there is rebalanced haemostasis (including increased levels of pro-coagulant factors VIII and VWF and decreased levels of anti-coagulant proteins e.g., protein C, protein S and antithrombin III).[1,3,16, 17] Procedural risk depends on procedural factors (low vs high bleeding risk) and patient specific factors. Significant predictors for procedural bleeding include the severity of liver disease (Child Pugh C status or decompensated disease), renal impairment and infection.[18]

Inappropriate usage of Frozen Plasma (FP)

	FP should NOT be given for the indications below	Remarks
1.	Hypovolemia[3]	Frozen plasma should not be used as simple intravascular volume expander.[1]
2.	Reversal of warfarin (if 4-Factor PCC is available), heparin, low molecular weight heparin (LMWH), and the DOACs (Direct Oral Anticoagulant)[1,12]	Frozen plasma is not effective for the reversal of heparin, LMWH and DOACs. 4-Factor PCC is more effective than frozen plasma in the reversal of warfarin.
3.	Abnormal coagulation tests in the absence of bleeding and invasive procedures[1,3,13,14]	The impact of commonly used doses of FP to correct coagulation results is very limited particularly when the PT ratio or International Normalised Ratio (INR) are between 1.5 –1.9.[1,15]
4.	Reversal of warfarin effect in the absence of major bleeding and invasive procedures[1,12]	In the absence of major bleeding or invasive procedures, correction of INR with FP or 4-Factor PCC is not recommended. Withholding warfarin and administering Vitamin K may be helpful depending on the extent of INR elevation and severity of the patient's clinical condition.[12]
5.	Treatment of immunodeficiency states[3]	Frozen Plasma is not indicated for treatment of immunodeficiency states. Purified intravenous immunoglobulin preparations are available.[3]
6.	Acquired Vitamin K deficiency in seriously ill patients who have inadequate vitamin K intake resulting in prolongation of PT and aPTT[1,3]	This should be corrected with oral or intravenous vitamin K administration.[3]

Adverse effects of Plasma infusion

- The most common adverse reactions following plasma infusion include allergic, febrile and anaphylactic reactions, transfusion associated circulatory overload (TACO) and transfusion related acute lung injury (TRALI).

References

1. Green, L., Bolton-Maggs, P., Beattie, C. *et al.* British Society of Haematology Guidelines on the spectrum of fresh frozen plasma and cryoprecipitate products: their handling and use in various patient groups in the absence of major bleeding. *British Journal of Haematology* **181**, 54–67 (2018).
2. Ang, A.L, Wong, W., Tan, J. *et al.* Ex vivo haemostatic capacity of plasma upon thawing and beyond: a comparison between fresh frozen plasma (FFP) and frozen plasma prepared from whole blood stored at room temperature up to 24 hours postcollection (RTFP24). *Vox Sanguinis* **114**, 198–206 (2019).
3. Wong, M.P., Droubatchevskaia, N., Chipperfield, K.M. *et al.* Guidelines for frozen plasma transfusion. *British Columbia Medical Journal* **49**, 311–319 (2007).
4. Robinson, S., Harris, A., Atkinson, S. *et al.* The administration of blood components: a British Society for Haematology Guideline. *Transfusion Medicine* **28**, 3–21 (2018).
5. Hunt, B. J., Allard, S., Keeling, D. *et al.* A practical guideline for the haematological management of major haemorrhage. *British Journal of Haematology* **170**, 788–803 (2015).

6. Levi, M., Toh, C. H., Thachil, J. *et al.* Guidelines for the diagnosis and management of disseminated intravascular coagulation. *British Journal of Haematology* **145**, 24–33 (2009).
7. Wada, H., Thachil, J., Di Nisio, M. *et al.* Guidance for diagnosis and treatment of disseminated intravascular coagulation from harmonization of the recommendations from three guidelines. *Journal of Thrombosis and Haemostasis* **11**, 761–767 (2013).
8. Mumford, A. D., Ackroyd, S., Alikhan, R. *et al.* Guideline for the diagnosis and management of the rare coagulation disorders. *British Journal of Haematology* **167**, 304–326 (2014).
9. Scully, M., Hunt, B.J., Benjamin, S. *et al.* Guidelines on the diagnosis and management of thrombotic thrombocytopaenic purpura and other thrombotic microangiopathies. *British Journal of Haematology* **158**, 323–35 (2012).
10. Simmons, S.C., Adamski, J., Berg, M. *et al.* The apheresis management of patients undergoing transplantation: a concise review. *Transfusion (Paris)* **59**, 1863–1869 (2019).
11. Schwartz, J., Padmanabhan, A., Aqui, N. *et al.* Guidelines on the Use of Therapeutic Apheresis in Clinical Practice-Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Seventh Special Issue. *Journal of Clinical Apheresis* **31**, 149–338 (2016).
12. Makris, M., Van Veen, J. J., Tait, C. R. *et al.* Guideline on the management of bleeding in patients on antithrombotic agents. *British Journal of Haematology* **160**, 35–46 (2013).
13. Müller, M. C., Arbous, M.S., Spoelstra-de Man, A.M. *et al.* Transfusion of fresh frozen plasma in non-bleeding ICU patients -TOPIC TRIAL: study protocol for a randomized controlled trial. *Trials* **12**, 266 (2011).
14. Chee, Y. L., Crawford, J. C., Watson, H. G. *et al.* Guidelines on the assessment of bleeding risk prior to surgery or invasive procedures. British Committee for Standards in Haematology. *British Journal of Haematology* **140**, 496–504 (2008).
15. Stanworth, S. J., Walsh, T.S., Prescott, R.J. *et al.* A national study of plasma use in critical care: clinical indications, dose and effect on prothrombin time. *Critical Care* **15**, R108 (2011).
16. DeAngelis, G.A., Khot, R., Haskal, Z.J. *et al.* Bleeding Risk and Management in Interventional Procedures in Chronic Liver Disease. *Journal of Vascular and Interventional Radiology* **27**, 1665–1674 (2016).
17. Lisman T, Hernandez-Gea V, Magnusson M *et al*. The concept of rebalanced hemostasis in patients with liver disease: Communication from the ISTH SSC working group on hemostatic management of patients with liver disease. *Journal of thrombosis and haemostasis* **19**, 1116-1122 (2021).
18. Roberts LN, Lisman T, Stanworth S *et al*. Periprocedural management of abnormal coagulation parameters and thrombocytopaenia in patients with cirrhosis: Guidance from the SSC of the ISTH. *Journal of thrombosis and haemostasis* **20**, 39-47 (2021).

5 Cryoprecipitate Transfusion

Key Points

- **Cryoprecipitate can be used as a source of concentrated fibrinogen for the treatment of patients with acquired hypofibrinogenaemia (fibrinogen level < 1.0 g/L) who are bleeding or going for interventions with high bleeding risks. *(Strong recommendation; low-quality evidence)***
- **Cryoprecipitate should be considered early in the management of patients with obstetric haemorrhage if their fibrinogen levels are <2.0 g/L. *(Strong recommendation; low-quality evidence)***

General information

- Cryoprecipitate is the cryoglobulin fraction of plasma obtained by thawing of frozen plasma at 1-6°C. When frozen plasma is thawed between 1-6°C, the cold-insoluble portion of plasma that precipitates is called cryoprecipitate. The cold-insoluble precipitates are re-frozen after separation and re-suspended in a small volume of plasma.
- Cryoprecipitate is a concentrated source of Factor VIII, vWF (von Willebrand Factor), fibrinogen and factor XIII. It is primarily used as source of concentrated fibrinogen for the treatment of patients with acquired fibrinogen deficiency.
- Thawed cryoprecipitate must be stored and transported at 20-24°C. The shelf life of single unit cryoprecipitate or the pre-pooled cryoprecipitate prepared in a closed system is 6 hours after thawing. If pooled after thawing, it must be transfused within 4 hours of pooling due to the potential risk of bacterial contamination arising from storing cryoprecipitate at ambient temperature.[1–3]
- 1 unit cryoprecipitate = 10-15 ml (approximately 300 (150-500) mg of fibrinogen)
- 1 unit pre-pooled cryoprecipitate = 5 units cryoprecipitate

Compatibility

ABO blood group compatibility

- ABO compatible cryoprecipitate will be provided as far as possible. However, ABO compatibility is strongly recommended in neonates, paediatrics, and hematopoietic cell transplant recipients.[2]

RhD blood group compatibility

- Cryoprecipitate of any RhD group may be transfused.[1,2]
- If RhD positive cryoprecipitate is given to an RhD negative individual, no anti-D immunoglobulin prophylaxis is required.[1]

Dose and Administration

- In the management of hypofibrinogenaemia, 10 units of cryoprecipitate (or 2 units of pre-pooled cryoprecipitate) will increase fibrinogen in an average-sized adult by approximately 1g/L.[1,4]
- Cryoprecipitate should be infused at a rate of 10-20ml/kg/hr. At this rate, a pool of 10 bags can be infused in approximately 15-30 minutes.[5]
- Further therapy should be guided by fibrinogen levels.

Indications

Use of cryoprecipitate is considered appropriate for hypofibrinogenaemia (fibrinogen level < 1.0 g/L) in the following conditions:

	Clinical indications	Remarks
1	In patients with low fibrinogen (<1.0g/L) who are bleeding or who are planned for interventions with high bleeding risk or involving critical sites [2] *(Strong recommendation; low-quality evidence)*	There is no role for cryoprecipitate in patients who are not bleeding or who do not require interventions.
2.	Management of obstetric haemorrhage [6,7] *(Strong recommendation; low-quality evidence)*	Should be considered early when fibrinogen level is <2.0 g/L. [6,7]
3.	Disseminated intravascular coagulation (DIC) with bleeding [2,8,9] *(Strong recommendation; low-quality evidence)*	Appropriate in the acute phase of acute promyelocytic leukaemia with DIC and low fibrinogen level (<1.0g/L), even in the absence of bleeding.[10]
4.	Bleeding or expected bleeding in individuals with deficiencies of factor XIII [3,11] *(Strong recommendation; low-quality evidence)*	Indicated only if a recombinant FXIII product or factor concentrate is unavailable. [3,11]
5.	Inherited disorders of fibrinogen (hypo- or afibrinogenaemia) going for major surgery or severe bleeding[11] *(Strong recommendation; low-quality evidence)*	Indicated only if fibrinogen concentrate is unavailable.[11]
6.	Bleeding associated with thrombolytic therapy causing hypofibrinogenaemia [3] *(Strong recommendation; low-quality evidence)*	E.g., Intracranial bleeding
7.	In advanced liver disease patients to stop bleeding or as prophylaxis before surgery[2] *(Conditional recommendation; low-quality evidence)*	For patients with liver disease and bleeding or need for a surgical procedure who have very low fibrinogen levels (<1.0g/L), administration of a source of fibrinogen may be appropriate.
8.	Massive blood transfusion In massive blood loss or major haemorrhage, fibrinogen supplementation should be given if fibrinogen levels fall below 1.5 g/L [4,12,13] *(Strong recommendation; high-quality evidence)* Consideration of higher fibrinogen levels (transfusion threshold of 1.5 to 2.0 g/L) should be given in major trauma *(Conditional recommendation; low quality evidence)[12]*	Refer to Massive Transfusion Protocol

Inappropriate usage of cryoprecipitate

- For clotting factor deficiency or von Willebrand disease unless processed, virally inactivated products are not readily available.
- For preparation of fibrin glue with commercial sources of thrombin. Factor V inhibitors have been reported following exposure to such preparations. Commercially produced fibrin sealants containing human thrombin are preferred.

Alternatives to Cryoprecipitate

- Fibrinogen concentrates are licensed for treatment of bleeding and peri-operative prophylaxis in patients with congenital hypo- or afibrinogenemia with bleeding tendency and in acquired hypofibrinogenaemia.

Adverse effects of cryoprecipitate infusion

- The most common adverse reactions following plasma infusion related to the administration of cryoprecipitate include transfusion-related acute lung injury (TRALI), allergic reactions, and febrile non-haemolytic reactions.

References

1. Green, L., Bolton-Maggs, P., Beattie, C. *et al.* British Society of Haematology Guidelines on the spectrum of fresh frozen plasma and cryoprecipitate products: their handling and use in various patient groups in the absence of major bleeding. *British Journal of Haematology* **181**, 54–67 (2018).
2. Silvergleid, A.J., Kleinman, S., Tirnauer, J.S. Clinical use of Cryoprecipitate. *https://www.uptodate.com/contents/clinical-use-of-cryoprecipitate (last accessed May 2022) (2019)*
3. Droubatchevskaia, N., Wong, M.P., Chipperfield, K.M. *et al.* Guidelines for cryoprecipitate transfusion. *British Columbia Medical Journal* **49**, 441–445 (2007).
4. Hunt, B. J., Allard, S., Keeling, D. *et al.* A practical guideline for the haematological management of major haemorrhage. *British Journal of Haematology* **170**, 788–803 (2015).
5. Robinson, S., Harris, A., Atkinson, S. *et al*. The administration of blood components: a British Society for Haematology Guideline. *Transfusion Medicine* **28**, 3–21 (2018).
6. Mavrides, E., Allard S, Chandraharan E. *et al.* Prevention and Management of Postpartum Haemorrhage. *BJOG: An International Journal of Obstetrics & Gynaecology* **124**, e106–e149 (2017).
7. Australia National Blood Authority. Patient Blood Management Guidelines: Module 5 Obstetrics and Maternity. *https://www.blood.gov.au/pubs/pbm/module5/* (*last accessed May 2022). (2015)*
8. Levi, M., Toh, C. H., Thachil, J. *et al.* Guidelines for the diagnosis and management of disseminated intravascular coagulation. *British Journal of Haematology* **145**, 24–33 (2009).
9. Wada, H., Thachil, J., Nisio, M. Di. *et al.* Guidance for diagnosis and treatment of disseminated intravascular coagulation from harmonization of the recommendations from three guidelines. *Journal of Thrombosis and Haemostasis* **11**, 761–767 (2013).
10. British Committee for Standards in Haematology. Milligan, D.W., Grimwade, D., Cullis, J.O. *et al.* Guidelines on the management of acute myeloid leukaemia in adults. *British Journal of Haematology* **135**, 450–74 (2006).
11. Mumford, A. D., Ackroyd, S., Alikhan, R. *et al.* Guideline for the diagnosis and management of the rare coagulation disorders. *British Journal of Haematology* **167**, 304–326 (2014).
12. Spahn, D. R., Bouillon, B., Cerny, V. *et al.* Management of bleeding and coagulopathy following major trauma: an updated European guideline. *Critical Care* **17**, R76 (2013).
13. Nascimento, B., Goodnough, L.T., Levy, J. H. Cryoprecipitate therapy. *British Journal of Anaesthesia* **113**, 922–934 (2014).

