MOH/P/PAK/537.24(GU)-e

Consensus Statement ON PATIENT BLOOD MANAGEMENT

MEDICAL DEVELOPMENT DIVISION
MINISTRY OF HEALTH MALAYSIA

Ministry of Health Malaysia
National Blood Centre of Malaysia
Malaysian Transfusion Blood Society

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FOREWORD

Director General *of* Health Malaysia

Patient Blood Management (PBM) program employs a multidisciplinary, evidence-based, patient-centered strategy to improve patient outcomes by managing and preserving their own blood. This approach is implemented through a personalized management plan that revolves around three pillars of PBM: screening, diagnosing, and treating anaemia; minimizing blood loss during procedures; and optimizing the patient's tolerance to anaemia. PBM should be the standard of care in all clinical fields, especially when dealing with patients in medical or surgical areas who require interventions and are at high risk of bleeding.

Anaemia and iron deficiency are recognized as public health issues affecting both poor and developed countries. The prevalence of anaemia spread through all walks of life from children to adult and also elderly individuals. However, children, women, and pregnant women are the most affected by the devastating effects of anaemia. Preoperative anaemia is independently associated with an increased risk of morbidity & mortality and it also can increase the likelihood of red blood cell transfusion. Effective anaemia management can improve patient outcomes and reduce morbidity and mortality. The first pillar of PBM requires the implementation of a framework to address early anaemia screening, establish diagnosis, and institute early and appropriate treatment. Yet this is often overlooked by the medical personnel. Hence, there is an urgent need to address this issue throughout the healthcare system, starting from primary care settings up to reference centers.

Patient Blood Management is an integral part of patient safety initiative and good clinical practice. All stakeholders must work together for optimization of strategy to minimize unnecessary exposure to blood products and better patient outcome. Support and commitment from all stakeholders will be required to ensure the success of the PBM implementation in Malaysia.

Having this first Consensus of PBM published marked a new era of PBM implementation in the country and showed the level of commitment from Ministry of Health to embark on this PBM journey. It is my greatest hope that this consensus will pave the way to a more systematic PBM program implementation in all clinical disciplines towards the betterment of service to our patients. It will indeed help to improve the coordination of the existing initiatives pertaining to patient centered care, patient safety and quality of care.

DATUK DR MUHAMMAD RADZI BIN ABU HASSAN

FOREWORD

Deputy Director General *of* Health (Medicine) Malaysia

It is with great pride and enthusiasm that I introduce our first National Patient Blood Management (PBM) Consensus. As we navigate through the ever-evolving landscape of healthcare, it is imperative that we remain committed to deliver the highest standards of patient care, and PBM stands as a shining example of this commitment.

Patient Blood Management is more than a set of principles; it is a comprehensive approach that encapsulates the essence of quality healthcare. In a world of ever-increasing medical complexities, PBM offers a beacon of clarity. It prioritizes the welfare of patients, making them active partners in their own healing journey.

The three fundamental pillars of PBM — (1) optimizing anaemia management, (2) minimizing blood loss, and (3) harnessing and conserving a patient's own blood — are the cornerstones upon which this approach rests. These pillars provide a framework for healthcare professionals to implement PBM principles in their daily practice.

This PBM Consensus is the culmination of the collective efforts of a multidisciplinary team of all clinical disciplines involved, each contributing their expertise to ensure that every patient is entitled to individualized, evidence-based management. It reflects a commitment to patient-centered care that acknowledges the contributions of every member of the healthcare team.

The benefits of PBM are profound and far-reaching. By adopting PBM principles, healthcare providers can enhance patient outcomes, reduce hospital stays, and, most importantly, ensure patient safety. Additionally, it offers a cost-effective solution that not only saves resources but also leads to long-term financial efficiencies in healthcare institutions.

I encourage healthcare institutions to embrace the recommendations and practice points outlined in this Consensus and to identify clinical champion of PBM within their organizations. This proactive approach will undoubtedly improve patient care and reduce healthcare costs, ultimately serving the best interests of both patients and healthcare providers.

Patient Blood Management is not just a guideline; it is a commitment to excellence in patient care. It is a pledge to prioritize the well-being of patients, to reduce risks, and to enhance the quality of healthcare services. As we explore the pages of this book, let us embark on a journey that ultimately elevates the standards of care for patients around the world.

DATO' INDERA DR NOR AZIMI BINTI YUNUS

FOREWORD

Director
of National Blood Centre

Blood transfusion is recognized as one of the important treatment modalities for planned treatment and to save a patient's life. However, allogeneic blood transfusion until today is not risks-free particularly transfusion transmissible infection, transfusion related acute lung injury (TRALI), anaphylactic reaction and other transfusion reaction complications. Therefore, blood transfusion should be used with adequate clinical justification weighing between the benefits and its risks.

Patient blood management (PBM) concept is another milestone in medicine where its play a role to avoid unnecessary blood transfusion by implementing other treatment modalities to optimize patient care for patients who may require blood transfusion. Thus, blood transfusion is reserved for those patients who are really required based on clear clinical justification.

With the ultimate goal of doing no harm to the patient, PBM is believed able to improve patient safety and optimize the patient care. With PBM concept, multidisciplinary involvement from healthcare provider is top priority to ensure the rhythm is synchronized to achieve the same target goal.

Therefore, the first consensus on PBM document is developed by an expert from multidisciplinary representative to assist healthcare provider involved in implementing PBM concept in their daily patient management. As a result, patient will benefit the best patient outcome with minimizing transfusion-related complications. This document is designed with evidence based, suite to our local practice and provides valuable information on recommendations & practical information on PBM.

With publication of this consensus on PBM document, I hope it would assist all involved healthcare provider to understand more the idea of PBM. Thus, they can offer the best treatment to their patient and blood transfusion is transfused judicially.

Lastly, we extend our heartfelt appreciation to the former Director of the National Blood Centre, Dr Afifah binti Haji Hassan, for their invaluable contribution to the development of this Consensus Statement of PBM.

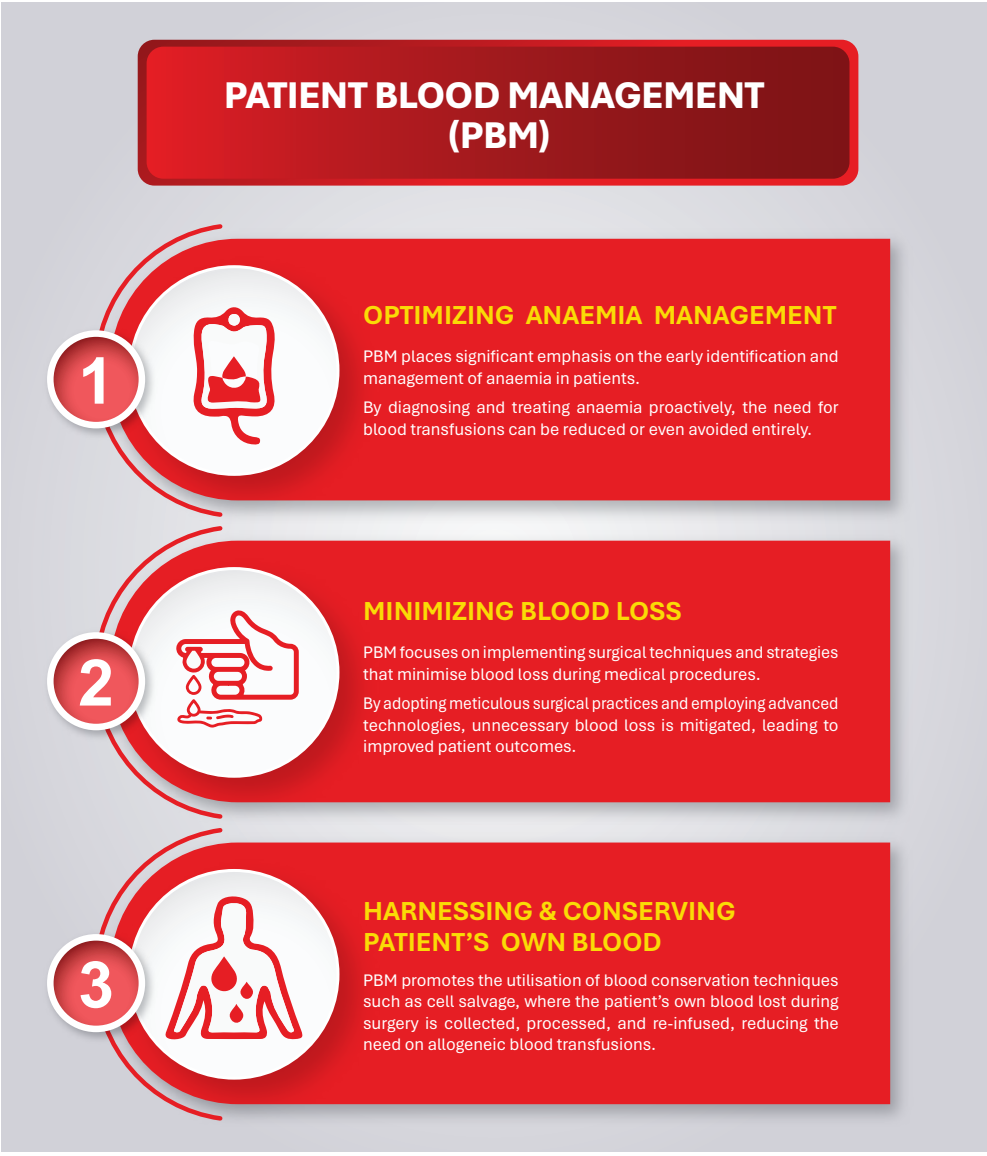
DR MOHAMMAD MASRIN BIN MD ZAHRIN

CONTENTS

INTRODUCTION

Introduction

Patient Blood Management (PBM) is a holistic and patient-centered approach to optimise the care of patients especially those who are at risk of blood transfusion or facing anaemia-related challenges. PBM is an evidence-based paradigm emphasises preserving the patient's own blood and minimising the need for transfusions, thereby ensuring better outcomes while enhancing safety and effective utilisation of medical resources, ultimately leading to reduced healthcare costs.



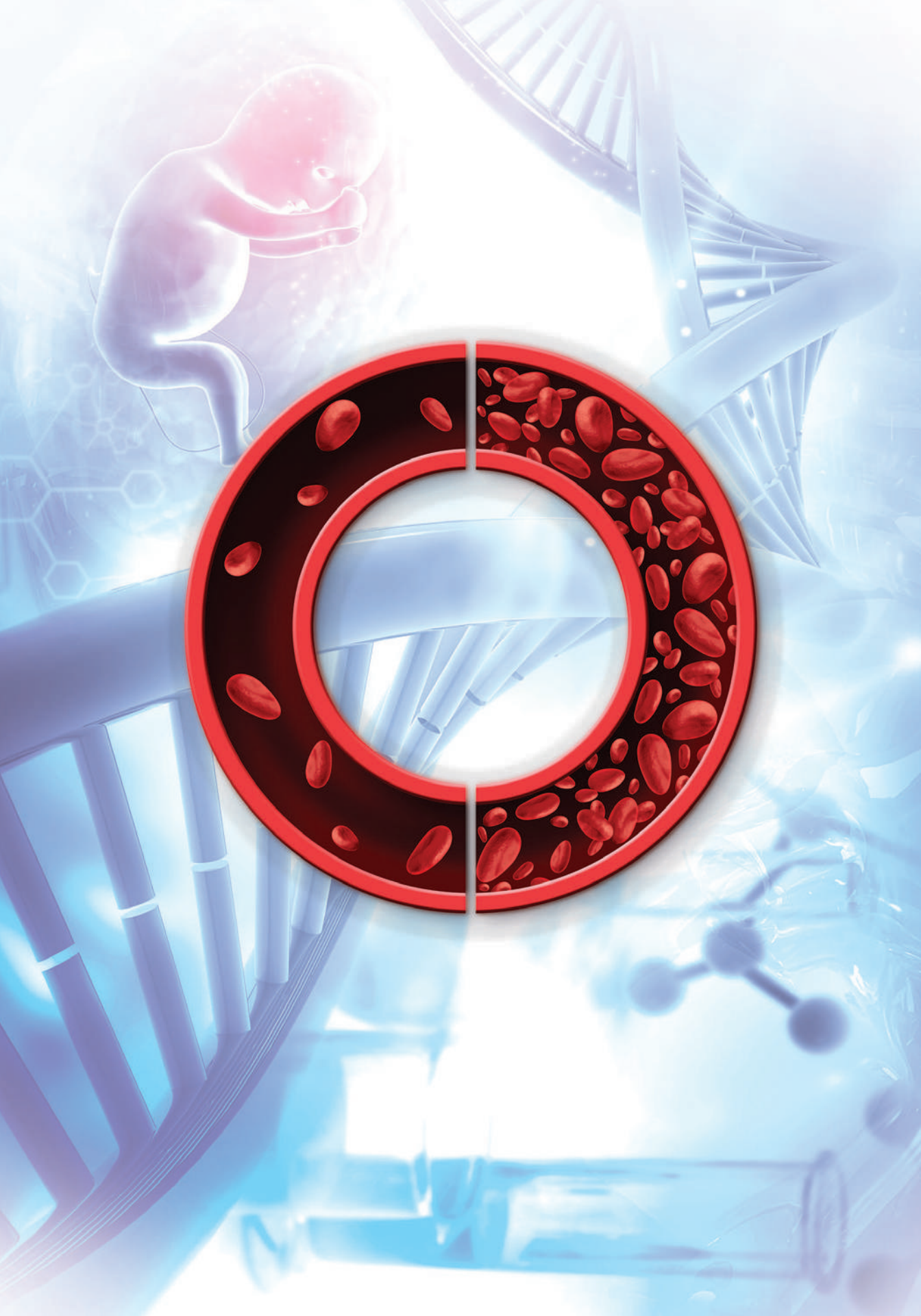
Benefits of Patient Blood Management

The implementation of PBM offers numerous benefits for patients as well as the healthcare providers. Some of the key advantages include **Improved Patient Outcomes:** leading to better patient outcomes and shorter hospital stays; **Enhanced Patient Safety:** minimise the risks associated with transfusions, such as infections and immune reactions. **Cost-effectiveness:** healthcare institutions can potentially reduce the costs associated with blood transfusions, including procurement, storage, testing and handling. PBM offers a sustainable approach that optimises resource utilisation and promotes long-term cost savings.

Forward Moving

The future of PBM lies in continual research and technological advancements. As medical science progresses, PBM aims to further enhance anaemia management, refine blood conservation techniques, and develop innovative approaches to reduce blood loss during medical procedures. By integrating cutting-edge technologies and evidence-based practices, PBM strives to become an indispensable aspect of patient care, improving medical outcomes and ensuring the well-being of patients around the world. A subcommittee championing PBM should be formed under the Hospital Transfusion Committee. This committee should be a champion in advocating PBM implementation in the hospital or local setting.

In conclusion, Patient Blood Management is a comprehensive and patient-centric approach to medical care, emphasising anaemia management, minimizing blood loss, and conserving a patient's own blood. The implementation of PBM leads to improved patient outcomes, enhanced safety, and cost-effectiveness in healthcare settings. The importance of practicing PBM cannot be overstated, and its future lies in a continual drive for excellence through research and medical advancements.



SUBMODULE 1

OBSTETRICS & GYNAECOLOGY

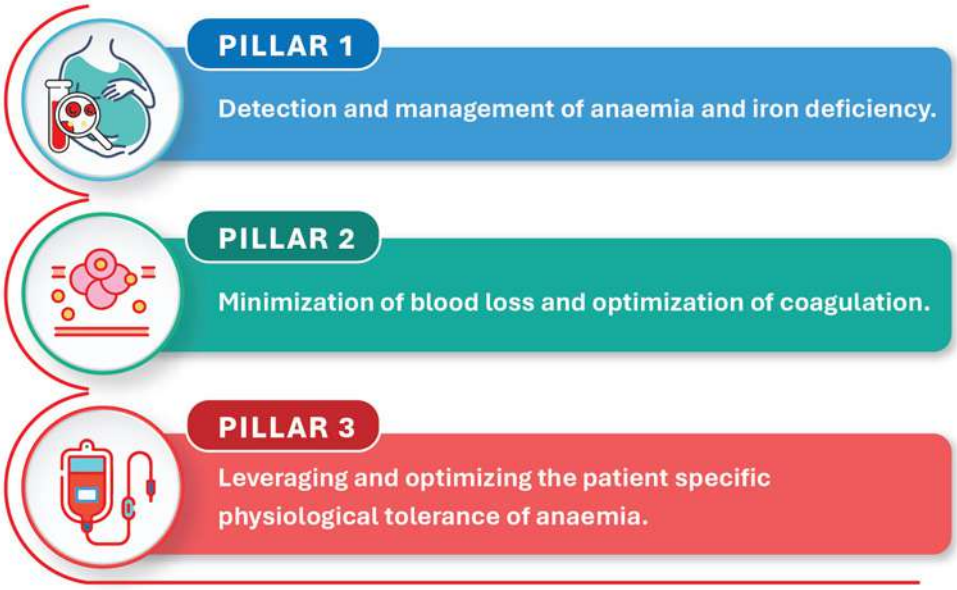
1.1 INTRODUCTION

Anaemia is a major health challenge which affects more than 500 million women in their reproductive age worldwide[1]. The overall prevalence of anaemia in pregnancy in Malaysia was reported to range between 19.3 and 57.4%[2] with 47.7 to 61.1%[3,4] being attributed to iron deficiency (ID). As 30% of women of reproductive age have iron deficiency anaemia (IDA) in Malaysia, it was estimated that 90% of them probably has underlying small or absent iron reserves[5]. Another study has shown that the prevalence of anaemia in women was twice than the men and IDA thrice in premenopausal compared to postmenopausal women. About 70% of all aneamia in premenopausal, 24.2% in postmenopausal and 20% of men is attributed to ID[6].

Anaemia in pregnancy is associated with significant increase in morbidity and mortality. Known consequences of maternal anaemia include preterm delivery, low birthweight, perinatal mortality and postpartum haemorrhage (PPH).