6 Modified Blood Components

Key Points

- **In an emergency, the provision of red cells and platelets must not be delayed by sourcing for irradiated, washed or leucoreduced components. *(Strong recommendation; low-quality evidence)***

Washed Blood Components

General Information

- Washed components (red cells) are typically prepared using 0.9% Sodium Chloride to remove unwanted plasma proteins, including antibodies and glycerol from previously frozen red cell units.
- Washing is not a substitute for leucoreduction and only cellular components should be washed.
- Washed blood components have shorter shelf-lives than the standard blood components.[1]

Indications

- Patients with documented history of severe allergic or anaphylactic transfusion reactions that are not prevented by medication. *(Strong recommendation; low quality evidence)*
- Patients with IgA deficiency and documented anti-IgA antibodies.[1] *(Strong recommendation; low quality evidence)*

Note: *Washed red cells are only prepared upon request and may not be available for urgent transfusion. The requesting physician needs to inform BSG in advance if washed red cells are required.*

Leucoreduced Blood Components

General Information

- Leucoreduction is a process by which white blood cells are removed from the blood component. This may be accomplished during apheresis collection or by filtration of the blood component, either in the blood component processing laboratory (pre-storage) or at the patient's bedside (post-storage).
  - All apheresis platelets or pooled platelets in Singapore are leucoreduced.
  - Red cells in Singapore are currently not universally leucoreduced. The need for leucoreduced red cells must be specified when indicated for a patient.
- Pre-storage leucoreduction is the preferred method for leucocyte reduction because it prevents the accumulation of cytokines responsible for febrile non-haemolytic transfusion reactions during component storage. Quality control of bedside filtration is problematic and the process has been associated with hypotensive transfusion reactions.
- It is generally accepted that pre-storage leucoreduced components are as efficacious in Cytomegalovirus (CMV) risk reduction as components collected from donors lacking antibodies to CMV (seronegative donors).[2,3]
  - CMV seronegative blood components are unavailable in Singapore and leucoreduced blood components are recommended for patients who are at risk of transfusion transmitted CMV infection.
  - Pre-storage leucoreduced red cells are recommended over bedside leucocyte filtration for patients who are at risk of transfusion transmitted CMV infection.

- Leucoreduction helps to prevent HLA alloimmunisation from platelet transfusion in selected groups of patients.
- Washing is not a substitute for leucoreduction and leucoreduction is not a substitute for irradiation.[1]

Indications

- Patients with a history of 2 or more febrile non-haemolytic transfusion reactions. *(Strong recommendation; moderate-quality evidence)*[2,3]
- To reduce the risk of transfusion transmitted CMV infection.[2,3] *(Strong recommendation; moderate-quality evidence)* in the following situations:
  - Patients undergoing Hematopoietic Stem Cell Transplant (also needs to be irradiated)
  - Premature infants and/or infants weighing less than 1500 g at birth
  - Intrauterine transfusions (also needs to be irradiated)
  - Neonates - first 28 days of life
  - Pregnant patients
  - Other immunocompromised patients not meeting criteria above but who may be at risk of CMV infections e.g., patients on chemotherapy, transplant patients on immunosuppressants
- To reduce the risk of HLA alloimmunization in the following situations:
  - To reduce the risk of platelet refractoriness due to HLA class 1 antibodies in patients on or anticipated to require multiple transfusions e.g., patients with haematological malignancies. [2–4] *(Strong recommendation; moderate-quality evidence)*
  - To reduce the risk of HLA alloimmunization in solid organ transplant candidates.[5] *(Conditional recommendation; low-quality evidence)*

Irradiated Blood Components

General Information

- Irradiation of cellular blood components (red cells, platelets and granulocytes) is intended to prevent the proliferation of viable T lymphocytes and prevent transfusion associated graft versus host disease (TA-GVHD).
- All granulocytes should be irradiated. Irradiated red cells and platelets are recommended for specific indications (see below). It is not necessary to irradiate frozen plasma and cryoprecipitate.[6]
- In emergency situations where irradiated components are unavailable, blood banks should consider preferentially issuing older red cells where possible (>14 days old).[6]
- Where the patient is at risk of hyperkalaemia (e.g., intrauterine transfusion or neonatal exchange blood transfusion) or other large-volume transfusion of neonates and infants, it is recommended that red cells are transfused within 24 hours of irradiation.[6]
- Platelets can be irradiated at any stage during storage and can thereafter be stored for up to their normal shelf life after collection.[6]

Indications for irradiation of red cells and platelets

- Allogeneic Haematopoietic stem cell transplant recipients (adult and paediatric), from the time of conditioning chemo/radiotherapy *(Strong recommendation; moderate quality evidence)* until all the following criteria are met.[6]
  - More than 6 months have elapsed since the transplant date
  - The lymphocyte count is more than 1.0×10^9/L
  - The patient is free of active chronic GvHD
  - The patient is off all immunosuppression

- Allogeneic cellular blood components transfused to bone marrow or peripheral blood stem cell donors of all ages require irradiated cellular blood components within 7 days prior to and during the harvest.[5] *(Conditional recommendation; low-quality evidence)*
- Patients undergoing bone marrow or peripheral blood stem cell collections for future autologous reinfusion should receive irradiated cellular blood components for 7 days prior to and during the bone marrow/stem cell harvest.[6] *(Strong recommendation; low-quality evidence)*
- Patients undergoing Autologous Stem Cell Transplant should receive irradiated cellular blood components from initiation of conditioning chemo/radiotherapy until at least 3 months post-transplant (6 months if total body irradiation was used in conditioning) unless the type of conditioning, underlying disease or previous treatment requires an indefinite duration. *(Strong recommendation; low-quality evidence)*
- Patients undergoing peripheral blood lymphocyte collections for future CAR-T cell re-infusion should receive irradiated cellular blood components for 7 days prior to and during the harvest, to prevent the collection of viable allogeneic T lymphocytes. Irradiated blood components should continue to be used until at least 3 months following CAR-T cell infusion unless the type of conditioning, underlying disease or previous treatment requires an indefinite duration. *(Strong recommendation; low-quality evidence)*
- Intrauterine transfusions.[6] *(Strong recommendation; low-quality evidence)*
- Neonatal exchange transfusion after intrauterine transfusions (irradiated cellular blood components should be administered until 6 months after the expected delivery date).[6] *(Strong recommendation; low-quality evidence)*
    - Neonatal exchange transfusion with no prior intra-uterine transfusion and no suspicion of severe congenital immunodeficiency – recommend irradiated blood components if it does not cause clinically significant delay.
- Patients with suspected or confirmed congenital T-cell immune deficiency disorders.[5] *(Strong recommendation, moderate-quality evidence)*
- Recipients (even if immunocompetent) of donated cellular blood components known to be from a first- or second-degree blood relative.[6,7] *(Strong recommendation; moderate-quality evidence)*
- Recipients (even if immunocompetent) of HLA selected cellular blood components.[6,7] *(Strong recommendation; moderate-quality evidence)*
- Patients with Hodgkin lymphoma at any stage of disease should receive irradiated cellular blood components indefinitely.[6] *(Conditional recommendation; low quality evidence)*
- Patients currently or previously treated with the following medications *(Conditional recommendation; low-quality evidence)*:
    - Purine analogue drugs (such as Fludarabine, Cladribine, Bendamustine and Pentostatin) should receive irradiated cellular blood components indefinitely
    - Patients with Chronic Lymphocytic Leukemia or other hematologic conditions treated with alemtuzumab
    - Anti-thymocyte Globulin (ATG) for rare types of immune dysfunction

Plasma Reduced Platelets

General Information

- Involves volume reduction of the platelet unit using centrifugation. The process removes excess plasma thereby reducing unwanted plasma proteins, including antibodies.[1]
- There will be some loss of platelet function through platelet activation as a result of volume reduction.[1]
- A unit of plasma reduced platelets contains 50 ml of plasma on average and hence, it can still be associated with risks of transfusion associated anaphylactic reaction.
- Plasma reduced platelets must be transfused within 6 hours of preparation.

Indications

- In the absence of washed platelets, plasma reduced platelets may be considered for patients with a history of anaphylactic or recurrent severe allergic reaction to transfusion of plasma or platelets if platelet transfusion is indicated *(Conditional recommendation; low quality evidence)*.[8]
  - Plasma reduced platelet transfusion should only be given to these patients when potential benefits of transfusion outweigh potential residual risk of anaphylaxis.
  - All patients must be observed closely both during and after transfusion for any potential transfusion reactions.

Note: *Plasma reduced platelets are only prepared upon request and may not be available for urgent transfusion. The requesting physician needs to inform BSG in advance if plasma reduced platelets are required.*

References

1. Circular of Information for the Use of Human Blood and Blood Components 2021. https://www.aabb.org/docs/default-source/default-document-library/resources/circular-of-information-watermark.pdf?sfvrsn=7f5d28ab_5. *(Last Accessed May 2022)*
2. Cohn, C., Delaney, M., Johnson *et al*. *Technical Manual*. AABB (2020).
3. Bianchi, M., Vaglio, S., Pupella, S. *et al.* Leucoreduction of blood components: an effective way to increase blood safety? *Blood Transfusion* **14**, 214–27 (2016).
4. Trial to Reduce Alloimmunization to Platelets Study Group. Leucocyte reduction and ultraviolet B irradiation of platelets to prevent alloimmunization and refractoriness to platelet transfusions. *New England Journal of Medicine* **337**, 1861–9 (1997).
5. Ratko, T. A., Cummings, JP., Oberman, HA. *et al.* Evidence-based recommendations for the use of WBC-reduced cellular blood components. *Transfusion* **41**, 1310–9 (2001).
6. Foukaneli, T., Kerr, P. Bolton-Maggs, P. *et al.* Guidelines on the use of irradiated blood components. *British Journal of Haematology* **191**, 704–724 (2020).
7. Kopolovic, I., Ostro, J., Tsubota, H., *et al.* A systematic review of transfusion-associated graft-versus-host disease. *Blood* **126**, 406–14 (2015).
8. Delaney, M., Wendel, S., Bercovitz, R. *et al.* Transfusion reactions: prevention, diagnosis, and treatment. *Lancet* **388**, 2825–2836 (2016).

7 Massive Transfusion

i. Management of Massive Transfusion

Key Points

- **In the absence of viscoelastic haemostatic assay guidance, massive transfusion should be managed with fixed ratio transfusion of blood components. *(Strong recommendation; moderate-quality evidence)***
- **Early use of tranexamic acid should be considered, particularly in the setting of trauma. *(Strong recommendation; high-quality evidence)***
- **Doctors should not wait for conventional laboratory results prior to transfusion of blood components. (*Strong recommendation; low-quality evidence*)**
- **Laboratory results can be used to guide further replacement once bleeding has stabilised. *(Conditional recommendation; low-quality evidence)***

Definition of Massive Transfusion

- There are currently a few definitions of massive transfusion, although for most of these, the diagnosis of massive transfusion would be made retrospectively. Acceptable definitions include:[1,2]
  1. Loss of one blood volume over 24 hours
  2. Loss of 50% blood volume over 3 hours
  3. Bleeding rate of more than 150ml/min
  4. Transfusion of $\geq$ 10 units of red cells over 24 hours
- In an acute setting, the above may be difficult to ascertain.
- Clinically, massive transfusion can be defined as a bleed that causes a drop of systolic blood pressure to less than 90mmHg and an increase of heart rate to more than 110 beats/min.[1]
- Clinicians can consider the use of a validated scoring system to help identify patients at risk of massive transfusion and aid decision making for Massive Transfusion Protocol (MTP) Activation (e.g., ABC Score).

Assessment of Blood Consumption Score (ABC)[3]

The ABC Score consists of 4 dichotomous, non-weighted components that are available at the bedside of the acutely injured patient early in the assessment phase. The presence of any one component contributes one point to the total score, for a possible range of scores from 0 to 4. The parameters include:

- Penetrating mechanism (0 = no, 1 = yes)
- ED SBP of 90 mmHg or less (0 = no, 1 = yes)
- ED HR of 120 bpm or greater (0 = no, 1 = yes)
- Positive FAST (0 = no, 1 = yes)

An ABC Score of 2 or more will trigger activation of the MTP.

Essential Components of Massive Transfusion

Blood Component	Indication	Remarks
Red Cells	Ensuring adequate oxygen carrying capacity May improve haemostasis through margination of platelets and plasma	Administration rate should be guided by rate of bleeding. Aim to transfuse through warming device to avoid hypothermia. Haemoglobin and haematocrit levels are not good indicators of blood loss.
Frozen Plasma	For clotting factor replacement in coagulopathy associated with trauma/ massive bleed/ dilution	Frozen plasma should be ordered in anticipation to allow for time to thaw.
Cryoprecipitate/ fibrinogen concentrate	For replacement of fibrinogen	Cryoprecipitate should be ordered in anticipation to allow for time to thaw. Fibrinogen is the first coagulation factor to fall to critical levels in trauma induced coagulopathy.[1]
Platelets	To replace thrombocytopaenia from platelet consumption and dilution for optimal haemostasis	Platelet transfusion should be anticipated if ongoing bleeding and once platelet count < 100 x 10^9/L.[1]
Tranexamic Acid	Antifibrinolytic agent	Adult trauma patients should be given 1g tranexamic acid within 3 hours of injury followed by 1g infusion over 8 hours.[1,2] Tranexamic acid 1g bolus should also be considered in non-trauma patients with massive bleeding if no contraindications.[1]

Non-transfusion Measures in MTP

- Addressing the specific cause of massive bleeding with surgical, radiological or other methods is crucial to reduce the amount of blood loss.
- Consideration should also be made for use of adjuncts where feasible such as cell salvage or pharmacological agents such as uterotonics in the case of obstetric bleeds.

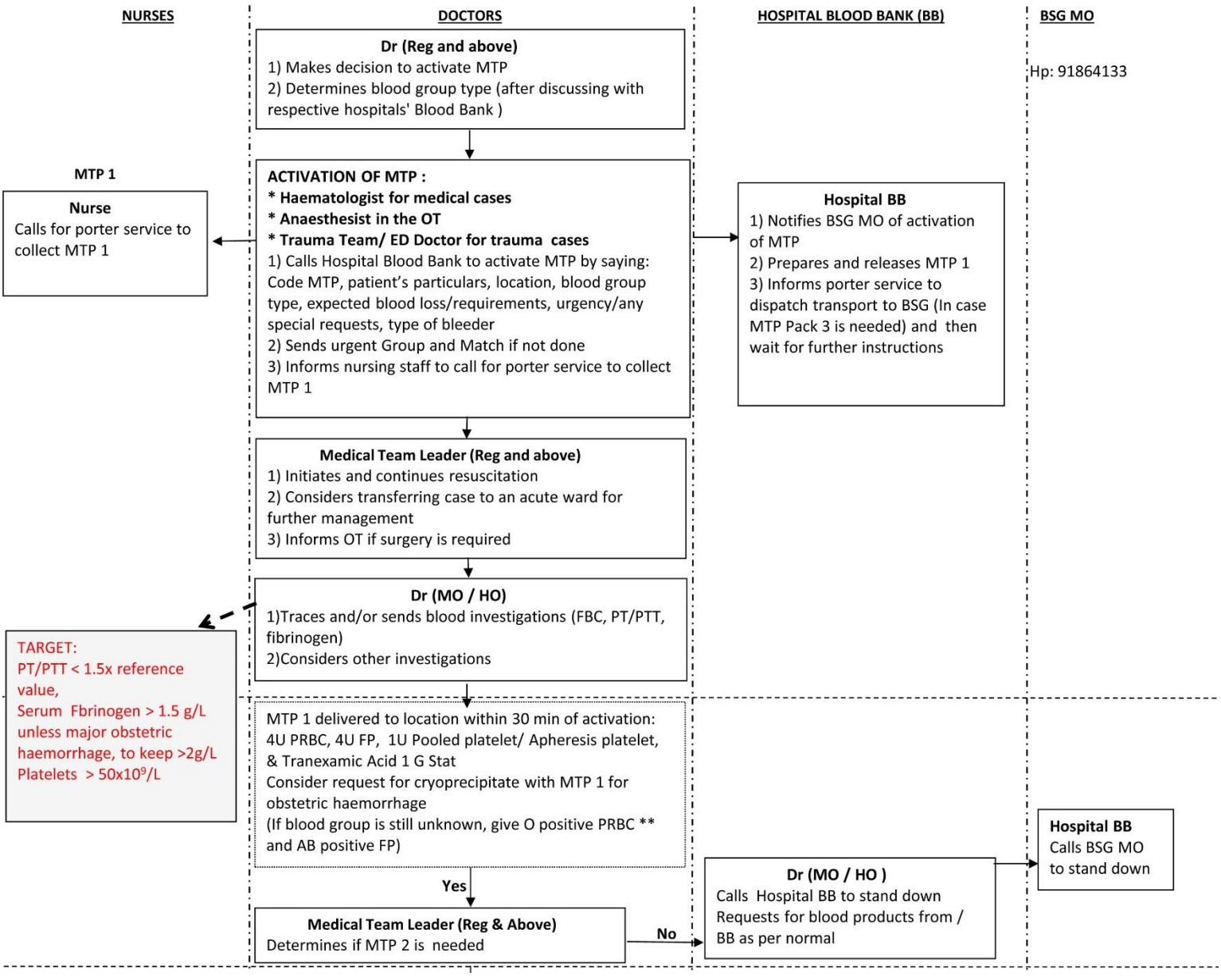
Fixed Ratio-Guided MTP

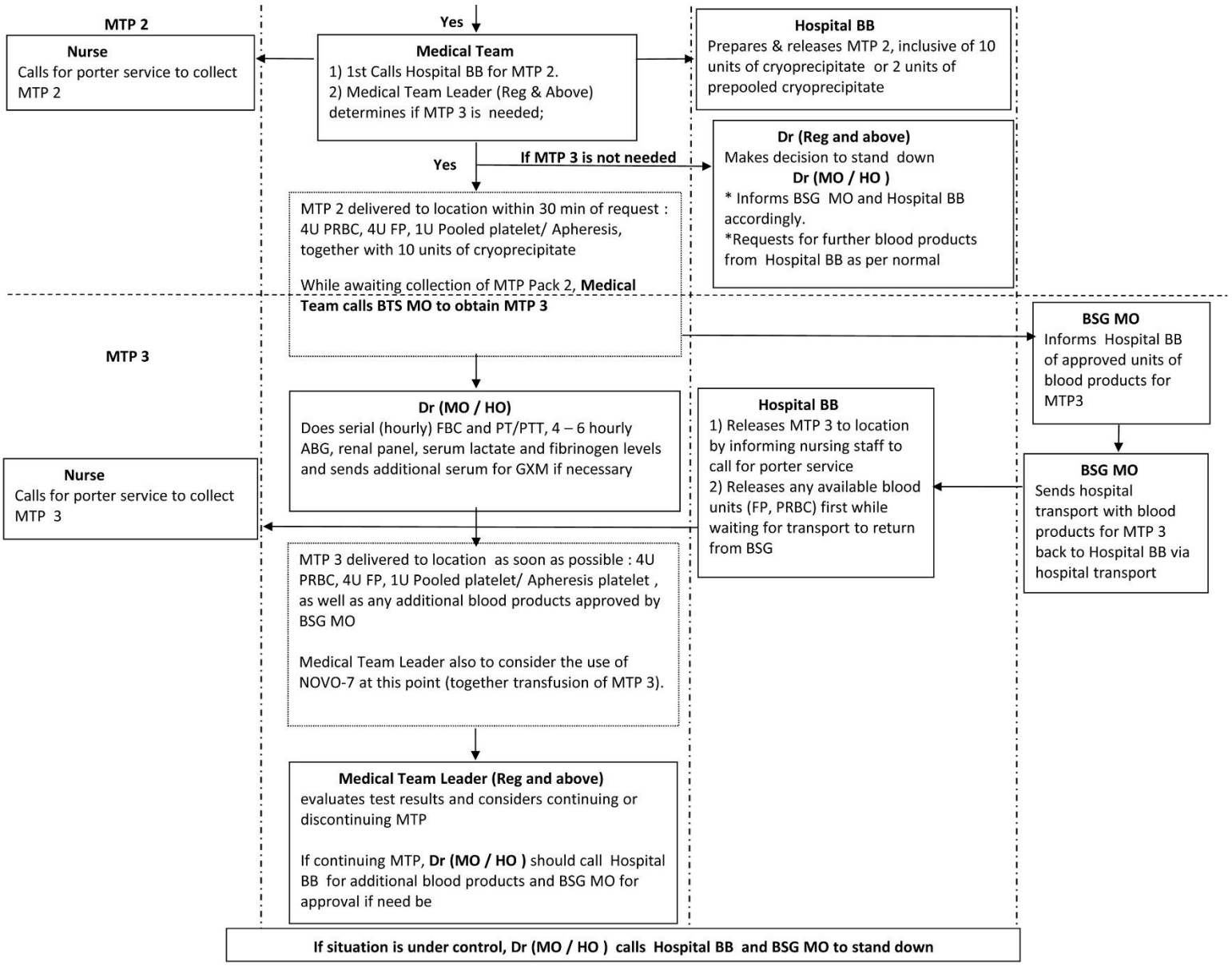
- Fixed ratio guided MTP involves giving blood components in fixed amounts and ratios to address expected deficiencies in all the main blood components (i.e., red cells, platelets, plasma and fibrinogen), in the setting of a massive bleed.
- Where available, the use of viscoelastic haemostatic assay guided transfusion in the setting of surgical or traumatic bleed may avoid the need for ratio-based MTP.
- The flowchart below shows the common National MTP used in Singapore.

COMMON NATIONAL MASSIVE TRANSFUSION PROTOCOL[4]

NB: Patients who are Rh D negative and who have positive red cell alloantibodies are excluded from this MTP. Attending doctor is to inform BSG MO and request for blood products in the usual manner.

If situation is under control, doctor (MO /HO) calls Hospital BB and BSG MO to stand down
PRBC **: packed red blood cells; FP: frozen plasma; BB: Blood Bank





Standard Laboratory Tests in Fixed-Ratio MTP

- Doctors should not wait for lab results when transfusing patients with MTP activation. Fixed ratio blood components transfusion should proceed as long as bleeding is ongoing. Lab results (when available) can be used to guide further correction beyond MTP replacement of haemostatic factors:

Lab test	Result	Transfusion Intervention
Fibrinogen	<1.5g/L For major obstetric haemorrhage, fibrinogen should be kept >2g/L	10 units of cryoprecipitate (or 2 pre-pooled units of cryoprecipitate)
PT/aPTT	>1.5 times upper limit of normal	15-20ml/kg FP
Platelet	<50 x 10^9/L	1 unit of platelets

		If ongoing bleeding, platelet unit should be ordered once platelet count < 100 x 10^9/L

Use of Group O RhD Negative Red Cells in MTP

- The initial use of Group O RhD negative red cells should be considered in the following groups of patients while awaiting ABO/RhD status confirmation, if RhD negative red cells are readily available:
  - Emergency red cell transfusions of females with current or future childbearing potential (less than 50 years of age) AND of Indian, Caucasian, Middle Eastern or African origin with unknown ABO and RhD blood group. (These ethnic groups have a higher prevalence of Rh D negativity)
  - ABO and RhD typing must be performed for the above patients urgently and they should be switched to ABO and RhD-specific red cells when ABO and RhD groups are known.
- All male patients, female patients with no current or future childbearing potential, and females of other ethnic groups regardless of childbearing potential should receive O positive red cell for emergency transfusions if their ABO and RhD blood groups are unknown.

i. Role of Viscoelastic Haemostatic Assays in Massive Transfusion

Key Points

- **Standard laboratory tests have limited value in the setting of massive transfusion *(Strong recommendation; low-quality evidence)***
- **Where available, viscoelastic haemostatic assays may be considered for guiding transfusion. *(Strong recommendation; low-quality evidence)***

Disadvantages of standard laboratory tests (SLT)

- Long turnaround times which are unable to guide the transfusion of blood components in a timely manner.
- PT and aPTT do not accurately reflect coagulopathy in the setting of massive bleeding.
- Limited value in predicting major bleeding.
- Unable to diagnose certain haemostatic abnormalities such as platelet dysfunction, low FXIII levels and hyperfibrinolysis.

Viscoelastic Haemostatic Assays (VHAs)

- VHAs include thromboelastography (TEG) and thromboelastometry (ROTEM).
- These assays examine various aspects of the haemostatic pathway which allow for more targeted treatment with blood products.
- The standard TEG and ROTEM phases can be divided into the following:
  - Clot initiation
  - Fibrin polymerisation
  - Clot strength
  - Clot lysis

Advantages of VHAs[5–8]

- When compared to standard laboratory tests, VHAs have shorter turnaround times.
- VHAs can detect hyperfibrinolysis while SLTs cannot.
- While SLTs only assess secondary haemostasis, VHAs assess all phases of coagulation.
- VHAs in specific clinical settings:

- VHAs have a better predictive value for bleeding in liver disease
- It has also been shown to lead to better outcomes when used in cardiac surgery
- In the setting of trauma, VHA parameters have been found to be good predictors of massive bleeding. There has been some low-quality evidence relating to the use of VHA guided transfusion with reduction in mortality and reduced allogenic transfusions due to ability to guide early targeted therapy in trauma-related massive transfusion.

ii. Complications of Massive Transfusion

Key Points

- **Massive transfusion results in physiological and biochemical changes with the potential to worsen coagulopathy.**
- **Potential complications of massive transfusion should be anticipated and actively monitored for and corrected. *(Strong recommendation; low-quality evidence)***

Potential risks associated with massive blood transfusion:

- Massive blood transfusion while potentially life-saving, is also associated with potential risks. Apart from potential adverse transfusion reactions and potential for transfusion transmitted infections, massive transfusion results in specific physiological and biochemical changes that will need early recognition and management: [7-11]

Complication	Aetiology	Potential Consequence	Management/ Prevention
Dilutional Coagulopathy	• Large volume crystalloid/colloid infusion • Large volume red blood cells transfusion	• Worsening of trauma induced coagulopathy	• Avoid large volume crystalloid/colloid and red cell transfusion without platelet and plasma transfusion
Hypothermia	• Infusion of cold crystalloids and blood products • Surgical exposure • Impaired thermoregulatory control	• Decrease in activity of clotting factors • Platelet dysfunction	• Maintain normothermia • Infuse large volume crystalloids and blood products through warmer • Direct warming of patient
Metabolic Acidosis	• Acidosis precipitated by systemic hypoperfusion • Citrate overload • Lactate released by red cells during storage	• Decrease in clotting factors activities	• Re-establish adequate tissue perfusion and oxygenation by surgical or endovascular techniques
Hypocalcaemia	• Impaired citrate clearance by liver	• Decrease in clotting factors activities • Decrease in vasomotor	• Check ionised calcium levels every 1-2 hours during large volume transfusion

		tone and myocardial contraction	
Hyperkalaemia	• Increased in concentration of extracellular potassium from stored red cells • Secondary to citrate administration • Infusion of large volumes of potassium poor solutions i.e., plasma, platelets, crystalloids • Release of catecholamines and aldosterone	• Cardiac arrythmias • Muscle dysfunction	• Check potassium levels during massive transfusion

References

1. Hunt, B.J., Allard, S., Keeling, D. *et al.* A practical guideline for the haematological management of major haemorrhage. *British Journal of Haematology* **170**, 788–803 (2015).
2. Roberts, I., Shakur, H., Coats, T. *et al.* The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients. *Health Technology Assessment* **17**, (2013).
3. Nunez, T.C., Voskresensky, I.V., Dossett, L.A. *et al.* Early prediction of massive transfusion in trauma: simple as ABC (assessment of blood consumption)? *Journal of Trauma and Acute Care Surgery* **66**, 346–52 (2009).
4. Chay, J., Koh, M., Tan, H.H. *et al.* A national common massive transfusion protocol (MTP) is a feasible and advantageous option for centralized blood services and hospitals. *Vox Sanguinis* **110**, 36–50 (2016).
5. Curry, N.S., Davenport, R., Pavord, S. *et al.* The use of viscoelastic haemostatic assays in the management of major bleeding: A British Society for Haematology Guideline. *British Journal of Haematology* **182**, 789–806 (2018).
6. Hsu, Y.M., Haas, T. & Cushing, M. Massive transfusion protocols: current best practice. *International Journal of Clinical Transfusion Medicine* 15 (2016) doi:10.2147/IJCTM.S61916.
7. Pham, H.P. & Shaz, B.H. Update on massive transfusion. *British Journal of Anaesthesia* **111 Suppl 1**, i71-82 (2013).
8. Spahn, D.R., Bouillon, B., Cerny, V. *et al*. The European guideline on management of major bleeding and coagulopathy following trauma: fifth edition. *Critical Care* **23**, 98 (2019).
9. Elmer, J., Wilcox, S. R. & Raja, A.S. Massive transfusion in traumatic shock. *Journal of Emergency Medicine* **44**, 829–38 (2013).
10. Guerado, E., Medina, A., Mata, M. I. *et al*. Protocols for massive blood transfusion: when and why, and potential complications. *European Journal of Trauma and Emergency Surgery* **42**, 283–95 (2016).
11. Hardcastle, T. C. Complications of massive transfusion in trauma patients. *ISBT Science Series* **1**, 180–184 (2006)