This PBM guideline on Obstetrics and Gynaecology focuses primarily on the management of anaemia in obstetrics as well as in certain gynaecological conditions such as heavy menstrual bleeding (HMB). The aim of this guideline is to improve maternal, fetal and neonatal outcome together with women's health in general.

The development PBM guideline on Obstetrics and Gynaecology is based on 3 main pillars:



The implementation of PBM in obstetrics and gynaecology must be multi-pronged which includes systematic and comprehensive approach at healthcare settings and hospitals. As medical, surgical and interventional modalities are important elements in managing as such, PBM will be a paradigm shift in addressing iron deficiency anaemia (IDA) and its complications.

This guideline is developed by referring and adapting the Australian Patient Blood Management Module 5 Obstetrics and Maternity National Blood Authority 2015[8]. In addition, multiple literatures were reviewed from the years 2016 till 2021. The consensus and recommendation were incorporated to the development of this guideline to ensure guidance of good clinical practice among clinicians.

1.2 CLINICAL GUIDANCE

1.2.1 PURPOSE AND AUDIENCE

This guideline is intended to guide and assist the healthcare professionals in prevention, detection and management of obstetrics and gynaecological patients.

1.2.2 SPECIFIC MANAGEMENT ISSUES

I. Definition of Anaemia in Obstetrics and Gynaecological Patients

- The haemoglobin concentration to define anaemia in pregnant women is adopted from the WHO guideline (based on historical values derived from non-pregnant population), which is haemoglobin level below 11 g/dL[9]. The severity of anaemia can be further classified into **Table 1.1**:

Table 1.1: Classification of Anaemia Severity

	Mild	Moderate	Severe
Haemoglobin (g/dL)	10 to 10.9	7 to 9.9	< 7.0

- WHO recognizes that *'mild'* is a misnomer as ID is already advanced by the time anaemia is detected, and that ID has consequences even when no anaemia is detected.
- In postnatal and non-pregnant women, anaemia is defined as haemoglobin level below 10 g/dL and below 12 g/dL respectively[9,10].
- Early detection and prevention of anaemia during pregnancy is crucial to avoid unnecessary blood transfusion and reduce morbidity. Such initiative includes screening for and treatment of ID even in the absence of anaemia to ensure favourable pregnancy outcome[10,11,12].

- Appropriate management of ID is pertinent as current guidelines now recommend targeting haemoglobin of more than 13 g/dL in patients undergoing major surgery, irrespective of gender[13]. Furthermore, the British Committee for Standards in Haematology recommends iron supplementation in patients with ID who are planned to undergo surgery with a predicted haemoglobin loss of more than 3 g/dL[14] (for example, > 1000 ml in 60 kg adult).
- We consider pregnant women to be in this group as they are at risk for operative births and major PPH. Data from Malaysian government tertiary hospitals showed an increasing trend in caesarean section over 5 years (2011 – 2015) period with rates up to 31.5%[15]. As such, when iron therapy is required, we deem it prudent to aim for higher haemoglobin level at least 13 g/dL in both obstetrics population and gynaecological patients due for surgery to prevent poor outcome[13].
- Postpartum haemoglobin investigation should be individualized based on clinical assessment; for example, pre-existing anaemia or incidence of PPH during delivery. Postpartum anaemia must be managed with appropriate iron administration and efforts taken to optimize patient's physiological response to anaemia, treat any underlying infection, and maximize systemic oxygen delivery to minimize transfusions[16].
- Routine haemoglobin investigation is recommended at 1 month postpartum during postnatal checkup.

II. Definition of Postpartum Haemorrhage (PPH) and Massive PPH

- PPH can be divided into primary or secondary[17]:
  - Primary PPH occurs within the first 24 hours after delivery.
  - Secondary PPH occurs after 24 hours till 6 weeks post-delivery.
- Traditionally, PPH is defined as blood loss more than 500 ml following vaginal delivery and 1000 ml after abdominal delivery[17]. A more practical clinical definition of PPH is any blood loss sufficient enough to cause haemodynamic instability.
- Massive PPH is defined as PPH with blood loss more than 1500 ml[17].
  - PPH should be detected early, and the Massive Transfusion Protocol (MTP) should be initiated in this event.
  - All delivery units should have an established MTP protocol in place.

1.2.3 MANAGEMENT OF ANAEMIA AND IRON DEFICIENCY

PILLAR 1

Detection and management of anaemia and iron deficiency.

Anaemia must be managed effectively during pregnancy by early detection. Full blood count should be checked at booking and at 35 to 36 weeks, besides monthly haemoglobin level and at 1 month postpartum. However, a more frequent haemoglobin assessment (every 2 to 4 weeks) may be necessary to monitor the response to iron therapy.

Women with heavy menstrual bleeding should have their haemoglobin level measured. Anaemia should be appropriately investigated and should be treated accordingly based on the underlying cause.

1.2.3.1 The Laboratory Tests

The laboratory tests include[10,18]:

1. Full blood count
2. Serum Ferritin
3. Serum Iron, Total Iron Binding Capacity (TIBC) and Transferrin Saturation (TSAT) may be required when there is anaemia of inflammation / iron sequestration.
4. Reticulocytes haemoglobin equivalent (RET-He) if available can replace Ferritin and Iron study.

The laboratory diagnosis for ID can be summarized as in **Table 1.2:**

Table 1.2: Summary of laboratory diagnosis for ID

Test	Formula	Interpretation
Serum Ferritin (µg/L)	-	Level less than 30 µg/L confirms IDA. However, serum ferritin is labile and will increase in an inflammatory state or hepatocellular injury. Level less than 100 µg/L also indicates low iron store and should receive iron therapy. Level more than 100 µg/L with TSAT value less than 20% may indicate ID in an inflammatory state.
TSAT (%)	Serum Iron/TIBC × 100	Level less than 20% is suggestive of inadequate iron supply for haemoglobin synthesis and red cell production. Level less than 15% is characteristic but not diagnostic of ID unless combined with serum ferritin.
RET-He (pg)		Level less than 27.2 pg is suggestive of iron deficiency.[19]

Anaemia that is not due to nutritional deficiency (for example haemoglobinopathies and bone marrow failures syndromes) should be managed with a physician or haematologist.

1.2.3.2 Treatment for Iron Deficiency Anaemia (IDA)

Treatment may include nutritional supplements and pharmacological agents as below:

a. Oral iron supplements
b. Parenteral iron
c. Concurrent treatment with anthelminthics if indicated
d. Combination of iron and folic acid
e. Combination of iron and Erythropoietin Stimulating Agent (ESA)

For thalassaemia carriers, iron deficiency status should be confirmed before commencing iron therapy.

a. Oral iron supplements

Prophylaxis iron supplements

All pregnant women should be given daily oral iron supplements, beginning as early as possible if tolerated[20]. The recommended dose of elemental iron is 40-80 mg once daily[10]. If the woman is unable to tolerate daily dosing, every other day (EOD) dosing can be considered as more recent studies suggest benefits[10]. Divided dosing (example twice daily) should be avoided because this will increase serum hepcidin and reduces iron absorption. Pregnant women should be counselled on how to take oral iron supplements correctly. It should be taken on empty stomach, preferably with orange juice or water with vitamin C supplements.

Therapeutic iron for iron deficiency

For IDA, iron therapy must be optimized. Oral iron should be the preferred first line treatment unless there is an urgency to correct anaemia. The recommended dose of elemental iron is 100–200 mg once-daily[10]. This should be taken in the morning when hepcidin levels are lowest. More than once-daily dosing of elemental iron would not improve efficacy as it may reduce gastrointestinal (GI) absorption and induce GI intolerance[10].

The expected rise in haemoglobin level is at a rate of 1.0 – 2.0 g/dL per month and iron supplementation should be continued for 6 months after normalization of haemoglobin level to allow replenishment of iron storage[21].

Examples of common iron supplements available in Malaysia are shown in **Table 1.3.**

Table 1.3: Common oral iron supplement preparations available in Malaysia

Iron Tablet Product (Type of Iron)	Iron Content Per Tablet (mg)	Elemental Iron Content (mg)
Ferrous Fumarate	200	60
Zincofer (Ferrous Fumarate)	350	115
Iberet Folic (Ferrous Sulphate)	525	105
Maltofer **(Iron (III) - hydroxide Polymaltose Complex)**	370	100
Ferrovit (Ferrous Fumarate)	162	53.25
Ferrocyte (Sulphate Ferrous Citrate)	470.9	50
Obimin (Ferrous Fumarate)	90	30
Sangobion (Ferrous Gluconate)	250	30

Compliance of medication and its benefits to women and children should be emphasized during patients' encounter.

b. Parenteral iron

Parenteral iron is indicated for those with moderate to severe IDA from the second trimester onwards who fail to respond to, or intolerant of oral iron supplements, or have issues with non-compliance[10]. The parenteral iron preparations available in Malaysia are as shown in **Appendix Table 1.4 (Refer Appendix 1)**[21,22].

Parenteral iron is safe to be used to rapidly correct anaemia but should be avoided in the first trimester due to uncertain fetal effects[10,11]. Parenteral iron of 200 mg increases haemoglobin level by 1.5 to 2.0 g/dL per week. It must be administered via intravenous route only[10]. Intramuscular (IM) administration is not recommended due to unreliable absorption, pain at injection sites and potential skin staining after the injection[10].

For parenteral iron therapy, iron deficit and target haemoglobin should be taken into consideration when calculating the replacement dose using the Ganzoni Formula as shown in **Table 1.5.**

Table 1.5: Parenteral Iron Replacement Calculation

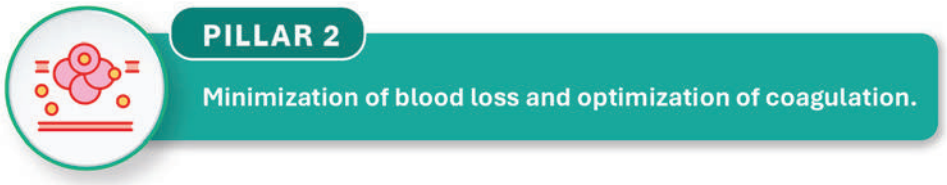
Ganzoni Formula
Iron dosage = Haemoglobin deficit (g/dL) x 2.4 x body weight (kg) + 500 mg iron store

The maximum single dose infusion calculation is 20 mg/kg, except for iron sucrose which is 7mg/kg.

c. Erythropoietin Stimulating Agent (ESA)

Consider the use of ESA in a woman with moderate to severe anaemia who does not respond to parenteral iron after consultation with a haematologist[20]. ESA should be used in combination with iron therapy[8].

1.2.4 USE OF BLOOD CONSERVATION STRATEGIES



1.2.4.1 Minimising Intrapartum Blood Loss

Modified active managements of third stage of labour are advocated[17]

- Prophylactic IM injection of 10 IU oxytocin or IV oxytocin 5 IU slow bolus or IM Syntometrine 500 µg/5 IU (if not contraindicated) is administered after delivery of anterior fetal shoulder
- Delayed cord clamping, not earlier than 1 minute but before 5 minutes from fetal delivery
- Palpate the uterus and ensure it is well contracted
- Deliver the placenta via controlled cord traction (CCT)
- Document the timing of placental delivery

- Examine the placenta and membranes for completeness
- Estimate and document the blood loss. This can be done using a pictogram on blood loss available in Malaysian PPH training manual
- Avoid hypothermia and acidosis

1.2.4.2 Tranexamic acid (TXA)

- The use of TXA in all cases of PPH must be given as early as possible and within 3 hours of the onset of PPH[16,24,27,38]. This may decrease the maternal mortality secondary to PPH and reduce the need for laparotomy to control the bleeding[24].
- It also can be used as prophylactic in addition to uterotonic agents in high-risk group of patients (patient who refuses blood products, patient with significant risk of PPH example placenta praevia, morbidly adherent placenta or patient with previous history of PPH)[26].
- The dose and timing of TXA administration is elaborated in **Table 1.6.**

Table 1.6: Administration of TXA in PPH

Dose and Timing of TXA Administration
Loading dose[17]: Infusion of 1 g in 100 ml 0.9% NaCl over 10 minutes **Maintenance dose[17]:** Infusion of 1g in 100 ml 0.9% NaCl over 8 hours *Or* Infusion of 1g in 10 ml 0.9% NaCl (100 mg/ml) at infusion rate of 1 ml/min over 10 minutes, with second dose of IV 1 g if bleeding persists after 30 minutes or if bleeding restarts within 24 hours of completing the first dose[24,25].
Slow infusion of TXA is required because infusion rate of > 1 ml/min carries potential risk of transient hypotension[17,24,25,26,27].

- The effect of TXA may last for 7 to 8 hours in the serum.
- A delay in treatment with TXA appears to reduce the benefit for management of PPH. The benefit appears to decrease by 10% for every 15-minute delay, with no benefit seen after 3 hours[16,24].

1.2.4.3 Point of Care Testing (POCT)

- If available, POCT such as Rotational Thromboelastometry (ROTEM) and Thromboelastography (TEG) allow rapid bedside assessment of all stages of coagulation[7,22].
- It has been shown to safely guide transfusion of blood products especially in massive bleeding.
- ROTEM and TEG can be used as a surrogate measure for fibrinogen level.

1.2.4.4 Cell Salvage

- Cell salvage involves the collection of blood lost during surgery, followed by reinfusion of the washed red blood cells (RBCs) which aims to reduce allogeneic transfusion and transfusion-related adverse events. Cell salvage is cost-effective in patients who are predicted to have high rates of transfusion[8,16].
- With advances in cell salvage technology, the risks of cell salvage in the obstetrics population are similar to the general population. Leukofiltration used in the cell salvage procedure reduces the amount of amniotic fluid contaminants in transfused blood to levels approaching those found in maternal blood (single or double filters has similar outcome).

1.2.4.5 Interventional Radiology

- In a haemodynamically stable patient, where interventional radiology service is readily available, embolization of the uterine arteries or internal iliac balloon occlusions are adjunct measures that can be used to manage severe postpartum blood loss and conserve fertility[7,16,26].
- Refer to the 'Training Manual for PPH (2016) for further information on more specific management of PPH[16].

1.2.4.6 Activated Factors

- Recombinant Factor VIIa (rFVIIa) is not licensed for massive bleeding in maternal population in Malaysia. As such, rFVIIa usage should be limited to massive bleeding where standard obstetrics, surgical, radiological and transfusion interventions have failed[7,17].
- The pre-requisites are[17]:
  - Haematocrit >24%
  - Fibrinogen >0.5-1.0 g/L (where available)
  - Platelets >50 x 10^9 /L
  - pH ≥ 7.2
- rFVIIa should be used in consultation with a haematologist as it may be associated with complications.

1.2.5 MANAGING ANAEMIA

PILLAR 3

Leveraging and optimizing the patient specific physiological tolerance of anaemia.

1.2.5.1 High Threshold for Blood Transfusion

Consensus for red cell transfusion for non-bleeding obstetrics patients[8,16,17,21] as mentioned in **Table 1.7**:

Table 1.7: Practice Points on Red Cell Transfusion for Non-Bleeding Obstetrics Patients

Haemoglobin Level	Recommendation
> 9g/dL	Red cell transfusion is usually inappropriate.
7–9 g/dL	Red cell transfusion is not associated with reduction in mortality. The decision to transfuse should be based on the need to relieve clinical signs and symptoms of anaemia, the availability of other therapies, the expected time frame before delivery and risk of haemorrhage.

Haemoglobin Level	Recommendation
< 7g/dL	Red cell transfusion may be appropriate as it may reduce mortality. However, it may not be required in well-compensated patients, or where other specific therapy is available.

When transfusion is required in the absence of massive haemorrhage, **a single unit transfusion policy** is recommended[8].

1.2.5.2 Heavy Menstrual Bleeding (HMB)

- Treatment for HMB is aimed to reduce blood loss by focusing on the appropriate management of its underlying causes.
- Specialist referral is recommended for early evaluation and timely intervention[28,29].
- There are 3 measures to be taken in treating patients with HMB:

  a. Non-pharmacological measures and lifestyle modifications to reduce body mass index (BMI) help to improve ovulatory dysfunction[30].

  b. Pharmacological treatment.

  c. Surgical intervention.

i. Non-Hormonal Treatment

a. Antifibrinolytics for example Tranexamic acid effectively reduces menstrual blood loss by 50% [30,35].

b. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) effectively reduces menstrual loss with additional benefits of analgesics properties[30].

ii. Hormonal Treatment

a. Levonorgestrel-releasing intrauterine system (LNG-IUS) is the first-line treatment for women with no identified gynaecological pathology. It has superior efficacy to oral treatment. It decreases menstrual loss by up to 96% after one year of use with no increased risk of thrombosis[30,31,36].

b. Cyclical combined oral contraceptive pill (COCP) reduces menstrual loss by 50%. It regulates menstrual cycles and improves dysmenorrhoea and acne[30,36].

c. Cyclical oral progestogens for example Norethisterone is highly effective in HMB and regulates menstrual cycle. They are usually used as a short-term therapy due to their progestogenic side effects[30,36].

d. Injectable progestogens for example DMPA (Depot Medroxyprogesterone Acetate) effectively induces amenorrhoea in up to 50% of users and reduces dysmenorrhoea[30].

e. Gonadotrophin-releasing hormone (GnRH) analogues effectively control heavy menstrual bleeding and hence boosts iron stores as well as facilitates less blood loss at surgery. The effect of estrogen deficiency limits its uses, but this can be treated with estrogen add-back therapy[30,32,33].

iii. Surgical Treatment

a. Hysteroscopy offers the benefits of a diagnostic and therapeutic modality at the same setting if endometrial pathology or uterine cavity abnormality is suspected[31,34].

1.2.6 SPECIAL GROUPS

- High risk groups for anaemia include without or with inadequate antenatal care, those with background history of nutritional anaemia, patients with no or infrequent antenatal care, low socioeconomic status and illiterate.
- Other high risk patients include those with bleeding disorders, on anticoagulants or poor treatment adherence and those at risk of PPH (e.g. multiple pregnancies, multiparity, placenta previa, past history of retained placenta or PPH, and others).

1.3 OTHER CONSIDERATIONS

1.3.1 SCREENING FOR RED CELL ANTIBODY

- Besides routine ABO and RH blood grouping at booking, pregnant women should also be screened for other alloantibody.

- Follow-up screening for RhD negative women and women with alloantibody is essential as this is associated with Haemolytic Disease of the Fetus and Newborn (HDFN).
- Women with antibody associated with moderate and severe HDFN should have an immediate consultation with a Maternal Fetal Medicine (MFM) specialist[37].
- Patients with clinically significant alloantibody should have a blood grouping and antibody identification done at booking, repeated at 28 weeks and in labour. If antibody was identified, they should be referred to a MFM specialist for diagnosis and monitoring of fetal anaemia[37].

1.3.2 MASSIVE TRANSFUSION PROTOCOL (MTP)

- Each Obstetrics & Gynaecology department must develop and maintain a MTP that includes access to RBC and the dose, timing, and ratio of blood components therapy, for use in maternity patients with massive haemorrhage.
- Massive haemorrhage must be recognized early and MTP activation must be done early[8,17].
- Fibrinogen levels approaching 2 g/L are associated with severe haemorrhage. Thus, early cryoprecipitate or fibrinogen concentrate is indicated[8,16,22,39].
- In women with major obstetric haemorrhage, in addition to clinical observations, the following parameters should be measured early and frequently[8].
    - Temperature
    - Acid–base status
    - Ionised calcium
    - Haemoglobin
    - Platelet count
    - PT/INR
    - APTT
    - Fibrinogen level

  With successful treatment, values should trend towards normal.

- Values indicative of critical physiologic derangement include[8]:
    - Temperature <35°C
    - pH <7.2, base excess worse than –6, lactate >4 mmol/L
    - Ionised calcium <1.1 mmol/L
    - Platelet count <50 × 10^9/L
    - PT >1.5 × normal
    - INR >1.5
    - APTT >1.5 × normal
    - Fibrinogen level <2.0 g/L

- In women with major obstetric haemorrhage requiring massive transfusion, suggested doses of blood components are[8]:
    - FFP: 15 ml/kg
    - Platelets: 1 adult therapeutic dose
    - Cryoprecipitate: 1 unit / 10 kg body weight (total of 3-4 g)

- When the is no further need for blood products, blood bank must be informed to deactivate MTP[26].
- Clinical audit on MTP in pregnancy shall be performed on a regular basis to evaluate patient outcome in term of mortality and morbidity.

1.4 FUTURE DIRECTION

- Ferritin POCT when available, is advocated to check level of ferritin to predict ID in pregnancy as this will help for better and earlier screening, diagnosis and treatment.
- RET-He should be used on a wider scale for screening, diagnosis of anaemia and monitoring of iron treatment response.

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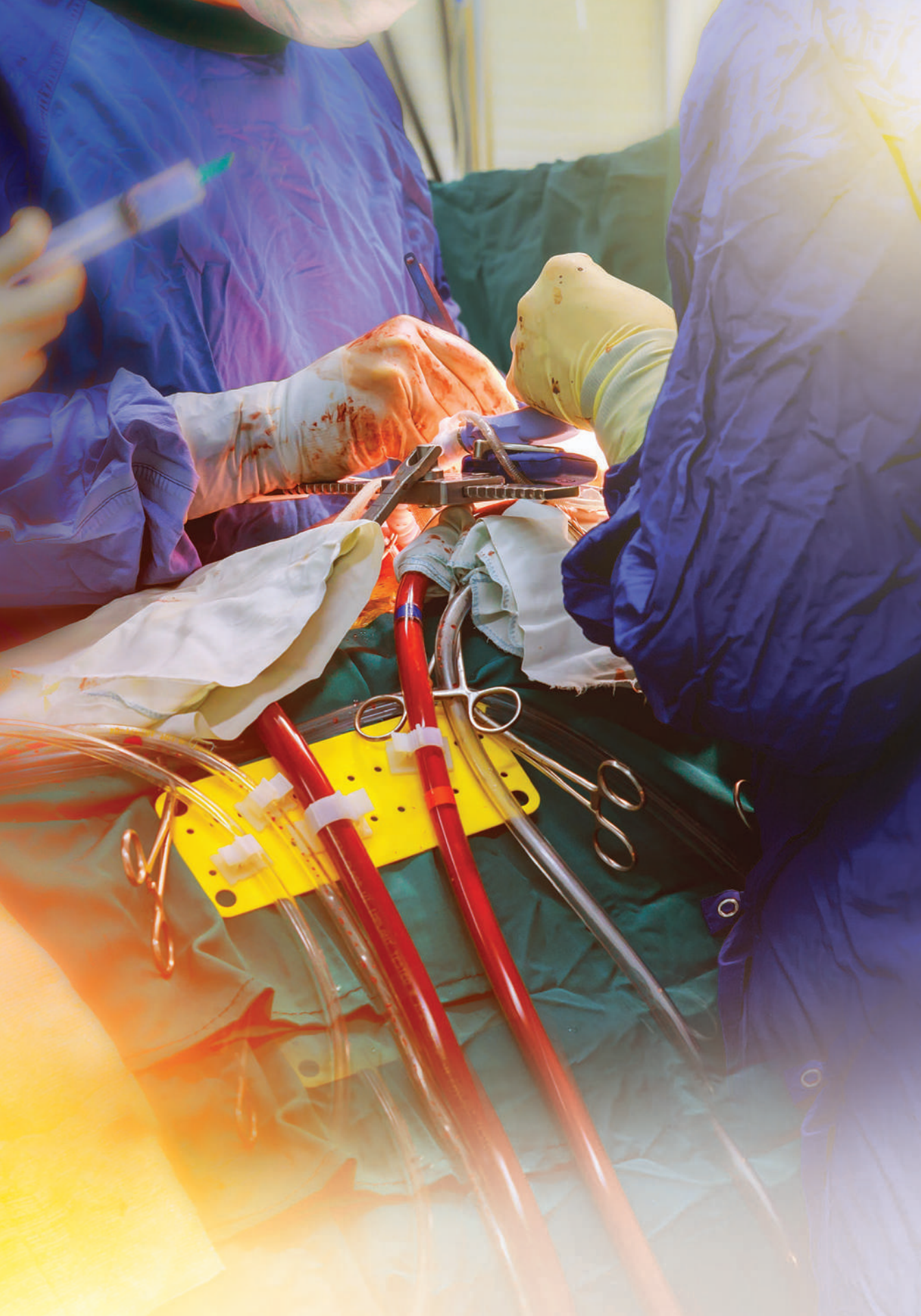
APPENDIX 1

Table 1.4: Summary of IV Iron Complexes Available in Malaysia

Product	Iron Sucrose		Iron Maltose		Low Molecular Weight Iron Dextran
Carbohydrate	Fe(III) hydroxide sucrose complex		Ferric carboxy-maltose	Ferric derisomaltose	Fe hydroxide dextran complex
Brand name	Venofer		Ferinject	Monofer	Cosmofer
Concentration (mg/ml)	100mg/5ml		500mg/10ml	1000mg/10ml 500mg/5ml	100mg/2ml
Maximum single dose	**IV injection:** 200mg(10ml) **IV infusion:** 7mg/kg (max 500mg per week)		**IV injection:** 15mg/kg **IV infusion:** 20mg/kg max 1000mg/week	20mg/kg infusion (1000 – 2000 mg)	20mg/kg infusion/ week
Administration summary	**Preparation:** 5-10ml (100-200mg) 1-3x/ week Slow IV push or IV infusion Dilution only in 0.9% Normal Saline (NS)		**Preparation:** Dilution only in 0.9% Normal Saline	**Preparation:** 500mg/ bolus Undiluted IV or diluted in max 20ml of Normal Saline	**Preparation:** Diluted in 500ml of Normal Saline
	Slow IV injection: 100mg (5ml) in 5 mins 200mg (10ml) in 10 mins **IV Infusion:** 200mg (10ml) in 30 min 300mg (15ml) in 1 ½ hr 400 mg (20ml) in 2 ½ hr 500mg (25ml) in 3 ½ hr	**Slow IV bolus injection:** 10ml / 10minute **IV Infusion:** 100mg iron (5ml) in 15 mins 200mg iron (10ml) in 30 mins	**IV infusion:** 100-200mg (2-4ml) in 50ml Normal Saline >200-500mg (>4-10ml) in 100ml NS in > 6 minutes >500-1000mg (>10-20ml) in 250ml NS in > 15 minutes	**IV bolus injection:** 20mg/kg single infusion up to 500 mg (max 3 times per week) Administration rate of 250 mg iron/minute. **IV Infusion:** 20mg/kg body weight or as weekly infusion until the accumulative iron dose has been administered. If the accumulative iron dose exceeded 20mg/ kg body weight, the dose must be split in two administrations with an interval of at least 1 week. It is recommended whenever possible to give 20 mg/kg body weight in the first administration. Doses up to 1000 mg must be administered over more than 15 minutes. Doses exceeding 1000 mg must be administered over 30 minutes or more.	**IV Infusion:** 20mg/kg body weight or as weekly infusion until the accumulative iron dose has been administered. If the accumulative iron dose exceeded 20mg/kg body weight, the dose must be split in two administrations with an interval of at least 1 week. It is recommended whenever possible to give 20 mg/kg body weight in the first administration. First 25mg should be infused over 15mins (if no adverse reaction) and continued over 4-6 hours till completion.
Route	Intravenous (IV)				

Note: Caution is strongly urged when using Iron Sucrose Similar (ISS) such as Avofer, Heamofer, Ranofer, Referis etc due to their potential different clinical efficacy, tolerability, safety and adverse event profile.



SUBMODULE 2

PERIOPERATIVE

2.1 INTRODUCTION

Severe haemorrhage is one of the leading causes of preventable death. Despite being in a controlled intraoperative environment, severe haemorrhage and massive transfusion is still possible especially in major surgery such cardiac, vascular, oncology, gastrointestinal, liver transplant, obstetrics as well as trauma.

As patient blood management is patient centric, it is crucial to ensure patient safety and patient empowerment through various key elements of perioperative care which includes the establishment/administrative of patient blood management, via preoperative, intraoperative and postoperative.

As Iron deficiency anaemia is still rampant, early diagnosis as well as management needs to be improved. This perioperative module is aimed at improving the overall approach by the multiple disciplines of surgery for patient that may require massive transfusion to ensure optimized cardiac output, tissue perfusion and haemostasis.

The elements of perioperative patient blood management will include a few recommendations with some practice points that will guide in the implementation and practices of patient blood management in perioperative setting. Specific perioperative approach in certain discipline namely, cardiothoracic, critical care and obstetrics & gynaecology will be covered in the respective submodules.

2.2 ADMINISTRATIVE / ESTABLISHMENT

Recommendation 1
1. Establishment of a perioperative patient blood management programme
Practice Points 1
1. A subcommittee championing PBM to be formed under the Hospital Transfusion Committee. This committee would be responsible for the implementation of PBM in the hospital / local setting. 2. All surgical patients should be evaluated as early as possible to coordinate scheduling of surgery with optimisation of the patient's haemoglobin and iron stores.

2.3 PREOPERATIVE ANAEMIA OPTIMIZATION

Recommendation 2

1. In patients undergoing surgery, preoperative anaemia should be identified, evaluated and managed to minimise RBC transfusion, which may be associated with transfusion related risks and an increase in ICU length of stay and hospital length of stay.

Practice Points 2

1. **Blood investigations that should be done for all surgical patients undergoing major surgery (anticipated blood loss > 500mls) are Full Blood Count (FBC), Serum Ferritin & Group Screen and Hold (GSH).**

2. **All surgical patients undergoing major surgery should be evaluated as early as possible to manage and optimise haemoglobin and iron stores.**

   In a recent presentation by the Director General of Health, Malaysia at International Surgical Week 2022, Vienna, Austria, more than 1 million surgeries are performed each year prior to 2020 in Malaysia (1,650,000 in 2018, 1,018,379 in 2019). The National Health and Morbidity Survey (NHMS) which periodically collects data on the burden of various diseases in the Malaysian population, reported that the prevalence of anaemia among Malaysia men was 12.6% (95% CI: 10.9, 14.5) and for women 30.4% (95% CI: 28.44, 32.47) in 2019. And specifically for women in the reproductive age group, it was 29.9% (95% CI: 27.53, 32.39). The National Health and Morbidity Survey (NHMS) which periodically collects data on the burden of various diseases in the Malaysian population, reported that the prevalence of anaemia among Malaysia men was 12.6% (95% CI: 10.9, 14.5) and for women 30.4% (95% CI: 28.44, 32.47) in 2019. And specifically for women in the reproductive age group, it was 29.9% (95% CI: 27.53, 32.39). The overall prevalence of anaemia was 21.3% (95% CI: 19.91, 22.85) in the Malaysian population. It can therefore be expected that up to one-fifth of patients undergoing surgery in Malaysia will have anaemia, more amongst women in the reproductive age group. Hence, all patients undergoing major surgery should be evaluated for anaemia.

Practice Points 2

3. **Elective surgery should be scheduled to allow optimisation of patients' haemoglobin and iron stores.**

   Although there are few studies that show that preoperative anaemia is associated with increased post operative complications, especially in those with moderate and severe anaemia, there is growing body of evidence which suggests that optimization of haemoglobin and iron stores preoperatively will decrease the need of blood transfusion in the perioperative period and during surgery. Perioperative allogenic blood transfusion is associated with poorer clinical outcomes and increased perioperative mortality. Hence preoperative optimization of haemoglobin and iron stores should be done before elective surgery to decrease the need of blood transfusion. It will also decrease the length of hospital stay and overall cost.

4. **Non-urgent elective surgery should be postponed until anaemia has been investigated and treated. Many guidelines recommend at least 4 weeks for the treatment of anaemia.**

   It is known that preoperative haemoglobin optimization will decrease the need of blood transfusion. Perioperative allogenic blood transfusion is shown to have more adverse clinical outcomes. Hence to avoid this, time may be required for the anaemia to be investigated and haemoglobin optimized before the non-urgent elective surgery is carried out. An average of 2 to 4 weeks may be required to optimize the haemoglobin levels. Wherever possible, non-urgent elective surgery should be postponed for at least 4 weeks until anaemia has been investigated and treated.

5. **Time interval between diagnosis of anaemia and surgery (ie malignancy) should be individualized.**

   Time to surgery has been identified as an independent predictor of overall survival.

   Different cancers may exhibit different tumour doubling time. The most common cancer in Malaysia is breast cancer[1]. In a population study of 94,544 patients with breast cancer, it is shown that with each 30-day interval (<30, 31-60,61-90,91-120,121-150, 151-180 days). the overall survival became lower, hazard ratio (HR) 1.09 ($p<0.001$), especially in stage I (HR 1.13, $p<0.001$) and II (HR 1.06, $p=0.010$.) The specific mortality is increased with each 60-d interval, (subhazard ratio= 1.26 ($p= 0.03$)[2]. Times to surgery do have an impact on the outcomes and the optimal time to surgery for breast cancer is within 90 days[3].

Another common cancer in Malaysia is colorectal cancer[1]. Robert J Kucejko et at investigated overall survival of patients with colorectal cancer from the time of diagnosis until surgery at 1-2, 3-4, 5-6 and more than 6 weeks and found that the adjusted 5-year survival was higher in those patients undergoing surgery between 3-6 weeks and concluded that 3-6 weeks after diagnosis is the ideal timing for definitive resection of colon cancer[4].

In a large retrospective cohort study of 37730 patients with head and neck squamous cell carcinoma by Chandler J. Rygalski, the biggest rise in hazard ratio in overall survival was at day 67 and therefore concluded that surgery should be done within 67 days from the time of diagnosis to achieve optimal survival outcomes[5].

While there is no one standard time to surgery for different tumours, delays do have a measurable impact on the outcomes. A balance must be made between diagnosing and treating the anaemia without delaying the surgery and affecting the survival outcome. Hence, the time interval between diagnosis of anaemia and surgery should be individualized to the patient and the type of cancer.

Recommendation 3

1. In surgical patients with, or at risk of iron-deficiency anaemia, preoperative iron therapy is recommended.
2. In patients with preoperative anaemia, where an ESA is indicated, it must be combined with iron therapy.

Practice Points 3

1. In patients with preoperative iron-deficiency anaemia or depleted iron stores, treatment should be with iron alone. In patients with anaemia of chronic disease (also known as anaemia of inflammation), the addition of ESAs may be indicated.
2. Surgical patients with suboptimal iron stores (as defined by a ferritin level <100 µg/L) in whom substantial blood loss (blood loss of a volume great enough to induce anaemia that would require therapy) is anticipated, should be treated with preoperative iron therapy.
3. The prescription of enteral and parenteral iron formulations should be made accessible to all disciplines

2.4 PREOPERATIVE OPTIMISATION OF HAEMOSTASIS

Recommendation 4

1. All surgical patients should be assessed for bleeding risk using a validated bleeding assessment tool.
2. Aspirin monotherapy can be continued for most invasive non cardiac surgeries including neuraxial anaesthesia.
3. Dual antiplatelet therapy (DAPT) can be continued for low bleeding risk procedures.
4. High bleeding risk procedures should be postponed in patients taking DAPT.

Practice Points 4

1. Coagulation screen blood test should not be performed unless there is a history suggestive of a bleeding disorder or a comorbidity associated with a bleeding risk. Validated tools for the assessment of bleeding risk are like the ISTH Bleeding Assessment Tool.
2. Aspirin can be omitted from day -3 to day +7 of surgery.
3. Clopidogrel / Ticagrelor can be omitted from day -5 of surgery, Prasugrel can be omitted from day -7 of surgery.
4. In patients receiving dual antiplatelet therapy (addition of clopidogrel or ticagrelor) who are scheduled for elective noncardiac surgery or other invasive procedures, a multidisciplinary approach should be used to decide whether to cease therapy or defer surgery, balancing the risk of bleeding and thrombotic events. Specific evaluation is required for patients who had a recent stroke or received a drug-eluting stent within the last 12 months or a bare metal stent within the last 6 weeks. If a decision is made to cease therapy preoperatively, this should occur 5 – 10 days before surgery.