8 Transfusion of Blood Components in Fetuses, Neonates and Children

Key Points

- **If the reason for anaemia is not known, ensure blood samples for investigations are taken prior to transfusion. *(Strong recommendation; low-quality evidence)***
- **If a treatable cause is identified e.g., iron, folate or vitamin B12 deficiency, start appropriate treatment immediately. It may be possible to avoid transfusion, regardless of haemoglobin level. *(Strong recommendation; low-quality evidence)***
- **Decisions for transfusion of red cells should be based on signs and symptoms of anaemia rather than absolute Hb value alone. *(Strong recommendation; low-quality evidence)***
- **In paediatric transfusion, including those who are critically ill, a restrictive transfusion strategy is suggested. *(Strong recommendation; moderate-quality evidence)***
- **After one unit of blood transfusion, patients should be reassessed clinically to see if further transfusions are required. *(Strong recommendation; low-quality evidence)***
- **Decisions to transfuse platelets, frozen plasma and cryoprecipitate should be based on patient's clinical condition such as site and severity of bleeding for therapeutic transfusions, and bleeding risks weighed against risks of transfusion for prophylactic transfusions. *(Strong recommendation; low-quality evidence)***
- **Informed consent should be taken from the parent or legal guardian after informing of the risks and benefits of transfusion and its alternatives.**
- **Global data has shown that transfusion in paediatrics is associated with a disproportionate number of errors, mostly due to incompatible blood components transfused or due to the lack of knowledge of special requirements. Efforts should be made to prevent errors and particular care should be paid to sample labelling and patient identification. *(Strong recommendation; low-quality evidence)***

i. Red Cells

Selection of red cells

All red cells	• Less than 4 months of age Compatible with maternal and neonatal ABO (usually supplied as group O if available) and RhD blood groups and clinically significant maternal red cell alloantibodies • From 4 months of age Compatible with recipient's ABO and RhD blood groups and any red cell alloantibodies • Leucoreduced red cells – recommended indications, may differ according to institutional practices ○ Premature infants and/or infants weighing less than 1500 g at birth (Pre-storage leucoreduced)[1] ○ Neonates: First 28 days of life (Pre-storage leucoreduced)[1] • A unit of red blood cell concentrate can be divided into 3 units and reserved for the same neonate/infant in order to limit donor exposure,

	should repeated transfusions be needed. However, the age of the blood will be correspondingly increased, leading to potential issues with storage lesions.
Intra-uterine transfusion (IUT)	• Group O RhD negative or RhD matched with mother and fetus • IAT crossmatch compatible with maternal serum and antigen negative for the mother's corresponding clinically significant red cell alloantibodies • < 5 days old • Haematocrit 0.70-0.85 • Irradiated (shelf-life 24h post irradiation) • Leucoreduced • Unit from a donor unlikely to have haemoglobin S (e.g., donor of Chinese ethnicity)
Neonatal exchange blood transfusion (EBT)	• Reconstituted blood from removing additive solution from leucoreduced red cells of < 5 days old and resuspending in group AB plasma • Compatible with maternal and neonatal ABO and RhD blood groups and clinically significant maternal antibodies (table 1) • Haematocrit 0.5-0.6 • Irradiated if history of IUT – until 6 months post expected delivery date (shelf-life 24h post irradiation) • Irradiation is recommended for other neonates requiring EBT provided it does not cause undue delay Single volume exchange transfusion: • Typically 80 to 100 ml/kg • Replaces approximately 60% of the blood volume Double volume exchange transfusion: • Typically 160 ml/kg + 100 ml for priming volume for tubing • Replaces approximately 85% of the blood volume
Large volume neonatal and infant transfusion e.g., cardiac surgery	• Hct 0.5-0.7 (standard) • < 7 days old

Indications for irradiated blood are discussed in the Modified Blood Components chapter.

Table 1. ABO selection of fresh or reconstituted whole blood for exchange blood transfusion

Mother's blood group	Neonate's blood group			
	A	B	O	AB
A	Group A	O RBC + AB FP	Group O	Choice 1 O RBC + AB FP OR Choice 2 A RBC + AB FP
B	O RBC + AB FP	Group B	Group O	Choice 1 O RBC + AB FP OR Choice 2 B RBC + AB FP
O	O RBC + AB FP	O RBC + AB FP	Group O	O RBC + AB FP
AB	Group A	Group B	Group O	Group AB
	Reconstituted whole blood using leucoreduced red cell concentrate and frozen plasma (FP) (ABO Group of the red cells and FP used for the reconstitution are as mentioned in the table)			

Red cell volume to be transfused for small volume top up transfusion

- Volume to be transfused (ml) = (Desired Hb minus current Hb in g/dL) x (Body weight in kg) x 3.5
  Volume of red cells to be transfused is usually between 10-15 ml/kg and should not exceed 20 ml/kg. It is administered at a rate of 5ml/kg/h.
- The prescription of blood components for paediatric transfusion for children weighing less than 30kg should be in millilitres and prescribers must take particular care in calculating paediatric transfusion volumes using a transfusion formula.

Indications for red cell transfusion

- **Red cell IUT**
  - They are performed for the treatment of fetal anaemia, most commonly due to haemolytic disease of the fetus and newborn (HDFN, caused by anti-D, -c or -K) or fetal parvovirus infection.[2]

- **Red cell EBT**
  - EBT is performed to manage a high or rapidly rising bilirubin not responsive to intensive phototherapy or IVIG, or for severe anaemia.
  - EBT is mainly used in the treatment of HDFN to prevent bilirubin encephalopathy by removing the antibody-coated red cells and excess bilirubin.

- **Transfusion Triggers for Neonates**

Preterm neonates < 32 weeks (adapted from New et al[2])

Postnatal age	Suggested transfusion threshold Hb (g/dL) *(Conditional recommendation; low-quality evidence)*		
	Ventilated	On oxygen or NIPPV**	Off oxygen
First 24 hours	<12	<12	<10
≤ week 1 (day 1-7)	<12	<10	<10
Week 2 (day 8-14)	<10	<10	<7.5-8.5*
≥ week 3 (day 15 onwards)	<10	<8.5*	<7.5-8.5*

* Depending on clinical situation

**Non-invasive positive pressure ventilation

  - The benefits of improved tissue oxygenation and lower cardiac output need to be balanced against the risk of adverse reactions, including necrotising enterocolitis.[3,4]

Neonates > 32 weeks

  - As there is little evidence regarding appropriate thresholds for ≥32 weeks gestational age and term infants, clinicians may consider similar thresholds to those used for preterm babies off oxygen.[2]

- **Transfusion triggers for children**
  - A restrictive red cell transfusion policy is safe for clinically stable children.[2,5,6]
  - There is little evidence to make recommendations for pre-transfusion Hb thresholds in paediatric haematology/oncology patients and those undergoing stem cell transplantation.[2]

Clinical situation	Hb Transfusion Trigger (g/dL)
Patient in intensive care	Hb 7 g/dL[2,5,7] *(Strong recommendation: high-quality evidence)* A more liberal threshold can be considered if the child is unstable or has symptomatic anaemia *(Strong recommendation; low-quality evidence)*
Asymptomatic stable non-bleeding patient*	Hb 7 g/dL[2,5,6] *(Conditional recommendation; low-quality evidence)*

*Strongly consider avoiding transfusion if reversible cause is present e.g., iron deficiency

- **Management of chronically transfused patients**
  - Please refer to the adult Red cell transfusion chapter for the transfusion management of patients with transfusion and non-transfusion dependant thalassaemia.
  - A threshold of 7 g/dL may be insufficient in the long term to support normal growth and development in children with chronic anaemia due to non-haemoglobinopathy causes.[2] *(Conditional recommendation; low-quality evidence)* In patients with Diamond-Blackfan

anaemia, transfusion to keep Hb above 8 g/dL has been recommended.[2] *(Conditional recommendation; low-quality evidence)*

ii. Frozen plasma (FP) and Cryoprecipitate

Selection of FP and Cryoprecipitate

- Please refer to guidelines on Frozen Plasma (FP) Transfusion and Cryoprecipitate Transfusion.

Volume to be transfused and rate of administration

- The recommended dose for FP is 10-15 ml/kg and it is administered at a rate of 10-20ml/kg/hr.
- The recommended dose for cryoprecipitate is 5-10 ml/kg and it is administered at a rate of 10-20ml/kg/hr.

Indications

- Please refer to guidelines on Frozen Plasma (FP) Transfusion and Cryoprecipitate Transfusion.

iii. Platelets

Selection of platelets

- **ABO and Rh D requirements**

ABO Group Selection for Platelet Transfusion (Neonates)				
Recipient	Component ABO Group			
ABO Group	1st choice	2nd Choice	3rd Choice	4th Choice
AB	AB			
A	A	AB		
B	B	AB		
O	O	AB		
ABO Group Selection for Platelet Transfusion (Paediatric patients excluding neonates)				
Recipient	Component ABO Group			
ABO Group	1st choice	2nd Choice	3rd Choice	4th Choice
AB	AB	A*	B*	O*/**
A	A	AB	B*	O*/**
B	B	AB	A*	O*/**
O	O	A	B	AB

*All paediatric patients, especially patients weighing < 15 kg or < 3 years of age should receive ABO compatible platelets, if available. This is because there is a risk of acute haemolytic transfusion

reactions in the recipient, if the donor plasma is ABO incompatible with the recipient's red blood cell ABO antigen (minor incompatibility).

**Group O platelets should be used only in emergency situations or shortages.

- RhD negative patients should receive RhD negative platelets if available.
- It is recommended that all RhD negative patients receive anti-D immunoglobulin if they are transfused with RhD positive platelets to prevent alloimmunisation.

- **Special platelet requirements**
  - Irradiated platelet requirements are covered in the Modified Blood Components chapter.
  - HPA selected platelets should be used in neonatal alloimmune thrombocytopaenia (NAIT) if available. HPA unselected platelets should be transfused if HPA selected platelets are not available.

Platelet volume to be transfused

- The volume of platelets to be transfused is 10ml/kg or 4 units/m^2 over 1 hour. This is expected to raise the platelet count by 30-50x10^9/L.
- Platelets for paediatric patients can be ordered as single units of apheresis platelets paediatrics (APP), standard apheresis platelets or pooled platelets. Each APP is derived by dividing each unit of standard apheresis platelets into four units and each APP unit has a volume of 50-70 ml.
- Children weighing > 15 kg can be transfused with a unit of standard apheresis or pooled platelets instead of APP.

Indications for platelet transfusion

- **Neonates**

Clinical situation to trigger platelet transfusion (excluding NAIT)	Platelet Transfusion Trigger (x10^9/L)
Neonates (including preterm infants) with no bleeding	25[2,5,8] *(Strong recommendation; moderate-quality evidence)*
Neonates with bleeding, current coagulopathy or requiring non-major surgery	50[2,5] *(Conditional recommendation; low-quality evidence)*
Neonates with major bleeding or requiring major surgery (e.g., neurosurgery)	100 [2,5] *(Conditional recommendation; low-quality evidence)*

Clinical situation to trigger platelet transfusion in neonates with NAIT	Platelet Transfusion Trigger (x 10^9/L)
Preterm neonates with NAIT with no bleeding	50[5] *(Conditional recommendation; low-quality evidence)*
Term neonates with NAIT with no bleeding and no previously affected sibling with ICH	30[9] *(Conditional recommendation; low-quality evidence)*
Neonate with NAIT and no bleeding, if previously affected sibling with ICH	50[2,5,9] *(Conditional recommendation; low-quality evidence)*
Neonate with NAIT and life-threatening bleeding (such as intracranial or gastrointestinal)	100[9] *(Conditional recommendation; low-quality evidence)*

NAIT, neonatal alloimmune thrombocytopaenia; ICH, intracranial haemorrhage

- Neonatal alloimmune thrombocytopaenia (NAIT) occurs when maternal IgG alloantibodies to human platelet antigens (HPA) traverse the placenta and cause fetal and/or neonatal platelet destruction.
- It is caused by feto-maternal incompatibility for a fetal HPA inherited from the father which is absent in the mother.
- Presentations range from an asymptomatic neonate to neonatal thrombocytopaenia, petechiae, ecchymosis and intracranial haemorrhage (ICH). When ICHs occur, they frequently occur in utero.
- The reported incidence ranges from 0.3 to 1 in 1000, but it is the most important cause of severe thrombocytopaenia (< 50 x 10^9/l) in a well, term infant in the first 72 hours of life.[2]

- **Infants and children**
  - Given a lack of studies in paediatrics, recommendations for platelet transfusions in critically ill children or those with haematological/oncological malignancies who develop severe thrombocytopaenia are drawn from the wider adult literature.
  - As pragmatic guidance, it is suggested that for most stable children, prophylactic platelet transfusions should be administered when the platelet count is below 10 x 10^9/L, excluding patients with immune thrombocytopaenia (ITP), thrombotic thrombocytopaenic purpura (TTP)/ haemolytic uraemic syndrome (HUS) and heparin-induced thrombocytopaenia (HIT) who should only be transfused with platelets for life-threatening bleeding.[2]

Clinical situation to trigger platelet transfusion	Platelet Transfusion Trigger (x10^9/L)
Irrespective of signs of haemorrhage (excluding ITP, TTP/HUS, HIT)	10[2] (*Conditional recommendation; low-quality evidence)*
Severe mucositis	20[2] *(Conditional recommendation; low-quality evidence)*
Sepsis	20[2] *(Conditional recommendation; low-quality evidence)*
Prior to lumbar puncture	50[2] *(Conditional recommendation; low-quality evidence)*
Prior to surgical procedures	50-80[2] *(Conditional recommendation; low-quality evidence)*
Prior to neurosurgical procedures	100[2] *(Conditional recommendation; low-quality evidence)*
Moderate haemorrhage	50[2] *(Conditional recommendation; low-quality evidence)*
Major haemorrhage or significant post-operative bleeding	80-100[2] *(Conditional recommendation; low-quality evidence)*

References

1. Girelli, G., Antoncechi, S., Casadei, A.M. *et al.* Recommendations for transfusion therapy in neonatology. *Blood Transfusion* **13**, 484–497 (2015).
2. New, H.V., Berryman, J., Bolton-Maggs, P.H.B. et al. Guidelines on transfusion for fetuses, neonates and older children. British Journal of Haematology 175, 784–828 (2016).
3. Christensen, R. D. & Ilstrup, S. Recent advances toward defining the benefits and risks of erythrocyte transfusions in neonates. Archives of Disease in Childhood – Fetal and Neonatal Edition 98, F365–F372 (2013).
4. Christensen, R. D. Association between Red Blood Cell Transfusions and Necrotizing Enterocolitis. The Journal of Pediatrics 158, 349–350 (2011).
5. Australia, N. B. A. Patient Blood Management Guidelines: Module 6 Neonatal and Paediatrics. https://www.blood.gov/au/pbm-module-6 (last accessed April 2022) (2016).
6. Australia, N. B. A. Patient Blood Management Guidelines: Module 3 Medical. https://www.blood.gov.au/pbm-module-3 (last accessed April 2022) (2012).
7. Carson, J. L., Grossman, B.J., Kleinman, S. et al. Red Blood Cell Transfusion: A Clinical Practice Guideline From the AABB*. Annals of Internal Medicine 157, 49 (2012).
8. Curley, A., Stanworth, S.J., Willoughby, K. et al. Randomized Trial of Platelet-Transfusion Thresholds in Neonates. New England Journal of Medicine 380, 242–251 (2019).
9. Lieberman, L., Greinacher, A., Murphy, M.F. et al. Fetal and neonatal alloimmune thrombocytopaenia: recommendations for evidence-based practice, an international approach. British Journal of Haematology 185, 549–562 (2019).