Recommendation 5

1. Warfarin should be stopped for 5 days before an elective procedure if anticoagulation needs to be discontinued.
2. Patients with normal renal function undergoing planned low risk procedures should not take a direct oral anticoagulant (DOAC) for 24 h before the procedure.
3. Patients with normal renal function undergoing planned higher risk procedures should not take a DOAC for 48 hours before the procedure.
4. Unfractionated heparin should be withheld 4 – 6 hours prior to surgery. Low molecular weight heparin should be withheld 12 to 24 hours prior to surgery.

Practice Points 5

1. In patients on oral anticoagulants, the need for bridging therapy and recommencing anticoagulants should follow the current local guidelines.
2. For patients with renal impairment, the duration of action of DOACs is prolonged and adjustments need to be made for withholding of treatment prior to surgery.

2.5 INTRAOPERATIVE INITIATIVES

Recommendation 6

1. In patients undergoing surgery, measures to prevent hypothermia should be used (Grade A).
2. Care should be taken ensure proper positioning of the patients that promotes good venous return.
3. In adult patients undergoing surgery in which substantial blood loss is anticipated, the use of acute normovolemic haemodilution (ANH) should be considered, especially for special circumstances (e.g., in rare blood group, religious belief) (Grade C).
4. In adult patients undergoing surgery in which substantial blood loss is anticipated, intraoperative cell salvage is recommended where possible (Grade C).

Practice Points 6

1. ANH requires a local procedural guideline that addresses patient selection, vascular access, volume of blood withdrawn, choice of replacement fluid, blood storage and handling, and timing of reinfusion.
2. Intraoperative cell salvage requires a local procedural guideline that should include patient selection, use of equipment and reinfusion. All staff operating cell salvage devices should receive appropriate training, to ensure knowledge of the technique and proficiency in using it.

Recommendation 7

1. **In adult patients undergoing noncardiac surgery, if substantial blood loss is anticipated, the use of intravenous Tranexamic acid is recommended (Grade B)**.

   Tranexamic acid inhibits fibrinolysis by binding to plasminogen in the fibrinolytic pathway and has been used in preventing bleeding in trauma and surgeries. In a large RCT on postpartum haemorrhage after vaginal birth or Caesarean section, the WOMAN (world maternal antifibrinolytic) trial showed that there is a significant reduction in bleeding related death in the tranexamic group as compared to the placebo group, even though it is only by 0.4%[1]. However, the need for hysterectomies and transfusions remained the same in both groups.

The ATACAS (Aspirin and Tranexamic acid for Coronary Artery Surgery) trial showed the tranexamic reduces blood loss, transfusions and the need for reoperation for coronary artery bypass surgery. There was no increased in thrombotic complications and death within 30 days of surgery[2].

For urological procedures like prostate surgery, Tranexamic acid has also shown to reduce blood loss and need of transfusion without increased in thrombotic complications[3,4].

In major orthopaedic surgeries, Tranexamic acid has been shown to reduce transfusion rates in total knee[5] and hip[6] arthroplasty. The usage of Tranexamic acid for major orthopaedic surgeries like total hip and knee replacement has been recommended (Grade 2A) in patient blood management programmes[7].

The Perioperative Ischaemic Evaluation-3 (POISE-3) trial showed that amongst patients going for non-cardiac surgery, the primary efficacy outcome, a composite bleeding outcome of life-threatening bleeding, major bleeding and bleeding into critical organ, at 30 days was 24% lower with Tranexamic acid than with placebo (9.1% vs. 11.7%; absolute difference, −2.6 percentage points; 95% confidence interval [CI], −3.8 to −1.4). However, the primary safety outcome, a composite cardiovascular outcome of myocardial injury after noncardiac surgery, non-haemorrhagic stroke and symptomatic proximal venous thromboembolism, did not meet the criteria of non-inferiority between Tranexamic acid and placebo[8].

Hence, while the use of Tranexamic acid decreases bleeding in non-cardiac surgeries and is widely recommended, the risk and benefits must be taken into consideration. Generally, the timing of intravenous Tranexamic acid administration is just before surgical incision.

2. **In the presence of suspected coagulopathy, transfusion of blood products should be guided by coagulation assays or viscoelastic testing where available.**

Practice Points 7

1. For all surgeries with an anticipated blood loss of > 500 mls, it is recommended that IV Tranexamic acid be given prophylactically prior to surgery.
2. Coagulation assays should include Prothrombin Time, Activated Partial Thromboplastin Time and serum Fibrinogen levels.
3. Viscoelastic testing can lead to reduction in blood product transfusions and improvement in postoperative bleeding risks.

2.6 INTRAOPERATIVE DECISIONS FOR TRANSFUSION

Recommendation 8

1. During surgery, in the absence of haemodynamic instability, a restrictive transfusion strategy should be employed. However, the clinical situation would dictate if blood transfusions would be indicated.
2. Prophylactic transfusion of blood products preoperatively without evidence of bleeding phenotype in a patient is not recommended. Any abnormal coagulation profile would need to be investigated prior to surgery.

Practice Points 8

1. RBC transfusion should not be dictated by a haemoglobin 'trigger' alone but should be based on assessment of the patient's clinical status. In the absence of acute myocardial or cerebrovascular ischaemia, postoperative transfusion may be inappropriate for patients with a haemoglobin level of >8 g/dL.
2. Patients should not receive a transfusion when the haemoglobin level is ≥10 g/dL. In postoperative patients with acute myocardial or cerebrovascular ischaemia and a haemoglobin level of 7–10 g/dL, transfusion of a single unit of RBC, followed by reassessment of clinical efficacy, is appropriate.
3. In general, patients with a platelet count ≥ 50 × 10^9/L or an INR ≤ 2 can undergo invasive procedures without any serious bleeding; however, lower platelet counts, and higher INRs may be tolerated.
4. Specialist guidelines or transfusion medicine specialist/haematology advice should be sought for at-risk patients undergoing intracranial, intraocular and neuraxial procedures, and for patients with platelet counts < 100 × 10^9/L or coagulopathy.

Recommendation 9

1. The prophylactic or routine therapeutic use of rFVIIa is not recommended because concerns remain about its safety profile, particularly in relation to thrombotic adverse events.

2. The prophylactic or routine therapeutic use of PCC is not recommended outside of licensed indications.

Practice Points 9

1. The administration of rFVIIa may be considered in the perioperative patient with life-threatening haemorrhage after conventional measures, including surgical haemostasis, use of antifibrinolytics and appropriate blood component therapy have failed.

2. The use of PCC should be limited to specific licensed indications (ie warfarin reversal). Consultation with a haematologist / transfusion physician is advisable.

2.7 POSTOPERATIVE INITIATIVES

Recommendation 10

1. Efforts should be made to reduce repeated blood draws by implementing a restrictive phlebotomy practice.

Practice Points 10

1. Restrictive phlebotomy encompasses reduction in blood draw frequencies and volume.

2. The request for routine blood investigations is not advisable and it should be done with clear indications.

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SUBMODULE 3

NEONATAL & PAEDIATRIC

3.1 INTRODUCTION

Intended to assist and guide health-care professionals in making clinical decisions on patient blood management in neonatal and paediatric patients.

Specific guidelines are needed for these age groups because there are considerable physiological differences between neonates, children and adults at different developmental stages.

Both the benefits and adverse consequences of transfusions in neonatal and paediatric patients may be lifelong.

Patient blood management (PBM) aims to improve clinical outcomes by avoiding unnecessary exposure to blood components based on three pillars:

- optimisation of blood volume, red cell mass and coagulation.
- minimisation of blood loss
- optimisation of the patient's tolerance of anaemia

3.2 RECOMMENDATION FOR RBC TRANSFUSION

3.2.1 BACKGROUND

The goal of transfusion in neonatal and paediatric patients is to reduce morbidity and mortality rates and to improve the quality of life for them.

In neonates and infants born preterm, blood is transfused primarily in small amounts (10–20 ml/kg) to treat anaemia of prematurity and improve tissue oxygenation. In some situations, neonates may also need large-volume transfusions, such as exchange transfusions to prevent kernicterus or pump priming for cardiac surgery and extracorporeal membrane oxygenation (ECMO).

Table 3.1: Recommendation & Practice Points

Recommendation & Practice Points
In neonates and paediatric patients, including those who are critically ill, a restrictive transfusion strategy is suggested.
The decision to give an RBC transfusion should not be dictated by a Hb concentration alone but also be based: • Underlying condition (e.g acquired or cong. heart disease, resp disease) • anaemia-related signs and symptoms • response to previous transfusions.
For neonatal and paediatric patients, a specific procedural guideline for RBC transfusion should be used that includes: • age specific Hb reference ranges • volume of transfusion and rate of administration • patient monitoring during and after transfusion • transfusion technique (e.g., use of syringe pumps) • recognition and reporting of adverse events.
Restrictive Transfusion
In haemodynamically stable paediatric patients (excluding neonates), consensus suggests that: • Hb of 70–90 g/L, RBC transfusion may be appropriate. The decision to transfuse patients should be based on the need to relieve clinical signs and symptoms of anaemia. • Hb >90 g/L, RBC transfusion is often unnecessary and may be inappropriate.

Table 3.2: Hemoglobin Increment formula

Hb Increment Formula
Transfusion Volume (ml) = Patient's wt (kg) x (desired Hb g/L - Patient's Hb (g/L) x Transfusion factor (4 for PC)

Table 3.3: Approximate Hb increments that can be expected following transfusion in neonates

ESTIMATED Hb (g/L) AFTER TRANSFUSION			
Current Hb (g/L)	**Transfusion of 10ml/kg**	**Transfusion of 15ml/kg**	**Transfusion of 20ml/kg**
Very preterm neonate with estimated blood volume 100ml/kg			
70	91	102	112
80	101	112	122
90	111	122	132
Term neonate with estimated blood volume 80ml/kg			
70	96	109	123
80	106	119	133
90	116	129	143

3.3 IRON SUPPLEMENTATION AND/OR ERYTHROPOIESIS STIMULATING AGENTS (ESA)

3.3.1 BACKGROUND

Anaemia is characterised by a low level of circulating RBCs in the blood, which can result in a low level of haemoglobin. As a result, less oxygen is circulated throughout the body, causing symptoms such as extreme tiredness, shortness of breath, and dizziness. In neonates, anaemia may result in poor weight gain, decreased activity, tachycardia, apnoea, respiratory distress, and feeding difficulties. As well as impairing cognitive and physical development in children, anaemia may also weaken their immunity.

The use of supplemental iron can minimize the need for RBC transfusions as a means of treating or preventing anaemia. In certain instances, ESAs may be useful as an adjuvant treatment.

Table 3.4: Recommendation & Practice Points

Iron Supplementation	
Preterm and low birth weight infants	• Iron supplementation is necessary to achieve the recommended nutrient intake. • However, routine supplementation in excess of the recommended nutrient intake, to reduce transfusion incidence, is not supported.
Infants and children	• If the adequate intake or recommended daily intake cannot be met by dietary means, iron supplementation is advised. • Those with iron deficiency should be treated with iron supplements and dietary modifications.
Surgical patients	• Patients with or at risk of iron deficiency anaemia, preoperative iron therapy is recommended in consultation with paediatric haematology • Patients in whom substantial blood loss is anticipated, preoperative anaemia should be identified, evaluated and managed to minimise RBC transfusion. • Patients should be evaluated as early as possible so that scheduling of surgery can be coordinated with optimisation of the patient's Hb and iron stores.
Critically ill	Patients should receive iron supplementation as necessary to achieve the recommended nutrient intake.

ESAs

- Paediatric patients with **chronic kidney disease**, ESA therapy to achieve a low to intermediate Hb target may be used to avoid RBC transfusion, after consideration of risks and benefits:
  - The Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend a Hb target of 110–120 g/L for paediatric patients and state that individualisation of ESA therapy is reasonable because some patients may have improvements in quality of life at higher Hb concentration.
  - The National Institute for Health and Care Excellence's (NICE) guidelines recommend a Hb target of 100–120 g/L for children aged 2 years and older, and 95–115 g/L for children younger than 2 years of age (reflecting the lower normal range in that age group).
- Paediatric **oncology patients** receiving chemotherapy, the routine use of ESAs is not advised.
- **Preterm with low birth weight**, routine use of ESA is not advised.

3.4 BLOOD PRODUCTS

3.4.1 BACKGROUND

Platelet transfusion is frequently used to treat thrombocytopenia in critically ill patients. Platelet transfusion has been associated with a number of side effects including bacterial infection (due to contamination), allergic reactions, febrile reactions, venous thromboembolism, TRALI, and TACO. Therefore, it is crucial to carefully consider the risks and benefits of platelet transfusion before using it in critically ill patients. The primary triggers for the transfusion of platelets are:

- In the event of a low platelet count and active bleeding prior to or during an invasive procedure.
- Prophylaxis after chemotherapy
- Bone marrow transplant
- Known or suspected disorder (inherited or acquired) affecting platelet function.

In neonatal and paediatric settings, fresh frozen plasma (FFP) is used to correct coagulation abnormalities by containing all the coagulation factors found in normal plasma.

Administration of FFP has been associated with a variety of side effects, including infection, allergic reactions, haemolysis, TACO, and TRALI. Therefore, it is imperative to carefully consider the risks and benefits of FFP transfusions before they are administered.

Hypofibrinogenaemia is corrected with cryoprecipitate. The following are the primary triggers for administering cryoprecipitate:

- hemostatic support during massive blood loss
- low fibrinogen and active bleeding before or during an invasive procedure
- dysfibrinogenaemia (structural abnormalities of the fibrinogen molecule that cause dysfunction)
- Active bleeding before or during an invasive procedure.

In patients with hypofibrinogenaemia, fibrinogen may also be administered.

Table 3.5: Recommendation & Practice Points

General Recommendation & Practice Points For Blood Products

• In neonatal and paediatric patients, the decision should be based not only on laboratory investigations but also on assessment of the patient's clinical condition.
• Factors that may influence the decision include :
  • active bleeding
  • medications affecting coagulation status
  • congenital and acquired bleeding disorders.

Platelet For Special Group Patients	

Oncology	• In patient undergoing chemotherapy and haematopoietic stem cell transplantation, the recommended strategies:
	  • prophylactic use of platelets is transfusion at a platelet count of <10 × 10^9/Lin the absence of risk factors
	  • in the presence of risk factors at <20 × 10^9/L (e.g. fever, minor bleeding)

Surgical	In general, neonatal and paediatric patientswith a platelet count ≥50 × 10^9/L* can undergo invasive procedure s without any serious bleeding; **the threshold may be varies depending on institution*

Critically ill	Suggested thresholds are:
	  • 10 × 10^9/L - in stable patient without bleeding,
	  • 20 × 10^9/L- in a nonbleeding patient with risk factors (sepsis, renal failure, medications) for bleeding,
	  • 50 × 10^9/L - in patient undergoing invasive procedures,
	  • In patients with active bleeding, higher thresholds may be appropriate.

FFP, Cryoprecipitate and Fibrinogen
• In neonatal and paediatric patients undergoing surgery, FFP is only indicated for treatment of active bleeding where coagulopathy is a contributing factor.   • Its use should be guided by clinical assessment, supplemented by point-of-care or laboratory testing.

3.5 SPECIAL CONSIDERATION

3.5.1 BACKGROUND

Children and neonates typically have lower absolute blood volumes and red cell masses compared to adults. Thus, depleting red blood cells (RBCs) through blood loss or haemolysis can exert a proportionately more significant impact on the necessity for transfusions in these patients.

Many hospitalised neonatal and paediatric patients are at risk of blood loss, which places them at risk for transfusion. Interventions such as the following were considered for their potential to improve outcomes and reduce the need for transfusions:

- Specific to neonates:
  - Placental transfusion to increase the circulating blood volume and red cell mass
  - Intravenous immunoglobulin (IVIg) to reduce haemolysis in infants born with neonatal alloimmune haemolysis (widely known as haemolytic disease of the foetus and newborn [HDFN])
- Neonatal and paediatric patients undergoing surgery:
  - prevention of hypothermia
  - controlled induced hypotension compared with no induced hypotension
  - acute normovolaemic haemodilution (ANH)
  - intraoperative cell salvage
  - viscoelastic POC testing
  - antifibrinolytics
  - recombinant activated factor VII (rFVIIa) (cardiac and extracorporeal membrane oxygenation [ECMO] patients only)
  - miniaturised CPB systems compared with standard-sized systems

Table 3.6: Recommendation & Practice Points

Nenonatal	
Placental transfusion	• In preterm infants, deferring cord clamping for between 30 seconds and 1 minute may reduce transfusion volume and incidence of intraventricular haemorrhage. • In term infants, deferring cord clamping for at least 1 minute is likely to reduce the risk of iron deficiency at 3–6 months.
HDFN-IVIg	• In neonates with haemolytic disease of the foetus and newborn, the use of IVIg should be considered • Neonates at risk of haemolytic disease of the foetus and newborn should be promptly assessed after birth. Those at high risk of severe jaundice should receive intensive phototherapy. • In maternity patients with a foetus affected by haemolytic disease of the foetus and newborn who is at high risk of early fetal hydrops or death, a course of weekly IVIg should be considered.
Surgical	

Prevention of Hypothermia	• In paediatric patients undergoing surgery, measures to prevent hypothermia should be used. e.g.:
	  • Air force warming blanket
	  • Fluid warmer
	  • Radiant heater

Intraoperative Cell Salvage	• In paediatric patients undergoing major surgery, intraoperative cell salvage may be considered. • It requires a local procedural guideline that should include patient selection, use of equipment and reinfusion. • All staff operating cell salvage devices should receive appropriate training, to ensure knowledge of the technique and proficiency in using it.

Surgical	
POCT-TEG	• In paediatric patients undergoing major surgery, viscoelastic point-of-care testing may be considered.
Antifibrinolytic	• Paediatric patients undergoing major surgery (e.g. craniofacial, spine) and cardiopulmonary bypass, the use of antifibrinolytics is suggested e.g. Tranexamic acid. • In acutely bleeding critically ill paediatrics trauma patients, Tranexamic acid should be administered within 3 hours of injury. • In paediatric trauma patients a Tranexamic acid dose of 15 mg/kg (maximum 1000 mg) infused intravenously over 10 minutes, followed by 2 mg/kg/hour (maximum 125 mg/hour) until bleeding is controlled or for up to 8 hours is suggested.

3.6 SELECTION OF BLOOD PRODUCTS

3.6.1 BACKGROUND

The following characteristics make neonatal and paediatric patients unique:

- The changes in their body composition and physiology as a result of development and growth. Due to this, the risks and benefits for this population may differ from those that apply to adults.
- Childhood and infancy treatments have the potential to have lifelong effects.
- Certain disorders that are unique to infancy and childhood.

Due to the special vulnerability of young patients, it is imperative to examine whether blood products that have been selected on the basis of specific characteristics or that have been specially treated could be more effective in short or long-term treatment.

Table 3.7: Recommendation and Practice Points

'Fresh' RBCs In Fetal, Neonatal and Paediatric Patients

- 'Fresh' (<5 days) RBCs may be considered in the following clinical situation:
  - Intrauterine transfusion (<5 days, if available)
  - Exchange transfusion
  - RBC <14 days can be used in transfusion-dependent patients e.g. thalassemia

Kell Antigen System

- Where possible, K-negative RBC should be selected for transfusion for all females of childbearing potential who are K negative or whose K antigen status is unable to be determined prior to transfusion. This includes fetal transfusion

Use Of Irradiated Cellular Blood Products In Neonates And Children

- Irradiated cellular blood products (RBCs and platelets) are used to prevent transfusion-associated graft-versus-host disease, and are indicated for:
  - intrauterine transfusion, and recipients of prior intrauterine transfusion up to 6 months of age
  - suspected or known severe congenital T-cell immunodeficiency (e.g. severe combined immunodeficiency)
  - severe acquired T-cell dysfunction, related to either disease or drug therapy (see published guidelines)
  - human leukocyte antigen-matched cellular blood products (RBCs, platelets and granulocytes).
- They may also be considered for:
  - neonatal exchange transfusion, provided this does not unduly delay transfusion
  - very low birth weight neonates, especially extremely preterm (<28 weeks) or extremely low birth weight infants
  - Certain patients undergoing chemotherapy (depending on degree of immunosuppression).

- Stem cells must not be irradiated.

- Hyperkalaemia may occur when large volumes of irradiated blood are transfused. In patients at risk, irradiated blood should be as fresh as possible (<7 days) and used within 24 hours of irradiation.

- Patients at high risk of transfusion-associated graft-versus-host disease should be informed of the need for irradiated blood products. Also, alerts should be incorporated in the information systems of the health service and transfusion laboratory.

Use Of Cytomegalovirus-Negative Blood Products

- CMV-negative products may be considered in the following situations:
  - intrauterine transfusion
  - preterm neonates (up to 28 days after expected date of delivery)
  - patients with severe combined immunodeficiency who are CMV negativE
  - stem cell transplantation where both donor and recipient are known to be CMV negative
  - granulocyte transfusions for recipients who are CMV seronegative, or whose status is unknown.
- CMV-negative products are generally not required in other clinical settings.

- In urgent situations, if CMV-seronegative blood components are not available, CMV-unscreened leucodepleted components should be used to avoid delays.

Use Of Human Platelet Antigen-Matched Platelets

- For neonates with known or suspected fetal and neonatal alloimmune thrombocytopenia:
  - urgent platelet transfusion should be given if platelets are below 30 × 10^9/L in a term infant or below 50 × 10^9/L in a preterm infant, even in the absence of clinically significant bleeding
  - if there is active bleeding, a higher threshold should be considered (100 × 10^9/L for intracranial bleeding, and 50 × 10^9/L for other sites of bleeding).
  - in all cases, a paediatric haematologist should be consulted.

- For neonates with known or suspected fetal and neonatal alloimmune thrombocytopenia, platelet count response to transfusion should be checked within 12 hours.

- For neonates with known or suspected fetal and neonatal alloimmune thrombocytopenia, random donor platelets should be used if antigen-matched platelets are not immediately available. Continued use of random donor platelets is acceptable if antigen-matched platelets cannot be obtained. Because of short survival of random donor platelets, repeated transfusion is likely to be needed.

- For neonates with fetal and neonatal alloimmune thrombocytopenia, IVIg may be considered.

Use Of Human Leucocyte Antigen-Matched Platelets

- For neonatal and paediatric patients with platelet refractoriness attributable to non-immune causes such as splenomegaly or infection, fresh, ABO-compatible, single-donor apheresis platelets may improve platelet increment.

- If the cause of platelet refractoriness is not obvious, investigation should include screening for HLA antibodies. HLA-matched platelets should be used if an HLA antibody is detected.

- In patients with inherited platelet disorders such as Bernard Soulier Syndrome and Glanzmann's thrombasthenia, platelet transfusions should be avoided if possible, to reduce the patient's risk of alloimmunisation. If platelet transfusion is unavoidable the patient should receive HLA-matched platelets.

Washed RBCs

- Washing of RBCs before transfusion is undertaken to remove substances (antibodies, plasma proteins, additive solutions, increased levels of electrolytes, other cellular metabolites or cytokines) that may be harmful to some patients. Washed units contain 10–20% less RBCs than the original units but are also depleted of 99% of plasma proteins and have reduced amounts of additive solution and extracellular potassium. Other potential benefits include reduced immunomodulatory effects of transfusion.

- In regard to risks, RBCs may be damaged during the process and thus be more susceptible to haemolysis. Washed RBCs may be considered for the management of severe transfusion reactions, including those due to IgA deficiency.

Table 3.8: Indications for irradiation of cellular products

	Absolute indications (RBCs, Platelet and Granulocytes must be irradiated)	Relative indications (irradiation of cellular products may be considered)
Fetus and neonates	• IUT (Intraunterine transfusion) • IUT and subsequent transfusion up to the age of 6 months	• Neonatal exchange transfusion (provided no critical delay in transfusion) • Neonates with a birth weight of ≤1300g (especially if gestation <28 weeks or birth weight <900 g)
Immunodeficiency	Known or suspected congenital cellular immunodeficiency (e.g. SCID, Wiskott Aldrich syndrome, ataxia telangiectasia and 22q11 deletion syndromes)	
Specific blood products	• HLA-matched cellular products other than stem cells • Blood components donated by first or second-degree relatives	
Stem cell transplantation	Allogeneic and autologous transplantation	
Chemotherapy and malignancy	• Hodgkin lymphoma indefinitely • Treatment with purine analogues – indefinitely • Treatment with Alemtuzumab (anti- CD52) therapy – at least 12 months from last dose • Treatment with ATG – recommendations for duration are not available, consider indefinitely	All other patients undergoing chemotherapy should be decided on an individual basis, taking into account the intensity of the immunosuppression

3.7 FETAL TRANSFUSION

3.7.1 BACKGROUND

It has been shown that the IUT of RBCs or platelets can reduce perinatal morbidity and mortality that are associated with severe fetal anaemia or thrombocytopenia. The most common causes of severe fetal anaemia and thrombocytopenia that may require IUT are described below, although IUT is not limited to these aetiologies.

Table 3.9: Recommendation & Practice Points

Fetal Transfusion
• Management of pregnancies at risk of fetal anaemia or thrombocytopenia should be undertaken in facilities with appropriate expertise in ultrasound imaging and invasive fetal interventions, and that have access to specific blood products and neonatal intensive care.
• Pregnancies at risk of fetal anaemia should be assessed by Doppler ultrasound of the fetal middle cerebral artery peak systolic velocity, to determine whether fetal blood sampling and intrauterine transfusion are necessary.
• Pregnant women who have had a prior pregnancy with fetal or neonatal intracranial haemorrhage or thrombocytopenia due to fetal and neonatal alloimmune thrombocytopenia should be managed with IVIg.
• Fetal blood sampling should be considered to assess response to IVIg in those who have had a previous child with intracranial haemorrhage due to fetal and neonatal alloimmune thrombocytopenia. The risk of fetal blood sampling should be balanced against the risk of bleeding due to suboptimal IVIg response.

Table 3.10: Products for intrauterine transfusion

Products For Intrauterine Transfusion	

• Both RBCs and platelets:
  • Leucodepleted
  • Irradiated to prevent TAGvHD	

RBCs	**Platelets**
• <5 days old • Group O RhD Negative (or ABO identical with the foetus) • RhD and Kell negative, and RBC antigen negative for maternal alloantibodies • Indirect antiglobulin test cross match compatible with the mother's plasma	Compatible with any maternal alloantibody (e.g. anti-HPA)

3.8 NON-PHARMACOLOGIC BLOOD CONSERVATION STRATEGIES

3.8.1 BACKGROUND

Children are most likely to experience blood loss due to phlebotomy during hospitalisation, and this is significantly associated with the need for red blood cell transfusions during hospitalisation. Therefore, routine blood conservation efforts should include strategies aimed at minimizing blood loss from sampling.

Table 3.11: Recommendation & Practice Points

Strategies To Safely Minimise Phlebotomy Losses Should Be Used For All Neonatal And Paediatric Patients.
• Use of 'as-needed' rather than routine sampling • Meticulous avoidance of blood overdraw • Return of void volumes to sampling lines • Use of closed inline sampling devices • Judicious use and 'on-time' removal of sampling lines • Optimal sampling technique and sample handling to minimise rejection of samples by laboratory • Laboratory equipment that uses the smallest possible sample volumes • Use of non-invasive techniques and point-of-care devices

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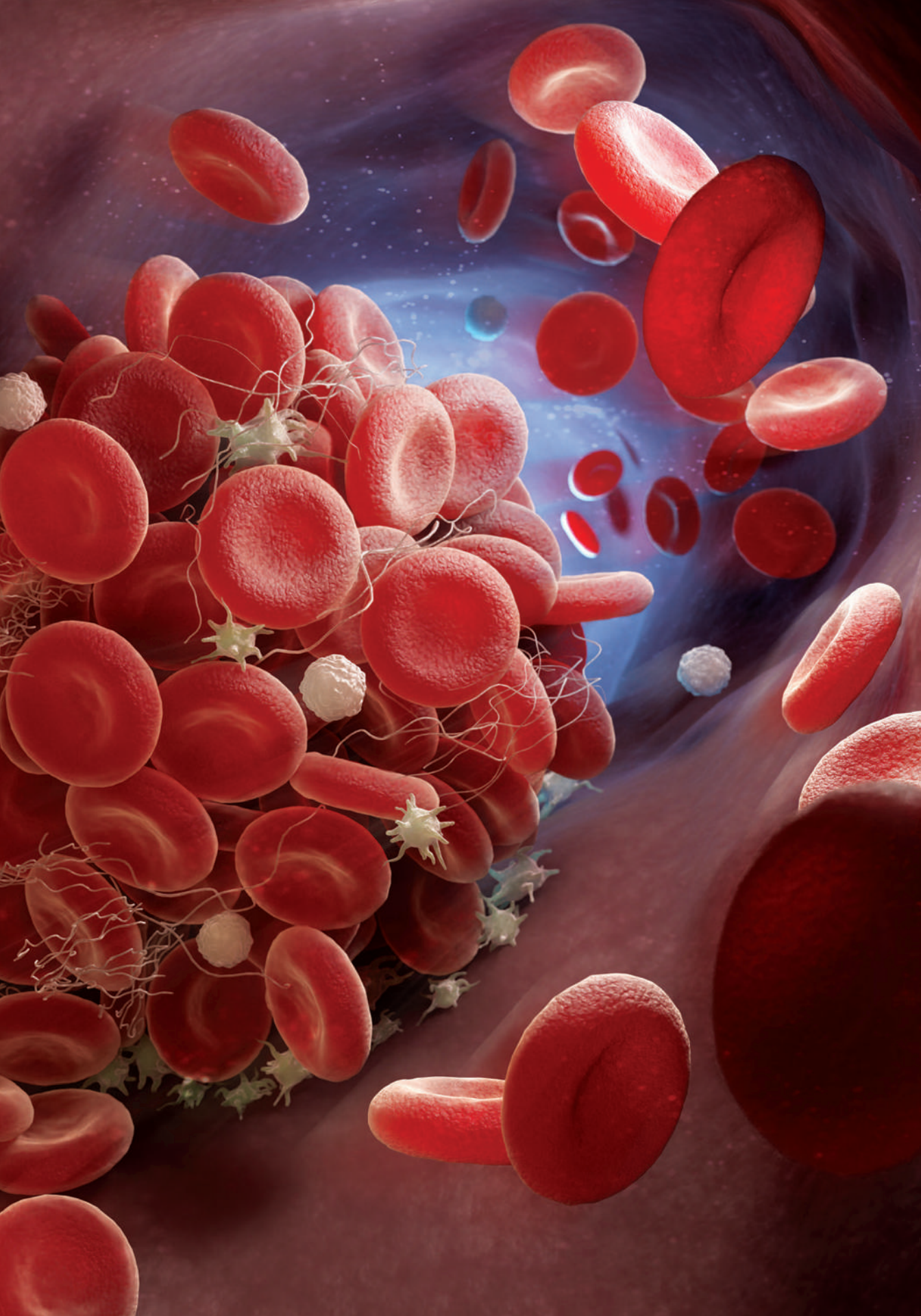


SUBMODULE 4

MASSIVE HAEMORRHAGE

4.1 INTRODUCTION

Severe haemorrhage is one of the leading causes of preventable death. Most common clinical situation leading to massive haemorrhage are trauma, cardiac surgery, vascular, gastrointestinal bleed, liver transplant, and obstetrics catastrophes. Management of haemorrhage patients requiring massive transfusion need careful and ongoing consideration of complex physiologic relationships. Massive transfusion is crucial for maintaining cardiac output, tissue perfusion and haemostasis.

4.2 OBJECTIVES

1. To improve the ability to identify patients who are experiencing massive haemorrhage.

2. To improve the management of massive haemorrhage patients with appropriate blood component replacement and pharmacological adjuncts.

3. To outline the principles of resuscitation in massive haemorrhage patients such as permissive hypotension, restrictive transfusion strategy, balanced resuscitation, limit ongoing haemorrhage as well as maintaining circulating volume and tissue perfusion.

4. To advocate multidisciplinary approach for the management of massive haemorrhage patients.

5. To implement evidence based clinical practice relating to blood transfusion and its limitation in massive haemorrhage patients.

4.3 DEFINITIONS

4.3.1 DEFINITION OF MASSIVE HAEMORRHAGE

1. Active ongoing haemorrhage at the rate of 150ml/min with hemodynamic instability (systolic blood pressure < 90mmHg and/or heart rate > 110 per minute).
2. Loss of 50% of blood volume** within 3 hours.
3. Loss of total body blood volume** in 24 hours.

*** Adult blood volume is approximately 70ml/kg*

4.3.2 DEFINITION OF MASSIVE TRANSFUSION

1. Transfusion of > 50% total body blood volume in 3 hours
2. Transfusion of > total body blood volume in 24 hours.

4.4 IDENTIFICATION AND VOLUME ESTIMATION OF ACUTE HAEMORRHAGE

1. It is crucial for clinicians to rapidly identify massive haemorrhage and estimate real time volume of blood loss. These estimations would provide critical information to adjunct resuscitation approach as well as transfusion strategies.

2. Massive haemorrhage can be manifested by evidence of active haemorrhage with concurrent hemodynamic instability (systolic blood pressure less than 90mmHg and/ or heart rate more than 110 per minute).

3. Volume of haemorrhage may be predicted by using either an anatomical **(Refer Table 4.1)**, physiological, physical method **(Refer Table 4.2)**, or in combination.

Table 4.1: Anatomical Method in Estimating Blood Loss

Anatomy	Approximate Blood Loss
Closed pelvic fracture	2000ml - 4000ml
Closed femoral fracture	1000ml - 1500ml
Closed tibial fracture	500ml - 1000ml
Closed humerus fracture	500ml - 1000ml
A hematoma the size of an adult fist	500ml
Fractured ribs	150ml each
One blood-filled hemithorax	2000ml

**In open fractures, blood loss may be twice the estimate of closed fractures.*

4. Massive haemorrhage gives rise to an acute physiological body response. This compensatory response differs as proportion of volume loss increases. The estimation of blood loss may be performed by utilising this physiological estimation method, interpretating various parameters such as blood pressure, heart rate, respiratory rate, pulse pressure, Glasgow Coma Scale (GCS), and others. i.e. Advanced Trauma Life Support (ATLS) classification of haemorrhagic **(Refer Table 4.3)** and Shock Index (SI) **(Refer Table 4.4)**.

Table 4.2: Pictorial Guide to a Physical Method in Estimating Acute Blood Loss

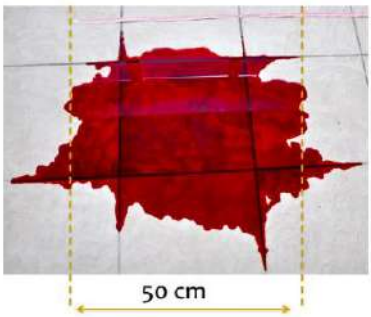
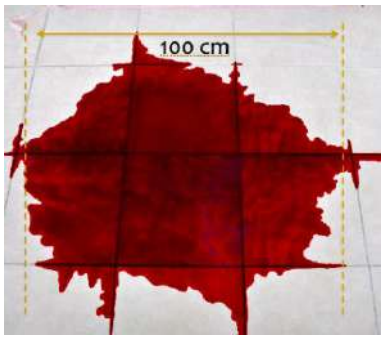
1. Maternity pad (21 x 7.5 cm)		
		
30ml	60ml	90ml

2. Blue sheet and soaked maternity pad (21 x 7.5 cm)	**3. Abdominal Pad (15 x 20 cm)**	
		
150ml	50ml	100ml

4. Surgical Gauze (7 x 7 cm)		5. Gamgee (20 x 20 cm)
		
10ml	30ml	250ml

6. Kidney Dish

500ml

7. Floor	Spill
	
500ml	1500ml

8. Postpartum Haemorrhage	
	
On bed only 1000ml	Spillage to floor 2000ml

4.4.1 ADVANCE TRAUMA LIFE SUPPORT HAEMORRHAGIC SHOCK CLASSIFICATION

The Advance Trauma Life Support haemorrhage classification provides an estimation of blood loss method using physiological response including heart rate, blood pressure, pulse pressure, respiratory rate, urine output, mental status and base deficit **(Refer Table 4.3)** However, there may be limitations to its clinical relevance in the elderly, patients with co morbidities and patients on medication such as beta-blockers.