9 Obstetric Transfusion

i. Optimisation of Haemoglobin in the Antenatal Period

Key Points

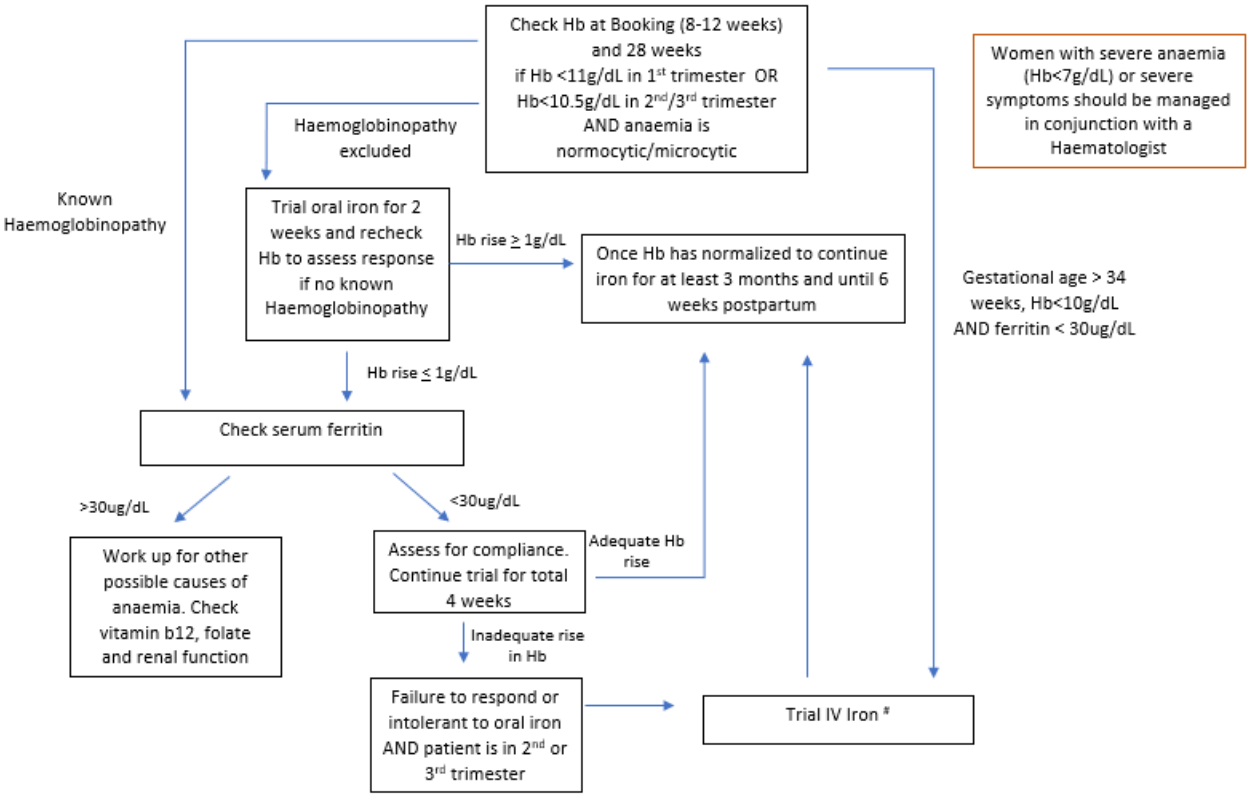
- **All women should be screened for anaemia at booking and at 28 weeks gestation.** ***(Strong recommendation; low-quality evidence)***
- **Iron deficiency anaemia should be treated early to avoid potential maternal and fetal morbidity.** ***(Strong recommendation; low-quality evidence)***
- **Patients with suspected postpartum anaemia should get a haemoglobin check and be treated accordingly.** ***(Strong recommendation; low-quality evidence)***

Introduction

- Anaemia in pregnancy is a global health issue. In Singapore, where most patients are on folate supplements and have a folate fortified diet, iron deficiency anaemia is the most common cause of anaemia in pregnancy.
- Anaemia in pregnancy has been defined as a haemoglobin (Hb) of less than 11.0g/dL in the first trimester, less than 10.5g/dL in the second and third trimester and less than 10.0g/dL postpartum.[1]
- Iron deficiency anaemia has been known to result in significant maternal and fetal morbidity and particular attention should be paid to detecting and treating anaemia early in pregnant women.
- In expectant mothers, it is associated with an increased risk of postpartum depression, poor cognition and work performance and fatigue, as well as postpartum haemorrhage.[1-3] In an already iron-depleted patient, intrapartum blood loss may further risk cardiac compromise and the need for blood transfusions. Severe anaemia has also been associated with an increased risk of mortality.[4]
- Maternal anaemia increases the risk of peri-natal and neonatal mortality, low birth weight and pre-term birth.[1] Children born to iron deficient mothers may exhibit impaired mental and psychomotor development.[1,2]
- Early and appropriate management of maternal anaemia prevents potential fetal and maternal morbidity of anaemia as well as potentially avoid the need for red blood cell transfusions.

Screening and Management of Anaemia in Pregnancy

Suggested Algorithm for Screening and Management of Anaemia in Pregnancy[1,2]



if no contraindications. Contraindications include: previous reactions/anaphylaxis, first trimester, active/chronic bacteraemia, decompensated liver disease

* serum ferritin of <30 µg/l in pregnancy is indicative of iron deficiency. However, levels higher than this do not rule out iron deficiency or depletion as serum ferritin is an acute phase protein and levels may rise in pregnancy

Early Recognition of Women at Risk of Anaemia

- Women with the following risk factors may not be anaemic at Hb check, however they may have underlying iron deficiency.
- Early recognition, screening and iron supplementation in these patients would prevent development of iron deficiency anaemia.

High risk of iron deficiency[1]	Previous anaemia Vegetarian Multiparous ≥ 3 Consecutive pregnancy ≤ 1 year from delivery Teenage pregnancy Recent bleeding
Where estimation of iron stores is necessary[1]	High bleeding risk Jehovah's witness

Iron Replacement

Elemental Oral Iron Doses

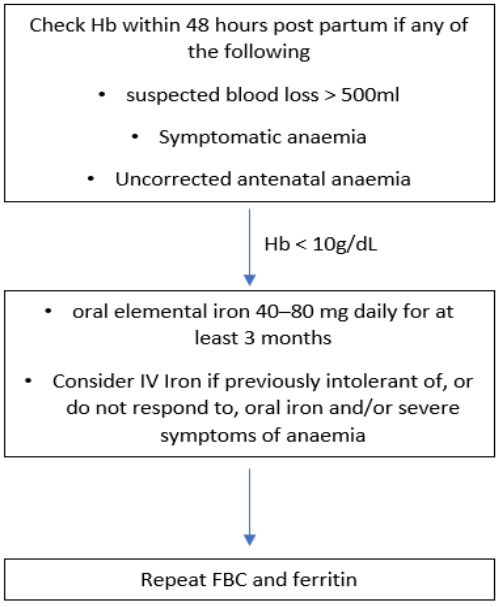
- Treatment for iron deficiency anaemia should be started promptly.
- In patients with iron deficiency anaemia, an elemental iron dose of 40-80mg/day can be considered.
- Alternate day dosing has been shown to have less gastrointestinal side effects and better fractional absorption.[5]

IV Iron

- IV Iron should be considered in the following groups of pregnant patients with iron deficiency anaemia from second trimester onwards:
    - Intolerant or not responsive to oral iron.
    - Presenting after 34 weeks with Hb < 10g/dL.

Labour and Postpartum Management in a Patient with Iron Deficiency Anaemia

- Send Full Blood Count (FBC) and Group and Crossmatch on admission to ward.
- Ensure intravenous access.
- Active management of 3rd stage of labour to minimise blood loss.
- Early recognition of iron deficiency post-partum is important to allow for prompt initiation of treatment to avoid post-partum anaemia as well as avoid the need for red cell transfusions.



ii. Antibody Screening and Monitoring

Key Points:

- **All pregnant women should be screened for presence of alloantibodies at booking and at 28 weeks.[6,7] *(Strong recommendation; moderate-quality evidence)***
- **Clinically significant antibodies require follow up with antibody titre monitoring or direct fetal monitoring in cases where risk of Haemolytic Disease of Fetus and Newborn (HDFN) is deemed to be high. *(Strong recommendation; moderate-quality evidence)***

Introduction

- Approximately 1% of women form clinically significant antibodies during pregnancy.[6]
- There is a risk these antibodies may cross the placenta into the fetus resulting in HDFN.
- Early antibody screening and identification strategies with appropriate fetal management is important in preventing HDFN.

Antibody Screening and Monitoring

- Clinically significant antibodies are antibodies that can result in haemolytic transfusion reactions and HDFN.
- The risk of HDFN is greatest with anti-D, anti-c and anti-K antibodies, however other alloantibodies may also be implicated.
- When clinically significant antibodies are detected, it is important to monitor the antibody titres.
- Any increase in titre by more than 1 dilution (compared to the last sample measured in parallel with current sample) is significant.
- Antibody titres of more than 16 are considered a HDFN risk whereby direct fetal monitoring is recommended.[6,8]
    - Maternal anti-K antibodies and warm acting anti-M antibodies have a risk of causing fetal anaemia due to maturation arrest of erythropoiesis even at low antibody titres.
    - Direct fetal monitoring is advisable once either of the above antibodies are detected. The babies should be monitored up to 2 months post birth for delayed onset of anaemia.[6,9,10]
- Presence of anti-E antibodies may potentiate fetal anaemia in the presence of anti-c antibodies, hence referral to fetal medicine specialist is recommended at lower titres.[10]
- Antibody titres should be performed 4-weekly up to 28 weeks, then 2 weekly till delivery for anti-D, anti-C, anti-c, anti-E and anti-e antibodies.
- With the exception of anti-K and warm acting anti-M antibodies, for all other antibodies which pose a risk of HDFN and have a titre of < 16 at booking, repeat antibody screen and titres at 28 weeks (clinicians may choose to recommend regular antibody monitoring for these antibodies even if at low titres because even though they are not the most commonly implicated antibodies in HDFN, they may still pose a risk)
- Patients with a history of HDFN should be referred to a fetal medicine specialist before 20 weeks regardless of antibody identified or the titres.[6] Serial antibody titres may not be useful in this case.[11,12]

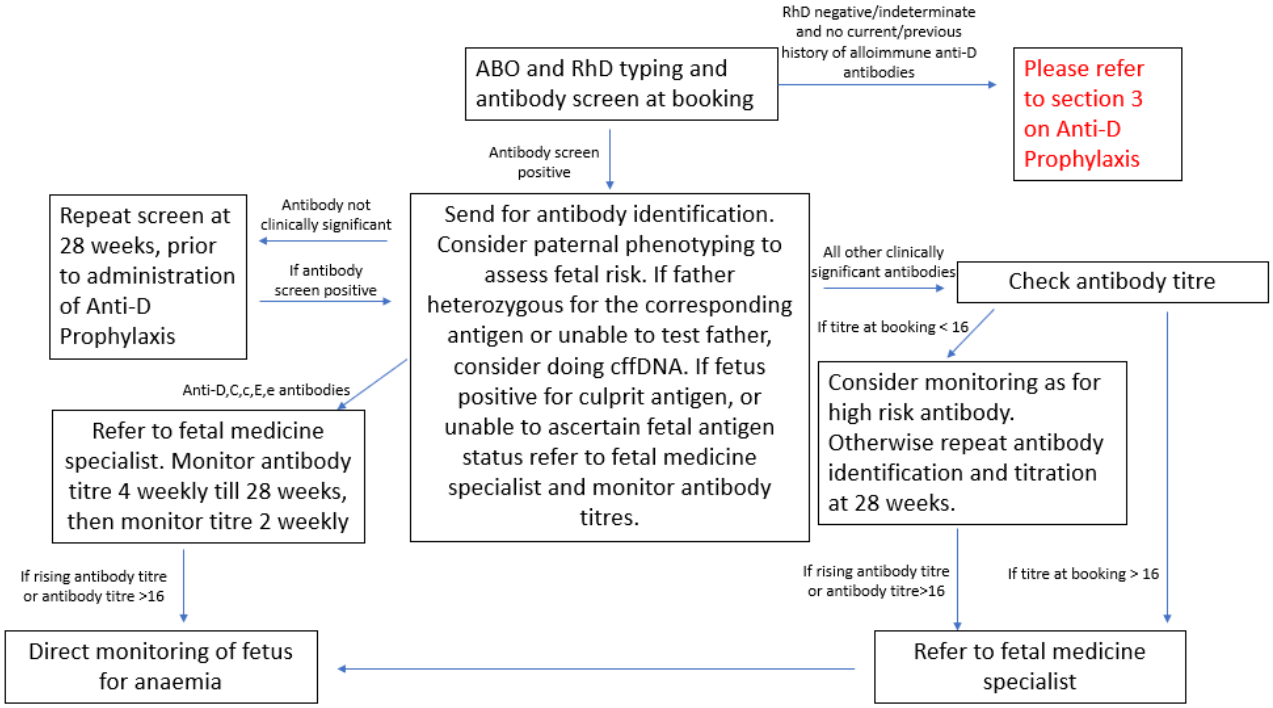
Common Clinically Significant Antibodies Implicated in HDFN:[10,11]

System	Antibody	HDFN Severity
ABO	Anti-A or Anti-B	Mild
Rh	Anti-D, c	Severe
Rh	Anti-C, E, e	Mild to severe
Kell	Anti-K	Mild to severe
Kell	Anti-k	Mild
Kidd	Anti-Jk^a	Mild to severe
Kidd	Anti-Jk^b	Mild
Duffy	Anti-Fy^a, Fy^b	Mild to severe
Diego	Anti-Di^a, Di^b	Mild to severe
MNS	S, s, U	Mild to severe

MNS	Mi^{a} (warm)	Moderate
MNS	Anti-M (warm)	Mild to severe

*anti-K and anti-M (warm acting) pose risks of fetal anaemia even at low titres

Flowchart for Antibody Screening and Titration during Pregnancy



*Maternal anti-K antibodies and warm acting anti-M antibodies have a risk of causing fetal anaemia due to maturation arrest of erythropoiesis even at low antibody titres. Fetal monitoring is advisable once the above antibodies are detected.

iii. Administration of Anti-D Prophylaxis

Key Points

- **All women who are RhD negative should be offered Routine Antenatal Anti-D Prophylaxis (RAADP). *(Strong recommendation; moderate-quality evidence)***
- **Prophylactic anti-D immunoglobulin may be warranted after sensitising events depending on the stage of gestation. *(Strong recommendation; low-quality evidence)***
- **Antibody screen should always be performed prior to administration of anti-D immunoglobulin prophylaxis so as not to confuse passive anti-D with immune anti-D. *(Strong recommendation; low quality evidence)***

Routine Antenatal Anti-D Prophylaxis

- All women who are RhD negative should be offered an Intramuscular (IM) dose of 1500 IU of Routine Antenatal Anti-D Prophylaxis (RAADP) between weeks 28 to 30 weeks to avoid potential alloimmunisation to anti-D.
- RAADP should only be administered after ascertaining the ABO and RhD type as well as performing antibody screening at 28 weeks. Samples taken after the RAADP injection may be mistaken for immune anti-D antibody resulting in inappropriate management subsequently.

Distinguishing Between Passive and Alloimmune Anti-D

- Some patients may not have a clear history of RAADP administration or may have received RAADP just prior to antibody screen.
- Passive and immune anti-D cannot be differentiated by serological testing. Nevertheless, it is important to try distinguishing passive from alloimmune anti-D in such cases as misinterpretation of an alloimmune anti-D for passive anti-D may result in lack of follow up of antibody titres and fetal monitoring for HDFN.[6]

	Passive Anti-D	Alloimmune Anti-D
Antibody titres	Fall over time	Remain stable or rise
Time to detection	Within minutes of administration	4 weeks post exposure
Duration to peak concentration	3 to 7 days	6 to 8 weeks

*In cases where > 1500 IU of anti-D immunoglobulin has been administered, higher titres may be detected. However, this will fall over time.

- Where it cannot be distinguished if the anti-D is passive or alloimmune:[6,13]
  - Monitor antibody titres at 4-weekly intervals to 28 weeks gestation and at 2-weekly intervals after 28 weeks until delivery, or until serial monitoring by middle cerebral artery (MCA) Doppler has been instituted.
  - Continue anti-D immunoglobulin prophylaxis unless it is established that anti-D antibody is alloimmune.

Management of Sensitising Events

- Anti-D immunoglobulin prophylaxis should be administered within 72 hours of a potentially sensitising event.[13]
  - Dose calculation is based on 125 IU anti-D Ig/mL of fetal red cells for IM administration.
  - If this has not been met, some protection may be offered if anti-D Ig is given up to 10 days after the sensitising event.
- Maternal blood group and antibody screen to determine or confirm the RhD group and check for the presence of immune anti-D should always be performed prior to anti-D prophylaxis.
- Depending on the gestational age, maternal blood sampling for fetal maternal haemorrhage (FMH) testing may be required to estimate volume of FMH and need for further anti-D immunoglobulin. FMH sampling should be performed 30-45 minutes after a sensitising event to ensure sufficient time for circulation of the fetal cells.[13]

Sensitising Events and Management
•Amniocentesis, chorionic villus biopsy and cordocentesis •Antepartum haemorrhage/uterine bleeding •External cephalic version •Abdominal trauma •Ectopic pregnancy •Evacuation of molar pregnancy •Intrauterine death and stillbirth •In-utero therapeutic interventions •Miscarriage/ threatened miscarriage •Therapeutic termination of pregnancy •Delivery – normal, instrumental or Caesarean section

•Intra-operative cell salvage			
Gestational Age	< 12 weeks	12-20 weeks	Beyond 20 weeks
Anti-D Immunoglobulin Prophylaxis	• Anti-D immunoglobulin prophylaxis only indicated if: ○ Ectopic pregnancy ○ Molar pregnancy ○ Therapeutic termination of pregnancy ○ Repeated, painful or heavy uterine bleeding	• Anti-D immunoglobulin prophylaxis indicated for all potentially sensitising events • In case of continued uterine bleeding, patient should receive 6-weekly anti D immunoglobulin prophylaxis	• Anti-D immunoglobulin prophylaxis indicated for all potentially sensitising events regardless of administration of 28 week RAADP
Anti-D Immunoglobulin dose	• Minimum 250IU	• Minimum 250IU	• Minimum 500IU
FMH testing	• Not indicated	• Not indicated	• FMH testing to estimate volume of FMH and need for additional anti-D immunoglobulin doses If estimated FMH volume exceed coverage of initial anti-D immunoglobulin dosing (1500 IU covers 12mL of FMH), follow-up samples are required 72 hours following IM dose to check for clearance of fetal cells

Anti-D Prophylaxis Following Transfusions

(i) Prophylaxis Following RhD Positive Platelet Transfusion to RhD Negative Mother

- Please refer to Platelet transfusion Chapter

(ii) Prophylaxis Following RhD Positive Red Cell Transfusion to RhD Negative Mother[13]

- Inadvertent transfusion of RhD positive red cells to a RhD negative mother should be managed in conjunction with a Haematologist.
- Anti-D immunoglobulin prophylaxis must be administered.
- If more than 15ml of RhD positive red cells has been transfused, intravenous (IV) anti-D immunoglobulin may be more practical if this is available (dose for IV administration: 100 IU will clear 1 ml of RhD positive red cells). Otherwise, larger IM anti-D immunoglobulin preparations (1500 IU) may also be considered. IM-only preparations of anti-D immunoglobulins must NOT be given IV.
- FMH should be quantified 48 hours post IV anti-D and 72 hours post IM anti-D immunoglobulin, with administration of further anti-D immunoglobulin prophylaxis as required until no further RhD positive cells are detected in the maternal circulation.
- Where more than 1 unit of RhD positive blood has been transfused, a Haematology consult should be sought for consideration of exchange transfusion.

(iii) Prophylaxis Following Reinfusion of Red Cells from Intraoperative Cell Salvage[13]

- If intraoperative cell salvage is used in a RhD negative mother, minimum anti-D immunoglobulin dose of 1500 IU should be administered after reinfusion of salvaged red cells if the cord blood group is RhD positive.
- Maternal samples should be taken for FMH estimation 30-45 minutes after reinfusion.

iv. Transfusion Measures in Management of Primary Postpartum Haemorrhage

Key Points

- **Early recognition and management of Primary Postpartum Haemorrhage (PPH) is important in optimising outcomes**
- **There is a role for administration of Tranexamic Acid in early PPH *(Strong recommendation; moderate-quality evidence)***
- **All obstetric units should have a clear PPH management pathway *(Conditional recommendation; low-quality evidence)***

Introduction

- Primary postpartum haemorrhage (PPH) is a leading cause of maternal morbidity and mortality worldwide.
- Minor PPH is defined as blood loss of 500-1000ml without clinical shock, while major PPH is defined as blood loss of more than 1000ml with continued bleed or clinical shock.[14]

Identifying and Minimising Risk Factors

- All women should be assessed for potential risk factors for PPH.
- Anaemia during pregnancy has been linked to greater blood loss at labour and should be actively treated to reduce morbidity associated with PPH.
- Active management of third stage of labour is important to reduce risk of PPH.[14]

Management of PPH

- Early recognition of PPH is vital in improving outcomes. Patients may not present with classical signs of tachycardia and hypotension till more than 25% of blood volume (or more than 1500ml) has been lost.[15]
- When PPH is identified, a rapid physical examination is important to identify the aetiology.
- All obstetric units should have protocols for management of minor and major PPH.
- All obstetric units are recommended to maintain a PPH Emergency Box. The box contents should include:

IV cannulae/syringes/needles

IV Fluids: Crystalloids x 2 litres

Blood collection bottles/ forms

Urinary catheter

Drugs: Syntometrine, Oxytocin, Misoprostol, Carboprost

- Initiation of blood transfusion should be based on haematological and obstetric assessment instead of Hb levels.
- When large volumes of blood are lost, consumptive coagulopathy follows, leading to the need for multicomponent transfusion therapy. A Massive transfusion protocol should be a part of the PPH management plan.
- In the absence of guidance by viscoelastic haemostatic assays, blood product transfusion should proceed at fixed ratios as per MTP protocol even in the absence of laboratory results as the laboratory results may be delayed.
- Fibrinogen is depleted during early PPH. Fibrinogen levels have also been found to correlate with the incidence and severity of bleeding.[16] Hence consideration for early fibrinogen replacement should be made. In the setting of a MTP activation, fibrinogen replacement should be requested with the first MTP pack.
- A plasma fibrinogen level of more than 2g/L should be maintained.[17] Critically low fibrinogen levels should be anticipated in amniotic fluid embolism and placental abruption, and early fibrinogen replacement should be considered in these instances.[18]
- Therapeutic goals of MTP are as follows:[17]

Laboratory Value	Target
Haemoglobin	>8g/dL
Platelet	>50 x 10^9/L
Fibrinogen	>2g/L
PT/PTT	< 1.5 times normal

Role of Tranexamic Acid in Management of PPH

- Tranexamic acid (TXA) is an antifibrinolytic agent which has a significant role in the management of PPH.[19,20]
- The WOMAN trial demonstrated the efficacy of the administration of 1g IV TXA in patients who have a diagnosis of PPH, with a repeat dose given if bleeding continued after 30 minutes.[19]
- Clinicians should consider the use of intravenous tranexamic acid (0.5–1.0 g), in addition to oxytocin at caesarean section to reduce blood loss in women at increased risk of PPH.[14]

v. Appropriate Red Cell Products in Pregnancy

Key Points

- **Pregnant women should receive ABO, RhD and Kell matched blood *(Strong recommendation, high-quality evidence)***
- **Pregnant women should receive leucoreduced blood products *(Conditional recommendation, low-quality evidence)***
- **All patients who are anticipated to be chronically transfused should have prior extended red cell phenotyping before the start of the transfusion program *(Strong recommendation; low-quality evidence)***

Routine Transfusion in Pregnancy

- For pregnant women requiring transfusion, ensure that GXM sample is no more than 3 days old.[21]
- Red cell units should be:[21]
    - ABO, RhD and Kell matched.
    - Leucodepleted to reduce transfusion transmitted CMV risk.
    - Antigen negative for corresponding current and historical clinically significant red cell alloantibodies.
- In emergency settings where leucodepleted blood may not be obtainable, a bedside leucocyte filter can be used in place.

Chronically Transfused Patients

- All patients who are embarking on a chronic transfusion program should undergo extended red cell antigen phenotyping prior to the first transfusion where possible.
- If patient has already been transfused, ensure phenotyping is performed at least 3 months from the last red cell transfusion to ensure accuracy.
- Chronically transfused patients are at risk of complications of iron overload including heart, liver and endocrine organs as well as alloimmunisation. Transfusion for patients with underlying Haemoglobinopathies such as thalassaemia and Sickle Cell Disease should be managed in conjunction with a Haematologist.
- All pregnant patients with clinically significant thalassaemic syndromes should receive leucodepleted ABO, Rh (D, C, c, E, e) and Kell matched units to reduce alloimmunisation risk.[22,23] Kidd (Jka, Jkb) matched red cells are also recommended in Singapore as alloantibodies to the Kidd blood group antigens are among the commonest red cell alloantibodies in such patients here.[24,25]
- All pregnant patients with Sickle Cell Disease should receive red cell units which are negative for HbS and that are leucodepleted as well as ABO, Rh (D, C, c, E, e) and Kell matched to reduce alloimmunisation risk.[24]

Emergency Transfusion where ABO and RhD Status is Unknown

- In an emergency setting where the ABO and RhD status of a pregnant patient is unknown, Group O RhD negative red cell units should be transfused to patients of Indian, Caucasian, Middle Eastern and African descent due to higher prevalence of RhD negativity in these ethnic groups.
- Pregnant patient of all other ethnicities should be given Group O RhD positive red cells.

References

1. Pavord, S., Daru, J, Prasannan, N. et al. UK guidelines on the management of iron deficiency in pregnancy. British Journal of Haematology 188, 819–830 (2020).
2. Achebe, M.M. & Gafter-Gvili, A. How I treat anemia in pregnancy: iron, cobalamin, and folate. Blood 129, 940–949 (2017).
3. Bieber, E.J., Scott, L., Muller, C. et al. What you can do to optimize blood conservation in ObGyn practice. OBG Management 22, 28-38 (2010).
4. Daru, J., Zamora, J., Fernandez-Felix, B.M. et al. Risk of maternal mortality in women with severe anaemia during pregnancy and post partum: a multilevel analysis. Lancet Global Health 6, e548–e554 (2018).
5. Stoffel, N.U., Cercamondi, C.I., Brittenham, G. et al. Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women: two open-label, randomised controlled trials. Lancet Haematology 4, e524–e533 (2017).
6. White, J., Qureshi, H., Massey, E. et al. Guideline for blood grouping and red cell antibody testing in pregnancy. Transfusion Medicine 26, 246–63 (2016).
7. Dajak, S., Stefanović, V. & Capkun, V. Severe hemolytic disease of fetus and newborn caused by red blood cell antibodies undetected at first-trimester screening (CME). Transfusion (Paris) 51, 1380–8 (2011).
8. Cacciatore, A., Rapiti, S., Carrara, S. et al. Obstetric management in Rh alloimmunized pregnancy. Journal of Prenatal Medicine 3, 25–7 (2009).
9. Learoyd, P., Knight, R., Rogan, P., et al. An Introduction to Blood Transfusion Science and Blood Bank Practice. British Blood Transfusion Society (2009).
10. Royal College of Obstetricians and Gynaecologists. The management of women with red cell antibodies during pregnancy. Green-top Guideline No. 65 (2014).
11. ACOG Practice Bulletin No. 192: Management of Alloimmunization During Pregnancy. Obstetrics & Gynecology 131, e82–e90 (2018).
12. Delaney, M. & Matthews, D.C. Hemolytic disease of the fetus and newborn: managing the mother, fetus, and newborn. Hematology 2015, 146–151 (2015).
13. Qureshi, H., Massey, E., Kirwan, T. et al. BCSH guideline for the use of anti-D immunoglobulin for the prevention of haemolytic disease of the fetus and newborn. Transfusion Medicine 24, 8–20 (2014).
14. Prevention and Management of Postpartum Haemorrhage. BJOG: An International Journal of Obstetrics & Gynaecology 124, e106–e149 (2017).
15. Bonnar, J. Massive obstetric haemorrhage. Bailliere's best practice & research. Clinical obstetrics & gynaecology 14, 1–18 (2000).
16. Solomon, C., Collis, R.E. & Collins, P.W. Haemostatic monitoring during postpartum haemorrhage and implications for management. British Journal of Anaesthesia 109, 851–863 (2012).
17. Hunt, B.J., Allard, S., Keeling, D. et al. A practical guideline for the haematological management of major haemorrhage. British Journal of Haematolgy 170, 788–803 (2015).
18. ACOG Practice Bulletin No. 183: Postpartum Hemorrhage. Obstetrics & Gynecology 130, e168–e186 (2017).
19. Shakur, H., Roberts, I., Fawole, B. et al. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. The Lancet 389, 2105–2116 (2017).
20. Novikova, N., Hofmeyr, G.J. & Cluver, C. Tranexamic acid for preventing postpartum haemorrhage. Cochrane Database of Systematic Reviews (2015)
21. Royal College of Obstetricians and Gynaecologists. Blood Transfusion in Obstetrics Green-top Guideline No.47. (2015).

22. Royal College of Obstetricians and Gynaecologists. Management of Beta Thalassaemia in Pregnancy Green-top Guideline No. 66. (2014).
23. Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee Transfusion Handbook. Haemoglobinopathies. https://www.transfusionguidelines.org/transfusion-handbook (last accessed May 2022) (2014)
24. Royal College of Obstetricians and Gynaecologists. Management of Sickle Cell Disease in Pregnancy Green-top Guideline No. 61. (2011).
25. Ang, A.L., Lim, C.Y., Ng, W.Y. et al. Non-transfusion dependent thalassemia is independently associated with higher alloimmunization risk than transfusion dependent thalassemia and would benefit the most from extended red cell antigen-matching. Transfusion 61, 2566-2577 (2021).