Table 4.3: The ATLS Classification of Haemorrhage

ATLS Classification of Haemorrhage				
Parameter	**Class 1**	**Class 2 (mild)**	**Class 3 (moderate)**	**Class 4 (severe)**
Approximate blood loss	<15%	15-30%	31-45%	>45%
Blood Pressure	Normal	Normal	Normal/ Decreased	Decreased
Heart rate	Normal	Normal/ Increased	Increased	Greatly Increased
Pulse Pressure	Normal	Decreased	Decreased	Decreased
Respiratory Rate	Normal	Normal	Normal/ Increased	Increased
GCS	Normal	Normal	Decreased	Decreased
Urine Output	Normal	Normal	Decreased	Greatly decreased
Base Deficit	0 to -2 meq/L	-2 to -6 mEq/L	-6 to -10 mEq/L	-10 mEq/L or less
Need for blood products	Monitor	Possible	Yes	Massive Transfusion Protocol

4.4.2 SHOCK INDEX (SI)

Shock Index (SI) was initially described in 1967; it provides an approximation of hemodynamic status in addition to traditionally vital signs. It is defined as the ratio of the heart rate (HR) to the systolic blood pressure (SBP). In addition to SI, modified SI (MSI) have been proposed in continued efforts to improve the prognostic value.MSI was developed to incorporate the MAP rather than only SBP, as DBP is also useful to determine clinical severity of illness.

Meanwhile, the Paediatric Adjusted Shock Index (SIPA) was developed for paediatric populations and has proven to be more reliable than the standard adult cut offs **(Refer Table 4.4)**.

In healthy adults, the normal SI range is between 0.5 - 0.7. The SI is utilised as a physiological score to assess the severity of hypovolemia, shock and has been advocated to better risk – stratify critical bleeding patients. Worsening of SI is associated with increasing injury severity score, mortality, fluid requirements, vasopressor use and blood transfusion.

Table 4.4: Shock Index (SI)

Shock Index (SI) name variation	Equation	Notes
SI	HR/SBP	-
Modified SI (MSI)	HR/MAP	MAP substituted for SBP
Shock Index Paediatric Adjusted (SIPA)	HR/SBP	Formula for SI is the same. Cut offs are different for each age group : • Ages 4 - 6 : > 1.22 • Ages 7 - 12 : > 1.0 • Ages 13 - 16 : > 0.9

4.5 PREDICTING THE NEED FOR MASSIVE TRANSFUSION

Predicting the need for massive blood transfusion is indeed challenging. Although rapid activation and transfusion improves survival, the risks and complications associated with blood transfusion should not be overlooked. Various prediction tools have been developed to aid the decision in triggering massive transfusions.

4.5.1 ASSUMPTION OF BLOOD CONSUMPTION (ABC)

Using 4 clinical variables, ABC score was developed to assist clinicians in identifying patients requiring massive transfusion. It is a tool used to predict the need for massive transfusion based on specific objective measures. A score of ≥ 2 was found to predict the need for massive transfusion with a sensitivity of 75% and specificity of 86% **(Refer Table 4.5).**

Table 4.5: Assumption of Blood Consumption (ABC) Score

Score Items	Points	Points
Positive Focused Assessment with Sonography for Trauma (FAST)	Yes = 1	No = 0
Systolic BP ≤ 90 mmHg in the Emergency Department	Yes = 1	No = 0
HR ≥ 120 in the Emergency Department	Yes = 1	No = 0
Penetrating mechanism	Yes = 1	No = 0
Score 0 or 1 : Patient is less likely to require massive transfusion **Score 2, 3 or 4** : Patient is likely to require massive transfusion		

4.5.2 PRINCE OF WALES HOSPITAL / RAINER (PWH)

This score **(Refer Table 4.6)** was developed based on a retrospective analysis of 1891 trauma patients derived from PWH trauma registry. It consists of 7 (seven) variables: heart rate, SBP, Glasgow Coma Scale, displaced pelvic fracture, CT or FAST scan positive for fluid, base deficit, and haemoglobin (Hb) level. With a sensitivity of 31.5% and a specificity of 99.7%, a PWH score > 6 indicates the need for MTP.

Table 4.6: Prince of Wales Hospital / Rainer (PWH) Score

Score items	Points
SBP < 90 mmHg	3
GCS ≤ 8	1
HR > 120 bpm	1
Displaced Pelvic Fracture	1
CT scan or FAST positive	2
Base deficit > 5 mmol/L	1
Haemoglobin (Hb) ≤ 7g/dL	10
Haemoglobin (Hb) 7.1 - 10 g/dL	1
Total score > 6 indicated the need for MTP	

4.5.3 TRAUMA ASSOCIATED SEVERE HAEMORRHAGE (TASH)

It is a score developed using 8 (eight) variables to predict the probability for massive transfusion at early stage of severe injuries. The probability of massive transfusion increases accordingly to the score. Trauma associated severe haemorrhage score of 18 corresponds well to a massive transfusion probability of almost 50% of the time **(Refer Table 4.7)**.

The score is mainly derived from a cohort of blunt trauma patients. It may be possible that the assumptions based upon the datasets may not be equally relevant for the penetrating trauma patient. Calculation of probability score to predict transfusion may be delayed as certain TASH score parameters will depend on the availability of haematological investigation results.

Table 4.7: Trauma Associated Severe Haemorrhage (TASH) Score

Score items	Description	Points
Gender	Male Female	1 0
Systolic Blood Pressure	<100mmHg <120mmHg ≥120mmHg	4 1 0
Heart Rate	<120 bpm ≥120 bpm	2 0
Clinically unstable pelvic fracture		6
Open or dislocated femur fracture		3
Positive Focused Assessment with Sonography for Trauma (FAST) for intra-abdominal fluid		3
Haemoglobin	< 7 g/dL < 9 g/dL < 10 g/dL < 11 g/dL < 12 g/dL ≥ 12 g/dL	8 6 4 3 2 0
Base Excess	< -10mmol/L < -6mmol/L < -2mmol/L ≥ -2mmol/L	4 3 1 0

4.6 MASSIVE HAEMORRHAGE MANAGEMENT

4.6.1 MASSIVE TRANSFUSION PROTOCOL (MTP)

It is a protocol that describes the process of blood transfusion management in the massive haemorrhage patient. The protocol is based upon a fixed ratio of Packed Red Blood Cells (PRBCs), Fresh Frozen Plasma (FFP), Platelet and Cryoprecipitate in each pack / cycle (1:1:1:1 ratio) .

In addition, MTP allows rapid volume restoration and maintenance of circulating volume resulting in improved organ perfusion and tissue oxygenation in a massive haemorrhage patient. Haemostatic and balanced resuscitation are strategic clinical approaches applied in the acute management massive transfusion guidelines ought to incorporate strategies that accommodate flexibility of volume or ratio of blood products to address the individual patient's needs.

Table 4.8: Massive Transfusion Protocol (MTP)

Massive Transfusion Protocol (MTP)

Definition of Massive Haemorrhage
- Active ongoing bleeding at the rate of 150ml/min with hemodynamic instability (SBP<90 mmHg and/or heart rate >110/min
- Loss of 50% of blood volume within 3 hours
- Loss of total blood volume in 24 hours

Activation Criteria
- Scoring Systems
- Clinical Judgement

Mechanism of activation
- Activation made by attending clinician

Information required by Lab
- Name of Clinician in charge
- Patient's details

Blood Samples and Forms as required by Lab
- Send GXM in EDTA bottle
- Ensure all relevant forms are completed accurately

Consider :
- Pharmacological Adjunct
- Reversal and Replacement therapy in anticoagulated and/or antiplatelet patients

Initiate MTP activation

GXM

Send Baseline Blood Investigation
FBC / Biochemistry
Coagulation screen (PT/INR/APTT/Fibrinogen)
Arterial / Venous Blood Gas

Fixed Package For Transfusion
4 units of PRBC
4 units of Fresh Frozen Plasma
4 units of Cryoprecipitate
4 units of Platelet

Assessment of Bleeding Control and requirement for further transfusion?

YES → **Clinician request continuation of MTP or Conversion to T-MTP**

NO → **Deactivate MTP**

OPTIMISE:
- oxygenation
- cardiac output
- tissue perfusion
- metabolic state

MONITOR (every 30-60 mins)
- Full blood count
- Coagulation screen
- Ionised calcium
- Arterial / venous blood gases

AIM FOR:
- temperature -normothermia
- pH:7.35 -7.45
- base excess: normalisation of BE -2 to +2
- lactate ≤ 2 mmol/L
- Ca^{2+} > 1.1 mmol/L
- platelets > 50 x 10^9/L
- INR ≤ 1.5
- PT/APTT < 1.5 x normal
- fibrinogen > 1.5g/L

Availability of blood and blood products during MTP activation		
Blood Products	*Availability (minutes)*	*Transportation*
Cross matched safe O	*Availability on site or blood bank*	*In blood box with ice pack (2-10°C)*
First stage cross matched blood	*Within 30 minutes*	
Full cross matched PRBC	*Within 45 minutes*	
Fresh Frozen Plasma	*Within 30 minutes*	
Cryoprecipitate	*Within 30 minutes*	*In blood box WITHOUT ice (20-24°C)*
Platelets	*Immediate*	

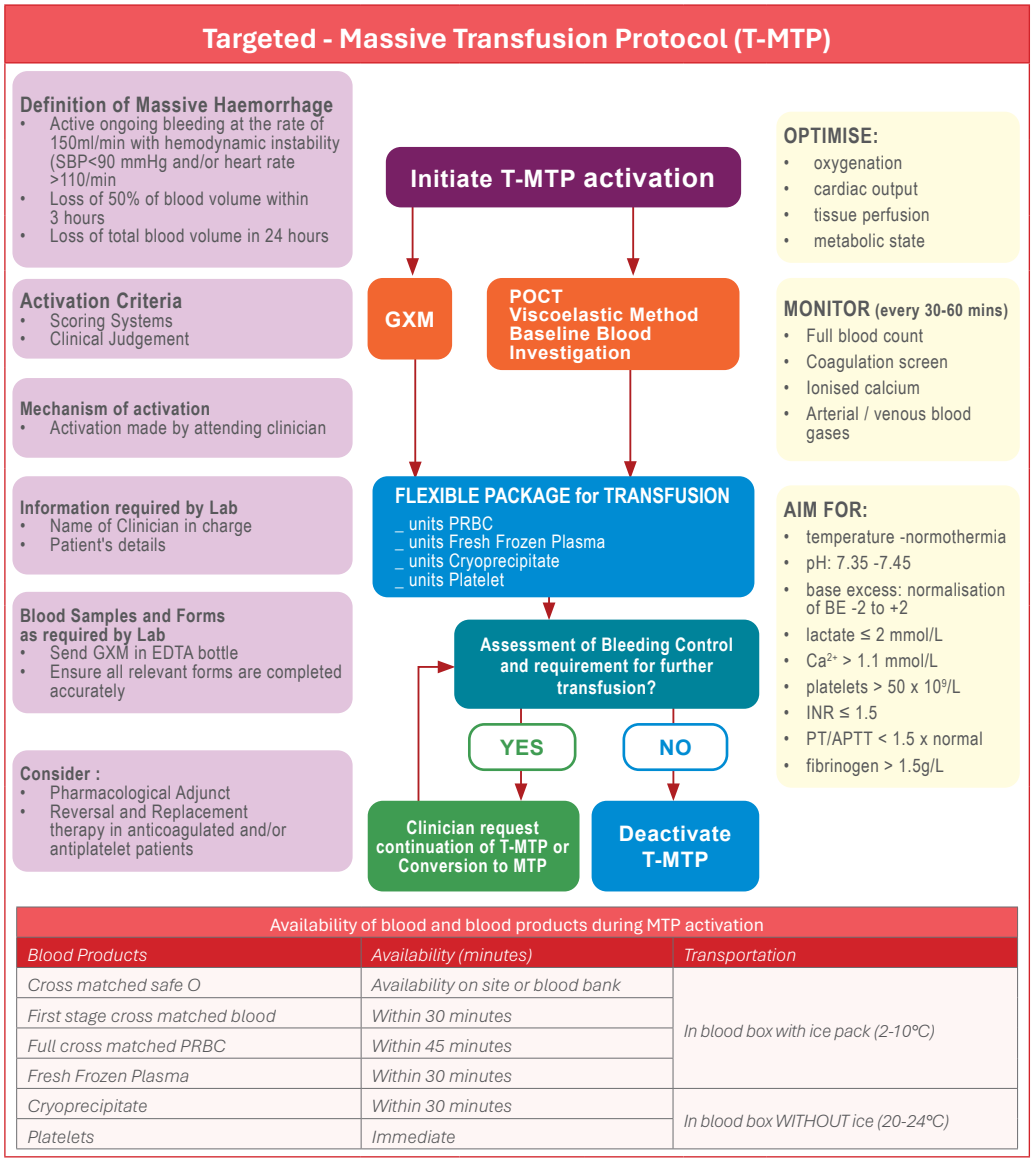
Note: MTP adapted from Hospital Sungai Buloh. Variation is expected depending on the local setting and available resources.

4.6.2 TARGETED MASSIVE TRANSFUSION PROTOCOL (T-MTP)

It is a massive blood transfusion strategy that enables attending clinicians to rapidly attain and individualise the amount, type or ratio of blood products required for resuscitation of the massively bleeding patient. The T-MTP provides rapid availability of blood products similarly to the MTP. The clinician will be able to determine desired ratios, type and amounts of blood products as opposed to a fixed and predetermined strategy.

The T-MTP is a guided massive transfusion strategy utilizing objective clinical assessment with the adjunct use of Point of Care Testing (POCT) i.e. Full Blood Count (FBC), Blood Gas Analysis, International Normalised Ratio (INR), Fibrinogen, Viscoelastic Assays (TEG or ROTEM) and others. The T-MTP provides clinicians the means to uniquely individualize massive transfusion protocol to the need of each patient, thus reducing unnecessary transfusions and avoiding potential complications.

Table 4.9: Targeted - Massive Transfusion Protocol (T-MTP)



Availability of blood and blood products during MTP activation		
Blood Products	*Availability (minutes)*	*Transportation*
Cross matched safe O	*Availability on site or blood bank*	*In blood box with ice pack (2-10°C)*
First stage cross matched blood	*Within 30 minutes*	
Full cross matched PRBC	*Within 45 minutes*	
Fresh Frozen Plasma	*Within 30 minutes*	
Cryoprecipitate	*Within 30 minutes*	*In blood box WITHOUT ice (20-24°C)*
Platelets	*Immediate*	

Note: T-MTP adapted from Hospital Sungai Buloh. Variation is expected depending on the local setting and available resources.

4.6.3 GUIDELINE OF MASSIVE TRANSFUSION PROTOCOL

4.6.3.1 Activation Criteria of MTP or T- MTP

Activation of massive bleeding management should include:

- Clinical Scoring Tool: Scoring systems may guide to identify patients that require massive transfusion **(refer 4.5: Predicting The Need for Massive Transfusion).**
- Clinical judgements: Various factors need to be taken into consideration to assess the extent of haemorrhage such as high mechanism of injury, anatomical injury pattern, patient's physiology, and rate of haemorrhage.

4.6.3.2 Mechanism of Activation

Decision to activate the MTP or T-MTP is made by the attending clinician preferably with high authority (Consultant / Specialist). A Medical Officer must act a Coordinator to ensure smooth communication with the transfusion laboratory personnel.

4.6.3.3 Information Required by the Transfusion Laboratory

Transfusion Laboratory requires the following relevant information:

- Name of the attending clinician (Specialist) who activated the MTP/ T-MTP.
- Name and contact number of MTP / T-MTP Coordinator (Medical Officer).
- Patient's details: full name, identification number, hospital registration number (at least 2 identifiers) and location of MTP / T- MTP activation.
- Clinical diagnosis of the patient.
- Score based on Clinical Scoring Tool used based on the hospital policy.

4.6.3.4 Blood samples and forms as required by the Transfusion Laboratory

Guided by local hospital policy, blood samples and relevant completed forms that may be required by the Transfusion Laboratory such as:

- 10 ml of blood in Ethylene-diamine-tetra-acetic acid (EDTA) bottle.
- Blood / Component Request form.

4.6.3.5 Baseline Blood Investigation

Blood investigations required for initial assessment are as follows:

- Full Blood Count
- Coagulation Profile
- Fibrinogen
- Renal Function Test (including the Electrolytes)
- Liver Function Test
- Troponin
- Creatine Kinase
- Arterial / Venous Blood Gases Analysis

4.6.3.6 MTP and T-MTP: Transfusion Protocols

Massive Transfusion Protocol (MTP) involves a fixed ratio and volume transfusion strategy, consisting of 4 units of Packed Red Blood Cells, 4 units of Fresh Frozen Plasma, 4 units of Random Platelets (or 1 unit of apheresis Platelet), and 4 units of Cryoprecipitates, all administered in a 1:1:1:1 ratio. Subsequent packs or cycles are prepared immediately after the initial delivery of blood products, or upon request by the attending clinician based on the patient's assessment. T-MTP, or Targeted Massive Transfusion Protocol, allows flexibility for the attending clinician to determine the ratio, type, and quantity of blood products, guided by clinical assessment and supported by point-of-care testing (POCT) including FBC, Blood Gas Analysis, INR, Fibrinogen, Viscoelastic Method, and others. The T-MTP and MTP can be activated interchangeably when necessary.

4.6.3.7 Assessment of Haemorrhage and Control

Patients with massive haemorrhage should be subjected for immediate haemostasis via surgical or interventional radiological measures. Pharmacological adjuncts also may be used. Tranexamic acid exerts an antifibrinolytic effect and prevents dissolution of haemostatic plug. Intravenous vitamin K, calcium, prothrombin concentrates complex and desmopressin may be used as an adjunct in haemostatic resuscitation when appropriate.

4.6.3.8 Deactivation of MTP / T-MTP

The deactivation of MTP / T-MTP is made based upon the combination of clinical assessment guided by POCT / laboratory markers delineating haematological end points. The decision to deactivate the MTP/ T-MTP should be made by the attending clinician and must be conveyed to the transfusion laboratory personnel in a clear manner. Clinical criteria that may be used to guide MTP/ T-MTP deactivation:

- Anatomical: Bleeding control is achieved.
- Physiological: Stabilization of hemodynamic.
- POCT / Laboratory: Improving and stabilizing laboratory values.

4.6.4 OPTIMIZATION AND MONITORING OF PARAMETERS DURING MASSIVE TRANSFUSION

Optimisation and monitoring of parameters are vital for successful resuscitation. Principles in managing massive haemorrhage include:

4.6.4.1 Optimisation of resuscitation

1. Restoring haemostasis.
2. Improving Oxygenation.
3. Ensuring Adequate Cardiac Output.
4. Improving Tissue Perfusion.
5. Correcting Metabolic Derangements.
6. Prevent Hypothermia.
7. Prevent further coagulopathy.

4.6.4.2 Monitoring of Haematological and Biochemical Parameters

1. Full Blood Count.
2. Coagulation Profile.
3. Ionized Calcium.
4. Blood Gas Analysis.
5. Viscoelastic Assay (TEG / ROTEM) if available.

4.6.4.3 Resuscitation Targets

1. Temperature - normothermia
2. pH 7.35 – 7.45
3. Base Excess- normalization (-2 to +2)
4. Lactate ≤ 2 mmol/L
5. Calcium > 1.1 mmol/L
6. Platelet > 50 x 10^9/L
7. PT/APTT < 1.5 x normal
8. INR ≤ 1.5
9. Fibrinogen > 1.5g/L

4.7 PHARMACOLOGICAL ADJUNCTS IN MASSIVE TRANSFUSION

Massive transfusions have played a crucial role in the management of massive haemorrhage. It is important to avoid complications and reverse existing coagulopathy throughout resuscitation in which pharmacological adjuncts play an important role.

4.7.1 CALCIUM

Acute hypocalcaemia is a common complication of massive transfusion, contributed by the actions of calcium chelators used as preservatives in transfused blood. It worsens coagulopathy subsequently leading to mortality; .hence it is crucial to perform regular monitoring of ionised serum calcium levels. Serum calcium should be kept within the normal range throughout resuscitation. Intravenous calcium chloride or calcium gluconate may be administered to correct hypocalcaemia.

Recommendation	Level
Ionised serum calcium levels should be regularly monitored and maintained within the normal range during massive transfusion.	Grade 1C
The administration of calcium chloride or calcium gluconate to correct hypocalcaemia.	Grade 1C

4.7.2 ANTIFIBRINOLYTIC AGENTS

Tranexamic acid (TXA) is a synthetic lysine derivative. TXA inhibits fibrinolysis by blocking the lysine binding site on plasminogen, subsequently preventing plasmin formation, fibrin degradation and promoting stabilisation of the fibrin clot matrix. Tranexamic acid has been proven to reduce deaths caused by traumatic haemorrhage; when administered early, within 3 hours of injury.

Recommendation	Level
Tranexamic acid (TXA) to be administered to the trauma patient who is bleeding or at risk of significant bleeding as soon as possible and within 3 hours after injury at a loading dose of 1g over 10 minutes, followed by an infusion of 1g over 8 hours.	Grade 1A
Protocols for the management of bleeding patients should consider administration of the first dose of TXA en-route to the hospital.	Grade 1C
TXA should be administered to patients with postpartum haemorrhage as soon as possible and no more than 3h after childbirth, followed by a second dose if bleeding continues after 30 minutes or restarts within 24h.	Grade 1B

4.7.3 PROTHROMBIN COMPLEX CONCENTRATE (PCC)

PCC can be considered in massive haemorrhage patients after performing a thorough clinical assessment and POCT evaluation. The use of PCC should only be administered after a risk vs benefit assessment. The use of PCC may promote early reversal of coagulopathy and reduce total volume of blood transfusion in the massive haemorrhage patient. However, the efficacy of administering PCC is largely dependent upon other physiological and anatomical parameters.

Recommendation	Level
Treatment with factor concentrates can be based on standard laboratory coagulation parameters and/or viscoelastic evidence of a functional coagulation factor deficiency.	Grade 1C

4.7.4 DESMOPRESSIN

Desmopressin is a synthetic analogue of the antidiuretic hormone arginine. It promotes the release of factor VIII and von Willebrand factor in plasma. Traditionally, it has been used for the treatment of mild haemophilia and von Willebrand disease (type 1). However, its use for other potential indications has been expanded. Desmopressin improves haemostasis by promoting platelet adherence and aggregation. Desmopressin may be considered in haemorrhaging patients who are treated with platelet-inhibiting drugs or have underlying von Willebrand disease. The use of desmopressin should only be administered after performing a comprehensive risk vs benefit assessment.

Recommendation	Level
Administration of desmopressin (0.3µg/kg) should be considered in the severe bleeding patient treated with platelet-inhibiting drugs or von Willebrand disease.	Grade 2C

4.7.5 VITAMIN K

Vitamin K is a critical cofactor in the synthesis of factor II, VII, IX, and X. Vitamin K is effective in reversing the anticoagulant effects of coumarin derivatives such as warfarin. It is recommended that Vitamin K is used as an adjunct therapy in the haemorrhaging patient treated with warfarin. Vitamin K can be concomitantly administered together with either PCC or plasma.

Recommendation	Level
In life threatening bleeding patients on warfarin therapy with an INR of ≥ 1.5, it is recommended to immediately cease warfarin therapy and administer: • Intravenous vitamin K • and /or Prothrombin Complex Concentrate (PCC) • and / or Fresh Frozen Plasma	Grade 1C

4.7.6 ANTICOAGULANT REVERSAL AND REPLACEMENT THERAPY

Described below are suggested agents used for purpose of reversal and replacement therapy in the actively haemorrhaging anticoagulated patients:

Table 4.10: Anticoagulants monitoring, reversal and replacement therapy

Drug	Targeted factors	Monitoring	Anticoagulant reversal / Replacement therapy
Warfarin	Factors II, VII,IX, X Protein C &S	INR	• Vitamin K • PCC • FFP
UFH	Factor IIa, Xa (VIIa, IXa,XIa, XIIa)	APTT	Protamine Sulfate
LMWH	Factor IIa, Xa	Anti-factor Xa	Protamine Sulfate
Fondaparinux	Factor Xa	Anti-factor Xa	PCC
Dabigatran	Factor IIa (Thrombin)	• APTT • Thrombin Time (TT) • Diluted Thrombin Time (dTT) • Ecarin Clotting Time (ECT)	• Idarucizumab • PCC
Rivaroxaban	Factor Xa	Anti-factor Xa	• Andexanet alfa • PCC
Apixaban	Factor Xa	Anti-factor Xa	• Andexanet alfa • PCC

4.8 COMPLICATIONS OF MASSIVE TRANSFUSION

Rapid high volume blood transfusion is associated with complications and adverse effects.

4.8.1 HYPOTHERMIA

Transfusion of cold blood products may lead to hypothermia which leads to:

- Impaired platelet and coagulation factor function.
- Enzyme inhibition.
- Fibrinolysis.
- Reduced citrate metabolism.
- Reduced hepatic metabolism.
- Reduced drug clearance.

Prevention such as reduction of heat loss and rewarming techniques should be commenced early to achieve / maintain normothermia such as:

- Remove any wet clothing.
- Raise the ambient room temperature.
- Warm the patient with heating blankets or heating lamps.
- Use heated and humidified oxygen for ventilators.
- Use validated inline blood and fluid warmers.

4.8.2 ACIDOSIS AND ALKALOSIS

Blood is typically stored in citrate phosphate dextrose adenine (CPDA) solutions with a pH of 7.0 for most fresh PRBC units. As blood ages, citrate is metabolized to bicarbonate, and in patients who require massive transfusion, metabolic alkalosis may occur. Metabolic acidosis arises a result of hypoperfusion of tissues; therefore, further resuscitation of the patient should be continued as acidosis results in impaired haemostasis and coagulopathy.

4.8.3 CITRATE TOXICITY, HYPOCALCAEMIA AND HYPOMAGNESEMIA

Blood is anticoagulated with sodium citrate and citric acid. As a result of massive transfusion, infusion of large amount of citrate occurs which may lead to citrate toxicity. In addition, citrate toxicity may develop due decreased citrate metabolism in the presence of hypothermia and hypoperfusion in massive haemorrhage.

As a consequence of massive transfusion, calcium levels may decrease significantly. Chelation of calcium by citrate reduces the availability of ionised calcium leading to hypocalcaemia. Hypocalcaemia further aggravates coagulopathy, worsen cardiac function and reduces systemic vascular resistance. Furthermore, massive blood transfusions may result in hypomagnesaemia, presumed to be due to citrate toxicity, haemodilution, and/or associated comorbidities.

4.8.4 HYPERKALAEMIA

Hyperkalaemia resulting from Packed Red Blood Cell (PRBC) transfusions has been recognized as a common transfusion complication. Stored PRBC units may contain a sufficient amount of supernatant [K+] which may result in hyperkalaemia if large volumes are transfused. Supernatant [K+] in PRBC units increases substantially with time because of the potassium leakage from RBC lysis. In addition, other factors may contribute to hyperkalaemia such as severity of tissue damage and underlying renal function insufficiency. Acidosis due to hypoperfusion may further worsen hyperkalaemia.

4.8.5 COAGULOPATHY

Haemostatic abnormalities may arise in patients requiring massive transfusion due to a combination of dilution, consumption of clotting factors and fibrinolysis. Coupled with hypothermia, impaired clot formation may further exacerbate blood loss. Coagulation status should be closely monitored with laboratory tests and point of care testing.

4.9 RECOMMENDATIONS

Recommendation	Level
Ionised serum calcium levels should be regularly monitored and maintained within the normal range during massive transfusion.	Grade 1C
Administration of calcium chloride or calcium gluconate to correct hypocalcaemia.	Grade 1C
Tranexamic acid (TXA) to be administered to the trauma patient who is bleeding or at risk of significant bleeding as soon as possible and within 3 hours after injury at a loading dose of 1g over 10 minutes, followed by an infusion of 1g over 8 hours.	Grade 1A
Protocols for the management of bleeding patients should consider administration of the first dose of TXA en-route to the hospital.	Grade 1C
TXA should be administered to patients with postpartum haemorrhage as soon as possible (no more than 3 hours after childbirth), followed by a second dose if bleeding continues after 30 min or restarts within 24 hours.	Grade 1B
Treatment with factor concentrates can be based on standard laboratory coagulation parameters and/or viscoelastic evidence of a functional coagulation factor deficiency	Grade 1C
Administration of desmopressin (0.3µg/kg) should be considered in the severe bleeding patient treated with platelet-inhibiting drugs or von Willebrand disease.	Grade 2C
In life threatening bleeding patients on warfarin therapy with an INR of ≥ 1.5, it is recommended to immediately cease warfarin therapy and administer : • Intravenous vitamin K • and / or Prothrombin Complex Concentrate • and / or Fresh Frozen Plasma	Grade 1C

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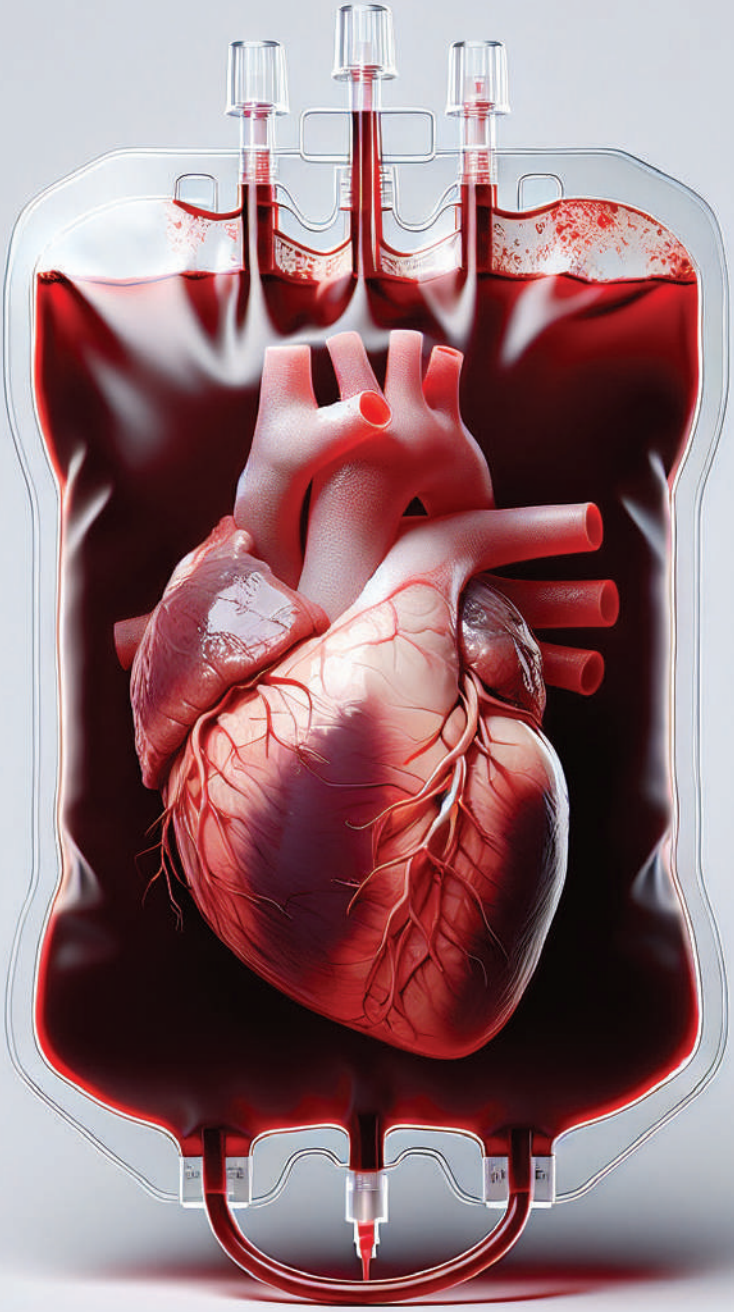


SUBMODULE 5

CARDIOTHORACIC

5.1 INTRODUCTION

Cardiac surgery is associated with high risk of perioperative bleeding that may require allogenic blood transfusion due to the nature of the invasiveness of the procedures, usage of high-dose anticoagulant and the effects of cardiopulmonary bypass (CPB).

Risk factors that contribute to increased risk of bleeding, include chest reopen, type of surgical procedure (aortic surgery, redo-sternotomy and complex cardiac surgery), prolonged CPB duration, renal dysfunction and patient factors such as advanced age, female gender and small body surface area.

Extracorporeal circuits cause mechanical damage to blood components such as haemolysis, platelet destruction and altered coagulation profile.

These haemostatic changes lead to consumptive coagulopathy, elevated D-dimers, low fibrinogen, prolonged PT/APTT, thrombocytopenia and low antithrombin level.

Blood transfusion in patients undergoing cardiac surgery, has been shown to increase morbidity and mortality. The first step towards creating PBM guidelines is to identify patients at high risk of bleeding and transfusion requirements. Meticulous surgical and perioperative haemostasis as well as minimization of blood loss will contribute to a reduction in transfusion requirement. This will translate into improvement in patient outcome and reduction of health care costs. Thus, a multifactorial strategy and multidisciplinary team approach are essential for a successful patient blood management (PBM) programme.

One of the multifactorial strategies is goal-directed perfusion management, with the aim of ensuring adequate oxygen delivery during cardiopulmonary bypass (CPB). Acute kidney injury is a common complication following cardiac surgery.

Goal directed perfusion management consist of perfusion flow adjustment during CPB, maintaining pulsatile vs non pulsatile CPB flow, preserving adequate HCT threshold with the guidance of haemodynamic monitoring such as cerebral oximetry, mean arterial pressure and management of acid base balance.

5.2 RECOMMENDATIONS

5.2.1 PREOPERATIVE RECOMMENDATIONS

Recommendation 1:

- All patients planned for cardiac surgery with Hb < 13 g/dL should be evaluated for iron deficiency anaemia (IDA)[1].
- The evaluation for IDA includes iron studies (serum iron, TIBC, TSAT, serum ferritin) and reticulocyte haemoglobin (CHr or Ret-He)[1].
- IDA should be present if serum ferritin is less than 30 µg/L (less than 100 ug/L in patient with co-existing inflammatory diseases) or a reticulocyte haemoglobin is less than 25 pg[1].

Recommendation 2:

- Non-IDA patient should be further evaluated to determine the aetiology of the anaemia[1].

Recommendation 3:

- All cardiac surgery patients identified with anaemia may be considered for iron supplement (oral or intravenous) (Class IIb)[1].

Recommendation 4:

- Erythropoietin stimulating agents (ESAs) with iron supplement should be considered for the treatment of preoperative non-IDA for elective cardiac surgery (Class IIa)[1].

Recommendation 5:

- Allogeneic packed cell transfusion is unlikely to improve oxygen transport when the haemoglobin concentration is greater than 10 g/dL and therefore it is not recommended (Class III: No Benefit, Level B-R)[2].

Recommendation 6:

- Appropriate duration of cessation of anti-platelet agent prior to elective cardiac surgery is recommended to reduce bleeding (Class I, Level B-NR)[2].

5.2.2 INTRAOPERATIVE RECOMMENDATIONS

Recommendation 1:

- It is recommended to implement measures to reduce haemodilution by reducing fluid infusion, priming volume and other CPB strategies to reduce the risk of bleeding and the need of transfusion (Class I, Level C)[1].

Recommendation 2:

- The use of red cell salvage is helpful for blood conservation in cardiac operations using CPB (Class II, Level B)[1].

Recommendation 3:

- Ultrafiltration and modified ultrafiltration (MUF) may be considered as part of a blood conservation strategy to minimize haemodilution (Class IIb, Level B)[1].

Recommendation 4:

- The use of a biocompatible extracorporeal circuit (ECC) coating may be considered to reduce perioperative bleeding and transfusion (Class IIb, Level B)[1].