10 Blood Safety, Adverse Transfusion Reactions and Haemovigilance

Key Points

- **Safety of the blood supply is dependent on collecting blood from voluntary unpaid donors from low-risk populations, screening donated blood for transfusion transmissible infections and avoiding unnecessary transfusion.**
- **Allergic reactions and febrile non haemolytic transfusion reactions are common but often mild, whereas acute haemolytic reactions, bacterial contamination, transfusion related acute lung injury (TRALI) and anaphylactic reactions are less common but potentially life threatening.**
- **Acute haemolytic reactions are commonly due to misidentification of the patient and therefore positive identification of the patient at the bedside when taking blood for crossmatch and before commencing transfusion is the most important step in the prevention of this complication.**
- **Transfusion associated circulatory overload (TACO) is the most commonly reported cause worldwide of transfusion-related mortality and major morbidity. Pre-transfusion risk assessment for circulatory overload should be undertaken for all patients.**
- **Transfusions should only be carried out where patients can be directly observed and where staff are trained in managing complications of transfusion, especially anaphylaxis.**
- **It is advisable that a policy be in place in each hospital for the management and reporting of adverse reactions following transfusion of blood and blood components.**
- **All transfusion reactions should be reported to the Singapore National Haemovigilance program.**

Blood safety

- In Singapore, blood is collected from voluntary and non-remunerated blood donors. Prospective blood donors are asked direct and specific questions regarding their medical history, sexual behaviour and recent travel to determine if they are in good health and at low risk of diseases that could be transmitted by blood transfusion.
- Directed and replacement donations from family and friends is not practiced in Singapore because there is a higher probability of transfusion transmissible infections among these donors due to psychological pressure placed on them to donate.
- If the donor is eligible to donate, the donated blood is tested for ABO and RhD typing and red blood cell antibody screen. Other tests performed on every donation include the following:
    1. HIV Nucleic Acid Testing and HIV Ag/antibody for HIV
    2. HBV Nucleic Acid Testing and HBs Ag for Hepatitis B Virus
    3. HCV Nucleic Acid Testing and anti-HCV for Hepatitis C Virus
    4. Treponema pallidum Particle Agglutination (TPPA) for Syphilis
    5. HEV Nucleic Acid Testing for Hepatitis E Virus
- Bacterial culture is performed on all pooled and apheresis platelets units at least 48 hours after collection, with a minimum incubation period of 12 hours prior to release to the hospitals. The bacteria culture will continue until the expiry of the platelets, and the clinical team will be informed of any positive culture results if the platelets have been transfused.

- Additional Malaria tests (antibody, with or without PCR depending on their risk factor) are performed for donors with risk factors such as recent travel to malaria endemic areas or history of residence in malaria endemic areas.

Adverse Transfusion Reactions

- Although blood transfusion is considered life-saving and beneficial to patients requiring blood and blood components, it is also associated with risks of adverse reactions.
- An adverse reaction to transfusion is defined as an undesirable response or effect in a patient temporally associated with the administration of blood or blood components.
- The risks of transfusion should be weighed against the expected therapeutic benefits, and only when the expected benefits outweigh the potential risks should transfusion of blood and blood components be initiated.
- All personnel involved in ordering and administering transfusions must be able to recognise adverse reactions to transfusion so that appropriate actions can be taken promptly.
- Institutional policies may vary regarding the initial steps in managing an adverse reaction, but the following key elements should be followed irrespective of the type of reaction.
    1. STOP the transfusion and keep the intravenous line open with normal isotonic saline.
    2. Check Airway, Breathing and Circulation
    3. Start supportive care to address the patient's cardiac, respiratory, and renal functions as necessary; and provide symptomatic therapy.
    4. The blood product labelling and patient identification should be rechecked to confirm that the patient received the intended product and the reaction should be reported to the blood transfusion laboratory for additional testing.
    5. Document all events on appropriate forms and in the patient's chart.

Categories, additional testing and management

Adverse Reaction	Clinical Presentation	Additional Testing	Treatment/Prevention
Febrile Non-Haemolytic Transfusion Reaction (FNHTR)	• **Mild**: Fever ≥ 38°C and a temperature rise of at least 1°C but <2°C from pre transfusion value occurring in the absence of chills, rigors, respiratory distress or haemodynamic instability[1] • **Non-mild**: Fever ≥ 39°C or a temperature rise ≥ 2°C and/or other symptoms (e.g., rigors, myalgia, nausea).[1] • Onset during or within 4 hours following transfusion	• Nil for mild FNHTR, provided acute haemolytic transfusion reaction (AHTR) can be excluded • Rule out bacterial contamination (Gram stain and culture of blood component, blood culture of patient) or haemolytic reaction (see AHTR) if symptoms are non-mild	• STOP transfusion • Give antipyretics *(Conditional recommendation; low-quality evidence)* • Transfusion may be restarted slowly if reaction is mild and doctor elects to continue transfusion • For non-mild reactions, notify the blood bank lab and return the implicated unit of blood component • Current evidence does not support routine premedication with antipyretics[2] *(Strong recommendation; high-quality evidence)* • Use of pre-storage leucoreduced blood components (red cells and platelets) has been shown to decrease the frequency of

			FNHTRs and are recommended in patients with 2 or more FNHTRs *(Strong recommendation; moderate-quality evidence)*
Allergic Reaction (Mild)[3]	• Minor or localised reaction Flushed skin, morbilliform rash, pruritus, urticaria (hives), localised angioedema, minor oedema of lips, tongue and uvula, conjunctival oedema, periorbital and conjunctival erythema • Occurs during or within 4 hours of transfusion • Fever is not a part of the allergic response	**Nil**	• STOP transfusion • Antihistamines *(Conditional recommendation; low-quality evidence)* • Transfusion may be restarted slowly once the symptoms subside, and blood component is still viable • Current evidence does not support routine premedication (antihistamines or glucocorticoids) to prevent allergic reactions (*Conditional recommendation; low-quality evidence)*[2]
Allergic Reaction (Moderate)	• Symptoms as for minor reactions and: • Cough, wheeze or angioedema • Chills and rigors • Onset usually within first 50-100 ml infused and within 4 hours of transfusion • No cardiovascular or respiratory compromise	• Investigate for IgA deficiency (IgA levels, IgA antibodies)	• STOP transfusion • Antihistamines *(Conditional recommendation; low-quality evidence)* • Replace blood administration set and give saline to keep vein open and/or maintain blood pressure • Monitor closely and treat as required with oxygen, antihistamines, glucocorticoids and inhaled bronchodilator (e.g., salbutamol) • Plasma reduced platelets may be considered for future transfusions if recurrent moderate allergic reactions *(Conditional recommendation; low-quality evidence)* • Notify blood bank lab and return the implicated unit of blood component
Severe Allergic (Anaphylactic) Transfusion Reaction	• A severe, life threatening, generalised or systemic hypersensitivity reaction characterised by rapidly developing	• Investigate for IgA deficiency (IgA levels, IgA antibodies)[4] • Rule out AHTR (see AHTR)	• STOP transfusion • Follow anaphylaxis guidelines: <u>Immediate treatment</u> ○ Administer adrenaline IM as per anaphylaxis

	airway and/or breathing and/or circulation problems usually associated with skin and mucosal changes[4] • Rapid onset		protocol (patients who are thrombocytopaenic or who have deranged coagulation should also receive IM adrenaline) *(Strong recommendation; high-quality evidence)* <u>Other supportive care:</u> ○ Replace blood administration set and give rapid IV colloids or saline ○ Following initial resuscitation, administer corticosteroids (IV) such as hydrocortisone ○ Following initial resuscitation, administer antihistamines (IV) ○ Consider inhaled or intravenous bronchodilator therapy if persistent wheeze • ICU liaison • Washed cellular blood components for future transfusions may be indicated especially if recurrent severe allergic reactions where the cause of the reaction is not identified *(Strong recommendation; low-quality evidence)* ○ If washed platelets are unavailable, plasma reduced platelets may be considered for future transfusions if these are indicated, with close monitoring of the patient and resuscitation facilities on standby *(Conditional recommendation; low-quality evidence)* • Washed cellular blood components are also recommended if recipient is known to have absolute IgA deficiency or to have anti-IgA

			antibodies (as IgA deficient blood components are unavailable in Singapore). *(Strong recommendation; low-quality evidence)* • The management of these patients should be discussed with a Haematologist or Immunologist. • Notify blood bank lab and return the implicated unit of blood component.
Acute Haemolytic Transfusion Reaction (AHTR)[5]	• Fever, chills, rigors, facial flushing, chest pain, abdominal pain, back/flank pain, nausea/ vomiting, diarrhoea, hypotension, pallor, jaundice, oligo- or anuria, diffuse intravascular coagulopathy (DIC), dark urine • During or within 24 hours of transfusion	• Evaluation for clerical error • Evaluation of a post-transfusion specimen for gross haemolysis • Repeat pre- and post-transfusion ABO, RhD typing, red cell antibody screen and identification, compatibility testing • Elution studies • Direct antiglobulin test (DAT) • Tests to detect haemolysis (e.g., Lactate Dehydrogenase (LDH), haptoglobin, bilirubin) • Monitor for complications such as renal impairment and DIC • Rule out non-immune causes of haemolysis (e.g., use of	• STOP transfusion • Check airway, breathing, circulation and maintain a large-bore IV access • Confirm patient identity • In severe reactions, immediate intervention with fluid resuscitation, cardiovascular, renal and/or respiratory support and blood component therapy for DIC with bleeding may be required. • Notify blood bank and return the implicated unit of blood component

		wrong IV fluid, blood warmer)	
Delayed Haemolytic Transfusion Reaction (DHTR)[5]	• Fever, jaundice • Inadequate rise of post-transfusion haemoglobin level or unexplained fall in haemoglobin after a transfusion • Occurs between 24 hours and 28 days after a transfusion	• DAT • Elution studies • Antibody screen and identification • Tests to detect haemolysis (e.g., LDH, haptoglobin, bilirubin)	• Transfusion of antigen negative and crossmatch compatible red cell units if further red cell transfusion if indicated.
Transfusion Associated Circulatory Overload (TACO)[5]	• Dyspnoea, orthopnoea, cough, tachycardia, hypertension, headache • Raised Jugular Venous Pressure (JVP) and Central Venous Pressure (CVP) • Acute or worsening pulmonary oedema on Chest X-ray • Occurs during or up to 12 hours after transfusion	• Chest X-ray • B-type natriuretic peptide (BNP) (raised) • Rule out TRALI	• STOP transfusion • Supplemental oxygen • IV diuretic administration *(Strong recommendation; moderate-quality evidence)* • Careful assessment of patient's pre-transfusion fluid balance and risk factors for TACO • Avoid coadministration of crystalloids • Only administer the minimum required quantity of blood products to achieve the clinical or laboratory parameter endpoint (i.e., **1 unit at a time)** • Notify blood bank lab and return remaining blood components
Transfusion Related Acute Lung Injury (TRALI)[6]	• Dyspnoea, hypoxemia, hypotension • Bilateral pulmonary infiltrates on chest X-ray • Absence of circulatory overload • Occurs during or up to 6 hours after transfusion	• Chest X-ray • Anti-HLA or anti-Human Neutrophil Antigen (HNA) antibodies in donor(s) and confirmation of cognate antigens in recipient is **NOT** required for diagnosis	• STOP transfusion • Supplemental oxygen • Mechanical ventilation • Diuretics are usually not helpful (*Strong recommendation; low-quality evidence)* • Requires urgent blood bank lab and Singapore National Haemovigilance Program notification so that donor(s) can be assessed for the relevant antibodies (HLA, HNA) and implicated donor(s) withdrawn from the active donor panel. • Return implicated unit of blood component to blood bank lab

Transfusion Associated Dyspnoea (TAD) [7]	• Respiratory distress within 24 hours of transfusion • Respiratory distress should be the most prominent clinical feature and should not be explained by the patient's underlying condition or any other known cause • Does not meet the criteria of TRALI, TACO or severe allergic (anaphylactic) reaction	• Nil • Exclude TRALI, TACO or severe allergic (anaphylactic) reaction	• STOP transfusion • Supplemental oxygen
Hypotensive Transfusion Reaction[7]	• Hypotension defined as a drop in systolic blood pressure of ≥ 30 mm Hg and systolic blood pressure ≤ 80 mm Hg • Occurs during or within one hour of completing transfusion • Most reactions do occur very rapidly after the start of the transfusion (within minutes)	• Nil • Rule out other causes e.g., allergic reaction, AHTR	• STOP transfusion • Discontinue use of ACE inhibitors while patient continues to require transfusions *(Conditional recommendation; low-quality evidence)* • Avoid use of bedside leucocyte filters (*Conditional recommendation; low-quality evidence*) • Notify blood bank lab and return implicated unit of blood component
Septic Transfusion Reaction (Bacterial Contamination)[5,7]	• Fever, rigors, hypotension are the most common signs/ symptoms • May also present with tachycardia, tachypnoea, dyspnoea, nausea, vomiting, shock and disseminated intravascular coagulation • Occurs during or within 4 hours of completion of transfusion	• Gram Stain and culture of blood component, blood culture of patient • Rule out haemolysis (see AHTR)	• STOP transfusion • Prompt clinical assessment of the patient, confirmation of patient's identity • Treat complications (e.g., shock) • Notification of the blood bank lab quickly so that other components from the same donation can be recalled and be subjected to bacterial investigation. Return implicated unit of blood component. • Empirical broad-spectrum antibiotics while awaiting for culture results.
Post Transfusion Purpura[5]	• Thrombocytopaenia arising 5 to 12 days following transfusion	• Human Platelet Antigen (HPA) antibodies	• Consult haematologist if a recipient of cellular blood components develops unexpected severe

	of cellular blood components • Associated clinical features may include widespread purpura, bleeding from mucous membranes, and in severe cases, intracranial haemorrhage and death		thrombocytopaenia in the following 5-12 days after the transfusion • IVIG *(Strong recommendation; low-quality evidence)* • Plasma exchange can be considered if refractory to IVIG *(Strong recommendation; low-quality evidence)* • Platelet transfusions are usually ineffective and not recommended unless life-threatening bleeding
Transfusion Associated Graft Versus Host Disease (TA-GVHD)[5,8]	• Erythematous maculopapular rash, fever, abdominal pain, diarrhoea, hepatitis, pancytopenia, nausea and vomiting • May occur 2 days to 6 weeks after transfusion	• Skin or liver biopsy (skin biopsy is preferred as less invasive) • HLA typing • Molecular chimerism analysis	• Management is supportive as TA-GVHD is nearly always fatal • Immunosuppressants such as corticosteroids, cyclosporin *(Conditional recommendation; low-quality evidence)* • Best is to prevent through irradiation of cellular blood components for patients at risk

Differential Diagnosis of Common Adverse Reactions to Transfusion Based on Presenting Symptoms

Main Symptom	Additional Sign/Symptoms (may not be present all the time)	Adverse Reaction
Fever		Febrile Non-Haemolytic Transfusion Reaction
	Hypotension	Bacterial (Septic) Transfusion Reaction
		Acute Haemolytic Transfusion Reaction
Dyspnoea	Hypertension, tachycardia	Transfusion Associated Circulatory Overload (TACO)
	Hypotension	Transfusion Related Acute Lung Injury (TRALI)
	Rash, urticaria	Anaphylactic Transfusion Reaction
		Transfusion Associated Dyspnoea (TAD)
Urticaria		Allergic Transfusion Reaction
	Dyspnoea, hypotension	Anaphylactic Transfusion Reaction

Haemovigilance

- Haemovigilance is defined by the International Haemovigilance Network 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”.

- The Singapore National Haemovigilance Program was introduced to hospitals through their Hospital Transfusion Committees during the Annual Meeting of Hospital Transfusion Committees in May 2002. The program is voluntary, non-mandatory and non-punitive, to encourage anonymous reporting of adverse reactions and events.
- To ensure accurate reporting and consistency, a standardised haemovigilance reporting form is made available to all participating hospitals for use in reporting adverse events and reactions. The identity of the patient and staff involved are not required, to maintain confidentiality and privacy of information.
- Immediate reporting to the blood transfusion service is essential when bacterial contamination of transfused components may have occurred or when TRALI is suspected, as associated components from the implicated donation must be quickly removed from the blood supply.

References

1. Annual Serious Hazards of Transfusion Report 2020. https://www.shotuk.org/wp-content/uploads/myimages/SHOT-REPORT-2020.pdf. *(Last accessed May 2022) (2020)*
2. Delaney, M., Wendel, S., Bercovitz, R. *et al.* Transfusion reactions: prevention, diagnosis, and treatment. *Lancet* **388**, 2825–2836 (2016).
3. Guidelines For Management of Adverse Transfusion Reactions. *https://www.nzblood.co.nz/assets/Transfusion-Medicine/PDFs/111I015.pdf. (Last accessed May 2022)(2014)*
4. Tinegate, H., Birchall, J., Gray A. *et al.* Guideline on the investigation and management of acute transfusion reactions. Prepared by the BCSH Blood Transfusion Task Force. *British Journal of Haematology* **159**, 143–53 (2012).
5. Cohn, C., Delaney, M., Johnson, S. *et al. Technical Manual*. AABB. (2020).
6. Vlaar, A. P. J., Yoy, P., Fung, M. *et al.* A consensus redefinition of transfusion-related acute lung injury. *Transfusion* **59**, 2465–2476 (2019).
7. Proposed Standard Definitions for Surveillance of Non Infectious Adverse Transfusion Reactions. *https://www.isbtweb.org/isbt-working-parties/haemovigilance/resources.htm. (Last accessed May 2022) (2021)*
8. National Healthcare Safety Network Biovigilance Component Hemovigilance Module Surveillance Protocol. https://www.cdc.gov/nhsn/pdfs/biovigilance/bv-hv-protocol-current.pdf" *https://www.cdc.gov/nhsn/pdfs/biovigilance/bv-hv-protocol-current.pdf. (Last accessed May 2022) (2021)*

Annex 1

RECOMMENDED RED CELL TRANSFUSION TRIGGERS FOR THE NON-HAEMORRHAGIC PATIENTS WITH CHRONIC ANAEMIA

Introduction

Red cell transfusion should not be solely dictated by absolute Hb "trigger levels", but should also be based on the assessment of the patient's overall clinical status. Transfusion decisions should always be guided by individual factors such as bleeding, cardiopulmonary status and intravascular volume status in addition to Hb level. Avoid transfusing blood components without clear physiological indications as the associated risks are likely to outweigh potential benefits.

Where indicated, transfusion of a single unit of RBC, followed by clinical reassessment to determine the need for further transfusion and whether to retest for Hb level, is appropriate.

In patients with iron deficiency anaemia, iron therapy is required to replenish iron stores regardless of whether a transfusion is indicated.

This recommendation only serves as guidance on red cell transfusion indications for common groups of patients (mainly adults) who have chronic anaemia with no significant active haemorrhage, and should be used in conjunction with the HSA-MOH Clinical Practice Guidelines on Clinical Blood Transfusion. **It does not provide guidance on patients with active and acute haemorrhage. It is also not meant to serve as a standard of medical care. It is prudent for clinicians to exercise individual clinical judgement when making transfusion decisions during daily practice.**

Recommendations

(1) General Medical Patients

A restrictive transfusion strategy is recommended in the majority of general medical patients.

- Hb concentration <7 g/dL: RBC transfusion may reduce mortality and is likely appropriate in most instances.

- Hb concentration of 7 to 10 g/dL: RBC transfusion has not been shown to be associated with reduced mortality. The decision to transfuse patients (with a single unit followed by reassessment) should be based on the need to relieve clinical signs and symptoms of anaemia, and the patient's response to previous transfusions. There is no evidence

for patients who are elderly or have respiratory or cerebrovascular diseases, and are stable to be managed differently.

- Hb concentration >10 g/dL: RBC transfusion is likely to be unnecessary and is usually inappropriate. Transfusion has been associated with increased mortality in patients with acute coronary syndrome.

Adapted from:
National Blood Authority, Australia. Patient Blood Management Guideline (2012) Module 3 - Medical. ISBN 978-0-9872519-8-5.

(2) Postoperative Patients

Restrictive transfusion thresholds can be safely applied to the majority of elective postoperative patients with controlled bleeding. For patients without cardiovascular disease, the tolerance for postoperative anaemia is generally good.

In postoperative surgical patients with Hb of 8 g/dL or more, transfusion is generally not indicated if the patient is well and asymptomatic.

In postoperative surgical patients with Hb of between 8 to 10 g/dL and having (i) acute myocardial infarction, (ii) cerebrovascular ischaemia and/or (iii) symptoms of chest pain (suspected cardiac origin), orthostatic hypotension, tachycardia unresponsive to fluid resuscitation, or congestive cardiac failure, transfusion of **a single unit of RBC** followed by reassessment of clinical efficacy, is appropriate.

Adapted from:
1) National Blood Authority, Australia. Patient Blood Management Guideline (2012) Module 2 - Peri-operative. ISBN 978-0-9775298-1-0.

2) Carson J L, Grossman B J, Kleinman S, Tinmouth A T et al. Red Blood Cell Transfusion: A Clinical Practice Guideline From the AABB. Ann Intern Med. 2012; 157: 49-58

(3) Critically Ill Patients – e.g., Intensive Care Unit (ICU) Setting

In critically ill patients, a restrictive transfusion strategy should be employed.

In ICU patients, transfusion should be considered at a Hb of 7 g/dL or less. The presence of specific co-morbidities or acute illness-related factors (see below) may modify clinical decision to transfuse, with a target Hb range of 7-9 g/dL.

Transfusion triggers should not exceed 9 g/dL in most critically ill patients.

- **Traumatic Brain Injury (TBI)**

  There is insufficient evidence to reach an evidence-based conclusion on transfusion triggers:
  (i) In patients with TBI without evidence of cerebral ischaemia, the target Hb of 7 to 9 g/dL should be considered.

(ii) In patients with TBI and evidence of cerebral ischaemia, the target Hb of > 9 g/dL should be considered.

- **Acute Ischaemic Stroke**

There is insufficient evidence to reach an evidence-based conclusion on transfusion triggers. Patients admitted to neurological critical care following an acute ischaemic stroke should be considered for a target Hb of above 9 g/dL.

- **Weaning off Mechanical Ventilation**

Red cell transfusion should not be used as a means to assist weaning from mechanical ventilation when the haemoglobin concentration is above 7 g/dL.

Adapted from:

1) Retter A, Wyncoll D, Pearse D, Mckechnie S et al. BCSH Guidelines on Management of anaemia and red cell transfusion in adult critically ill patients. Brit J Haematol 2013; 160: 445-464.

2) National Blood Authority, Australia. Patient Blood Management Guideline (2012) Module 3 - Medical. ISBN 978-0-9872519-8-5.

(4) Haemodynamically Stable Patients with Pre-existing Cardiovascular Disease

Transfusion should be considered at a Hb concentration of 8 g/dL or less. Transfusion may also be considered for patients with a Hb concentration between 8 to10 g/dL AND have symptoms of chest pain, orthostatic hypotension or tachycardia unresponsive to fluid resuscitation, or congestive cardiac failure.

Adapted from:

Carson J L, Grossman B J, Kleinman S, Tinmouth A T, et al. Red Blood Cell Transfusion: A Clinical Practice Guideline From the AABB. Ann Intern Med. 2012; 157: 49-58

(5) Acute Coronary Syndrome (ACS)

- Hb concentration <8 g/dL: RBC transfusion is likely appropriate.

- Hb concentration 8 to 10 g/dL: RBC transfusion has uncertain effects on mortality and has not been shown to be associated with an altered mortality risk. Any decision to transfuse should be based on careful consideration of the risks and benefits, taking into account the patient's clinical condition and symptoms.

- Hb >10 g/dL: RBC transfusion is not advisable because of a potential association with increased mortality**.**

Adapted from:

1) National Blood Authority, Australia. Patient Blood Management Guideline (2012) Module 3 - Medical. ISBN 978-0-9872519-8-5.

2) Retter A, Wyncoll D, Pearse D, Mckechnie S et al. BCSH Guidelines on Management of anaemia and red cell transfusion in adult critically ill patients. BJH 2013; 160: 445-464.

(6) Heart Failure

There is an increased risk of transfusion associated circulatory overload in patients with heart failure. If RBC transfusion is indicated, this should be carried out one unit at a time followed by reassessment of clinical response and fluid status after each unit. Patients with iron deficiency should have iron replacement therapy.

- Hb concentration <7 g/dL: RBC transfusion is appropriate.

- Hb concentration 7 to 10 g/dL: The decision to transfuse patients with Hb of 7 to 10 g/dL should be based on the need to relieve clinical signs and symptoms of anaemia, and the patient's previous response to transfusions. No evidence has been found to warrant a different approach for patients who are elderly or have respiratory or cerebrovascular diseases.

- Hb concentration >10 g/dL: RBC transfusion is usually unnecessary and inappropriate.

Adapted from:
National Blood Authority, Australia. Patient Blood Management Guideline (2012) Module 3 - Medical. ISBN 978-0-9872519-8-5.

(7) Cancer & Chemotherapy-Induced Anaemia

In patients with cancer, the aetiology of anaemia is often multi-factorial. Where appropriate, reversible causes should be identified and treated. The anaemia associated with cancer can be due to anaemia of chronic disease, myelosuppressive chemotherapy and / or nutritional deficiencies.

The goal of anaemia treatment, including the option of red cell transfusion, is to prevent or treat a deficit of oxygen carrying capacity, as well as correct haemodynamic instability. Any decision to transfuse should be based on the need to relieve clinical signs and symptoms of anaemia.

- **Asymptomatic Anaemia**

  For patients with haemodynamically stable chronic anaemia and no acute coronary syndrome, the target is to maintain a Hb concentration of 7 to 9 g/dL.

  Significant co-morbidities (Congestive Cardiac Failure, Coronary Heart Disease, Cerebrovascular Disease, Chronic Pulmonary Disease) and high-risk situations (progressive decline in Hb with recent chemotherapy or radiation) should be considered when deciding on the transfusion trigger.

- **Symptomatic Anaemia**

  This generally follows the guidelines of other groups of patients as detailed in the previous parts of this document.

Adapted from:

1) National Comprehensive Cancer Network, USA. NCCN Guidelines in Oncology, Cancer and Chemotherapy Induced Anaemia Version 2.2014. Retrieved 27 Sep 2013 from www.nccn.org/professionals/physician_gls/pdf/anemia.pdf

2) National Blood Authority, Australia. Patient Blood Management Guideline (2012) Module 3 - Medical. ISBN 978-0-9872519-8-5.

(8) Chronic Transfusion Dependent Patients

This refer to patients who require frequent and long-term red cell transfusions. Leucocyte-reduced blood components (including red cells) are recommended.

- **Thalassaemia Major**

  Maintain a target pre-transfusion Hb of at least 9 to 10 g/dL. This is usually achieved with red cell transfusions of 3 to 4 weekly intervals.

- **Myelodysplastic Syndrome (MDS)**

  There is no evidence to guide any particular target Hb in patients with MDS who are regularly and chronically transfused.

  Decisions on appropriate triggers and frequency of transfusion need to be individualised, taking into account symptoms from anaemia, patient's performance status and response to previous transfusions.

Adapted from:

National Blood Authority, Australia. Patient Blood Management Guideline (2012) Module 3 - Medical. ISBN 978-0-9872519-8-5.

(9) Red Cell Transfusion in the Non-haemorrhagic Pregnant Patient

The decision to transfuse women in the postpartum period is based on presence of bleeding risk, cardiac compromise or symptoms requiring urgent correction. Whenever possible, iron therapy should be considered as an alternative. Fit, healthy, asymptomatic patients are unlikely to require blood transfusion.

Timely recognition and treatment of iron deficiency (with iron replacement therapy) will likely reduce the need for blood transfusions in the antenatal period.

Adapted from:

British Committee on Standards in Haematology, UK (2011). Guidelines on the management of iron deficiency in pregnancy. Retrieved 27 Sep 2013 from www.bcshguidelines.com/documents/UK_Guidelines_iron_deficiency_in_pregnancy.pdf

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References

- Carson J L, Grossman B J, Kleinman S, Tinmouth A T et al. Red Blood Cell Transfusion: A Clinical Practice Guideline From the AABB. Ann Intern Med. 2012; 157: 49-58.

- National Blood Authority, Australia. Patient Blood Management Guideline (2012) Module 3 - Medical. ISBN 978-0-9872519-8-5. Retrieved 27 Sep 2013 from www.blood.gov.au/pbm-module-3.

- National Blood Authority, Australia. Patient Blood Management Guideline (2012) Module 2 - Peri-operative. ISBN 978-0-9775298-1-0. Retrieved 27 Sep 2013 from www.blood.gov.au/pbm-module-2.

- National Comprehensive Cancer Network, USA. Cancer and Chemotherapy Induced Anaemia Version 2.2014. NCCN Guidelines for Supportive care. Retrieved 27 Sep 2013 from www.nccn.org/professionals/physician_gls/pdf/anemia.pdf

- Retter A, Wyncoll D, Pearse D, Mckechnie S, et al. BCSH Guidelines on Management of anaemia and red cell transfusion in adult critically ill patients. Brit J Haemtol 2013; 160: 445-464.

- British Committee on Standards in Haematology, UK (2011). Guidelines on the management of iron deficiency in pregnancy. BCSH Guidelines. Retrieved 27 Sep 2013 from www.bcshguidelines.com/documents/UK_Guidelines_iron_deficiency_in_pregnancy.pdf

Other useful literature

- Herbert P C, Wells G W, Blajchman M A, Marshall J et al. A Multi-Center, Randomised Controlled Clinical Trial of Transfusion Requirements in Critical Care. N Engl J Med 1999; 340: 409-417.

- Hajjar L, Vincent J L, Galas F R B G, Nakamura R E, et al. Transfusion Requirements After Cardiac SurgeryThe TRACS Randomized Controlled Trial. JAMA 2010: 304: 1559-1568.

- Corwin H L, Gettinger A, Pearl R G, Fink M P, et al. CRIT Study: Anemia and blood transfusion in the critically ill - current clinical practice in the United States. Critical Care Med. 2004; 32: 39-52.

- Carson JL, Terrin ML, Noveck H, Sanders DW, et al. Liberal or restrictive transfusion in high-risk patients after hip surgery. N Engl J Med 2011; 365: 2453-62.

- Holst LB, Haase N, Wetterslev J, et al.: Lower versus Higher Hemoglobin Threshold for Transfusion in Septic Shock. N Eng J Med 2014; 371:1381–1391.