Recommendation 5:

- A haematocrit of 21–24% may be considered during CPB when an adequate DO_2 (>273 ml O_2/min/m^2) level is maintained (Class IIb, Level B)[1].

Recommendation 6:

- The use of leucocyte-depleted packed cell during CPB is recommended to reduce infectious complications (Class I, Level B)[1].

Recommendation 7:

- Synthetic anti-fibrinolytic agents such as Tranexamic acid or Epsilon-aminocaproic acid (EACA) are indicated to reduce blood loss and blood transfusion (Class 1, Level A)[1].
- Tranexamic acid reduces bleeding and total transfusion during off-pump CABG surgery (Class IIa, Level B-R)[2].

Recommendation 8:

- Restrictive perioperative allogeneic packed cell transfusion strategy is recommended in preference to a liberal transfusion strategy for perioperative blood conservation (Class 1, Level A)[2].

Recommendation 9:

- Prophylactic use of plasma in cardiac surgery in the absence of coagulopathy is not indicated, does not reduce blood loss and exposes patients to unnecessary risks and complications of allogeneic blood component transfusion (Class I, Level B-R)[2].

Recommendation 10:

- Point of care testing, such as with viscoelastic devices (ROTEM or TEG) is recommended to reduce peri-procedural bleeding and transfusion in cardiac surgical patients (Class IIa, Level B)[1].

Recommendation 11:

- Acute Normovolaemic Haemodilution (ANH) maybe considered to reduce postoperative transfusion (Class IIa, Level A)[1].
- Retrograde Autologous Priming (RAP) of the CPB circuit should be use whenever possible (Class I, Level B-R)[2].

Recommendation 12:

- Topical application of antifibrinolytic agents the surgical site after CPB is reasonable to limit chest tube drainage and transfusion requirement after cardiac operations using CPB (Class IIa, Level B–R)[2].

5.2.3 POSTOPERATIVE RECOMMENDATIONS

Recommendation 1:

- Transfusion of packed cells (PC) is recommended to base on the clinical condition of the patient, rather than on a fixed haemoglobin threshold (Class I, Level B)[1].

Recommendation 2:

- Platelet concentrate should be transfused in bleeding patients with a platelet count below 50 X 10^9/L) or to patients on antiplatelet therapy with bleeding complications (Class IIa, Level C)[1].

Recommendation 3:

- Prothrombin complex concentrate (PCC) or fresh frozen plasma (FFP) administration should be considered to reduce bleeding and transfusions in patients where bleeding is related to coagulation factor deficiency (Class IIa, Level B)[1].

Recommendation 4:

- Fibrinogen substitution may be considered to reduce postoperative bleeding and transfusions in the bleeding patient with a low fibrinogen level (<1.5 g/l) (Class IIb, Level B)[1].

Recommendation 5:

- Off-label use of rFVIIa may be considered to reduce bleeding in patients with refractory, nonsurgical bleeding (Class IIb, Level B)[1].

Recommendation 6:

- Prophylactic use of DDAVP is not recommended. However, it should be considered in bleeding patients with platelet dysfunction due to either inherited or acquired bleeding disorders (Class IIa, Level C)[1].

Recommendation 7:

- Restrictive perioperative allogeneic packed cell transfusion strategy is recommended in preference to a liberal transfusion strategy for perioperative blood conservation (Class 1, Level A)[2].

5.3 PREOPERATIVE

5.3.1 PREDICTORS FOR BLEEDING AND BLOOD TRANSFUSION

Factors associated with increased risk of bleeding, transfusion and reoperation:

- Advanced age
- Female gender
- Small body surface area
- Preoperative dual anti platelet (DAPT)
- Poor platelet function
- Preoperative anaemia
- History of recent myocardial infarction
- Coagulation/clotting abnormalities
- Multiple comorbidities.
- Non elective surgery
- Redo or complex surgery

5.3.2 PREOPERATIVE ANAEMIA MANAGEMENT

- Oral iron or intravenous Iron

Table 5.1: Cessation of anticoagulation and antiplatelet prior to surgery

Days prior to surgery	Recommendations (adapted from several guidelines)
-8	Stop prasugrel
-7	
-6	Stop warfarin, clopidogrel Stop aspirin for patients with high bleeding risk# or refuse transfusion
-5	For patients previously on warfarin, start UFH or therapeutic dosage LMWH*
-4	Stop ticagrelor
-3	Stop DOACs (dabigatran, apixaban, edoxaban)
-2	Stop LMWH Stop DOACs (rivaroxaban)
-1	Stop abciximab 12 hours before surgery Stop UFH 6 hours before surgery Stop eptifibatide & tirofiban 4 hours before surgery
0 (day of surgery)	Continue aspirin for normal or low bleeding risk patients

** This is a recommendation by the PBM cardiothoracic submodule, adapted from the 2017 EACTA guidelines.*

NOTES

 # High bleeding risks: complex/redo surgery, severe renal impairment, haematological disorders, hereditary platelet dysfunction.

** Bridging of warfarin with UFH/ LMWH is indicated in patients with high thrombotic risk.*

Patients with renal impairment:

- *Stop warfarin & DOACs a day earlier than the recommendation in the above table*
- *Stop LMWH earlier than the recommendation in the above table*

5.3.3 PREOPERATIVE AUTOLOGOUS BLOOD DONATION (PABD)

Introduction

Autologous blood donation is the collection of patient's own blood and stored prior to the planned surgery. It provides the safest blood for those who have alloantibodies and rare blood group. However, PABD require adequate bone marrow response, the need for multiple trained personnel and is also limited by multiple factors in cardiac surgical set up.

Selection of patient

Inclusion criteria

- Haemoglobin ≥ 13 g/dL (male), ≥ 12.5 g/dL (female)
- Anticipated excessive blood loss
- Rare blood group / alloantibodies
- Patient refusal to donor blood transfusion but will accept own blood (PABD)

Exclusion criteria

- Severe aortic stenosis
- Significant cardiopulmonary disease (symptomatic left main stem disease, congestive heart failure, EF ≤ 45%, Class 3 and 4)
- Preoperative anaemia
- Haemoglobinopathies
- Recent infection (7 - 14 days)
- Uncontrolled hypertension
- Active seizure

Method

- A unit of blood/week, a month prior to operation
- The last unit should be 72 hours prior to surgery.
- Iron supplement and erythropoietin therapy to enhance erythropoiesis.
- Labour intensive (collection, storage of blood and coordination of surgery dates)
- Pre-donated units are stored, depletion of 2,3 DPG and impaired ability of erythrocytes to unload oxygen to tissues.

5.4 INTRAOPERATIVE

5.4.1 METICULOUS HAEMOSTASIS

- Off-pump CABG
  - Lower dosing of systemic heparin
  - Absence of haemodilution and blood trauma caused by CPB
- Minimally invasive surgery
  - Smaller incision
  - Less tissue dissection
- Topical haemostatic agent
  - Haemostasis sealants
  - Topical antifibrinolytic agents (Tranexamic acid)

5.4.2 ACUTE NORMOVOLUMIC HAEMODILUTION (ANH)

Introduction

- Autologous blood transfusion / Blood conservation technique.
- An alternative to allogeneic blood transfusion.
- Can be perform safely with patient with coronary or valvular disease undergoing cardiac surgery.
- Removal of whole blood from patient before or shortly after induction of anaesthesia.
- Efficacy of the technique depends on the initial Hb, transfusion trigger and amount of blood volume removed and amount of blood volume loss by the patient.
- Maintenance of normovolaemia using crystalloid or colloid replacement fluid.

Patient Selection

Indication

- Normal or high initial haemoglobin level. Hb more than 11 g/dL.
- Expected blood loss > 1000 ml or 20% of estimated blood volume (EBV).
- Good option for patients who decline blood transfusions, including Jehovah's witnesses who generally agree to ANH.
- Patient with rare blood group or alloantibodies.

Contraindication

- Haemodynamically significant arrythmias
- Evidence of infection
- Impaired cardiac function – low ejection fraction < 45%
- Significant aortic stenosis
- Unstable or crescendo angina, symptomatic left main stem (LMS) disease, congestive cardiac failure
- Cyanotic heart disease
- Haematological disorders
- History of stroke
- Impaired renal function with oliguria
- Severe anaemia

Procedure

- Done before or after induction of anaesthesia in operating theatre (OT).
- Blood is collected via a large bore intravenous cannula or the side port of PA sheath.
- Blood is collected in standard anticoagulated blood bag.
- Crystalloid or colloid IV fluids are infused as blood is withdrawn.
- Label patient's name, registration number (RN) and time of collection.
- Ideally a rocker scale should be used and kept inside the same OT.
- Can be stored in the operation room at room temperature (20 - 24 ºC) for up to 8 hours.
- If not used immediately, it can be stored at 1 – 6 ºC for 24 hours.
- Blood is reinfused after major blood loss, during CPB or after protamine administration.
- Blood is reinfused in the reverse order of collection, eg. the last bag collected transfused first.

Amount of blood to withdraw:

- 1 to 3 units (max 4 units) blood removed (1 unit = 450 - 500 ml).
- Aim haemoglobin after completed ANH = 8 – 9 g/dL and target haematocrit between 25-30%.

Table 5.2: Estimated allowable blood to withdraw for acute normovolumic haemodilution

Calculation of Priming Volume

Estimate blood allowable to withdraw:

$V = EBV \times (Hbi - Hbt) / Hbm$

V: volume
Hbi: Hb initial
Hbm: Mean of Hbi and Hbt

EBV: Estimated Blood Volume
Hbt: Hb target

Example = 70 kg male with Hb of 14 g/dL (desire Hb 9 g/dL)
Volume = 70 kg x 70 ml/kg (14 g/dL - 9 g/dL) ÷ 11.5 g/dL
= 2130 ml

5.5 CARDIOPULMONARY BYPASS INTERVENTION

Techniques of optimizing blood product in CPB

1. Haematocrit Management in CPB
2. Selection of appropriate tubing sizes
3. Retrograde and antegrade autologous priming.
4. Vacuum-assisted venous return (VAVR)
5. Microplegia
6. Cell salvage
7. Ultrafiltration
8. Pump blood collection post CPB
9. Biocompatible coating of ECC circuit
10. Minimally Invasive Extracorporeal Circuit (MiECC)

5.5.1 HAEMATOCRIT MANAGEMENT IN CPB

Haemodilutional anaemia is an inevitable consequence of CPB using exsanguinous prime of circuits with conventional priming volumes.

The degree of haemodilutional anaemia that is observed on bypass is related to the patients' initial red cell mass (body size and haematocrit) and priming volume of the extracorporeal circuit (ECC).

Haemodilution is advantageous to a certain degree during CPB:

- Reduce blood viscosity
- Improve microcirculatory flow
- Reduce risk of hypertension during higher bypass flow
- Reduce in haemolysis

The harmful effects of haemodilution are perioperative and postoperative anaemia, tissue oedema and organ dysfunction such as acute kidney injury. Severe haemodilution may occur in smaller size patients.

Static priming volume is the fluid that is used to prime by filling and de-airing the CPB circuit to prevent the risk of air embolism.

Priming fluid commonly used in cardiac centres are Sterofundin or Plasma-lyte, both closely resemble ionic composition of blood. Some centres add mannitol 20% 0.5mg/kg for anti-inflammatory and osmotic diuretic effects. Colloid commonly used is Gelafusine. Blood priming is usually for those with lower pre-bypass haematocrit, paediatric age groups or smaller body surface area (BSA).

Average priming fluid in cardiac centres range from 800mls to 1500mls in adult cases.

Calculation of Priming Volume

$$\text{Priming Volume} = \left(\frac{\text{Patient's Blood Volume X pre-op HCT}}{\text{Required Target HCT}} \right) - \text{Blood Volume}$$

Calculation of estimated haematocrit on CPB:

$$\text{CPB HCT} = \frac{\text{preop HCT x PBV}}{\text{PBV + CPB Prime Volume}}$$

where PBV = patient's blood volume (l) and
CPB (prime volume = extracorporal prime volume (l).

- A haematocrit of 21–24% is considered adequate during CPB, when DO_2 (>273 ml O_2/min/m^2) level is maintained.
- But, if HCT less than 21%, PRBCs may be transfused based on evidence of inadequate organ perfusion:
  - Suboptimal cerebral perfusion (a decreased of cerebral oximetry by more than 20% from base line)
  - Reduced urine output
  - Increasing lactate levels
  - Worsening acidosis
  - High vasopressor requirements
- PRBCs is not recommended to be transfused if HCT is >24% unless worsening clinical condition or bleeding.
- Existing guidelines demonstrated that antithrombin concentrate is more effective than FFP in restoring heparin responsiveness and it allows a reduction in FFP transfusion and volume overload in patient.

To attenuate the harmful effects of haemodilution, oxygen delivery during CPB need to be improve, by increasing the CPB pump flow.

Ranucci et al demonstated *(Oxygen delivery during cardiopulmonary bypass and acute renal failure after coronary operations. Ann Thorac Surg 2005)* that in severe haemodilutional anaemia, increasing pump flows, will improve perfusion and organ damage can be averted.

Calculation of critical oxygen delivery:

$$DLO_2 = \text{pump flow X (haemoglobin X 1.36 X haemoglobin saturation)} + \text{(0.003 X arterial oxygen tension)}$$

$$= F \times (Hb \times 1.36 \times SaO_2) + (0.003 \times PaO_2)$$

5.5.2 SELECTION OF OXYGENATOR APPROPRIATE TUBING SIZES AND OTHER CPB COMPONENTS

Oxygenator

Considerations when choosing the type of oxygenator which depends on

- Flow rates required, prime volumes, pressure drop, heat exchanger efficiency, air handling capabilities, surface coatings.
- Patient's age, body weight and height, type of surgery planned or on the estimated bypass time.
- Integrated oxygenator with arterial filter: more expensive and uses less priming volume.
- Non-integrated: cheaper but more priming volume required.
- Adults require bigger oxygenator size, whilst the paediatric cases, needed smaller.

Cannula and tubing

- The aim of selection of arterial and venous cannula is for efficient CPB flow and optimal drainage.
- The length and size of tubing will affect the volume, shear stress, and pressure drop in the circuit.
- The shorter it is, the lower priming volume is needed.
- But if it is too short, it may restrict the mobility of the cardiac table in the operation theatre and sterility of the surgical area.
- The smaller diameter of the tubing, the higher its resistance, which will reduce the flow.
- Thus, this greater impedance to venous return to the pump, will need an active drainage system such as vacuum assisted venous return.

Reduction in prime volume is a major factor in blood conservation

- ↓ ECC size ↓ ECC Prime volume ↓ Haemodilution
- ↓ ECC size ↓ Blood contact surface ↓ SIRS

Table 5.3: Recommended arterial line and venous line size according to body weight

Patient's weight	Arterial Line Size	Venous Line Size
>3 kg	1/8 inch	3/16 inch
3-6 kg	3/16 inch	3/16 inch
6-9 kg	3/16 inch	1/4 inch
9-20 kg	1/4 inch	1/4 inch
20-35 kg	1/4 inch	3/8 inch
35-50 kg	3/8 inch	3/8 inch
Above 50 kg	3/8 inch	1/2 inch

The above recommendation of tubing sizes commonly practiced in Malaysia.

Pumps

Blood pumps in the current market provide adequate patient blood management in CPB.

The Society of Thoracic Surgeons (STS) Guideline stated that it is not unreasonable to choose centrifugal pump due to its perfusion safety features (Class IIb, Level B).

5.5.3 RETROGRADE AND ANTEGRADE AUTOLOGOUS PRIMING

- Priming CPB with patients' own venous blood through retrograde and antegrade priming method.
- CPB priming fluid is displaced with autologous blood from arterial line and venous line post-cannulation.

  → priming fluid is drained into the re-circulation bag.
- Reduces the level of haemodilution ↓haemodilution anaemia ↓transfusion requirement.
- Reduces ABT intraoperatively and post operatively.

** Retrograde and antegrade autologous priming should be considered as part of blood conservation strategy – Class IIa.*

5.5.4 VACUUM-ASSISTED VENOUS RETURN (VAVR)

- The main advantage of VAVR is the increase in venous return as compared to gravitational drainage.
- Decrease declivity of the membrane oxygenator and venous reservoir, significantly reduces length of CPB circuit and reduction in priming volume.

5.5.5 MICROPLEGIA

- Microplegia is a technique of delivering blood-cardioplegia to arrest the heart.
- Blood is diverted from the arterial line or from a specific built-in port of the oxygenator through an occlusive roller pump. Downstream of the roller pump, the arresting agent is added via a syringe pump.

  Advantages of microplegia:

  - a higher myocardial oxygen supply because of a higher haemoglobin level and a rightward shift of the oxyhaemoglobin dissociation curve
  - a decreased tendency for tissue edema with non-diluted vs diluted cardioplegia
  - cost-effective when compared to the standard cardioplegia technique.

  In crystalloid-based cardioplegia such as Del-Nido and HTK, the use of Ultrafiltration ameliorates the effects of haemodilution.

5.5.6 CELL SALVAGE

Introduction

- The process of collecting, filtering, and washing blood from the surgical field to produce autologous blood for transfusion back to the patient.
- This method can be used intraoperatively or postoperatively.
- Red cells are maintained but plasma, platelets, heparin, free haemoglobin, and inflammatory mediators are discarded along with a washing solution.
- Cell salvage of operative blood loss is treated, anti-coagulated, washed to remove debris and centrifuged in a cell-saver machine to obtain a concentrate of red blood cells, reducing the risk of cerebral thromboembolism, and improving neurological outcome.

- Unwashed blood contains lipid micro-emboli, gaseous emboli, and non-cellular debris, which can cause organ dysfunction, especially in the kidneys and brain.
- Cost effective if only blood loss is more than 500 ml, and cell salvage can recover about 1.5 to 2 bags of blood volume.
- The life span of washed blood is 6 hours post collection.

Patient Selection

- All elective or emergency surgical procedures with risk factors for bleeding or low preoperative haemoglobin level (including Haemophilia and Thalassaemia).
- Patients with rare blood type or antibodies.
- Patients who refused autologous blood transfusion for religious or other reasons.

Postoperative Cell Salvage

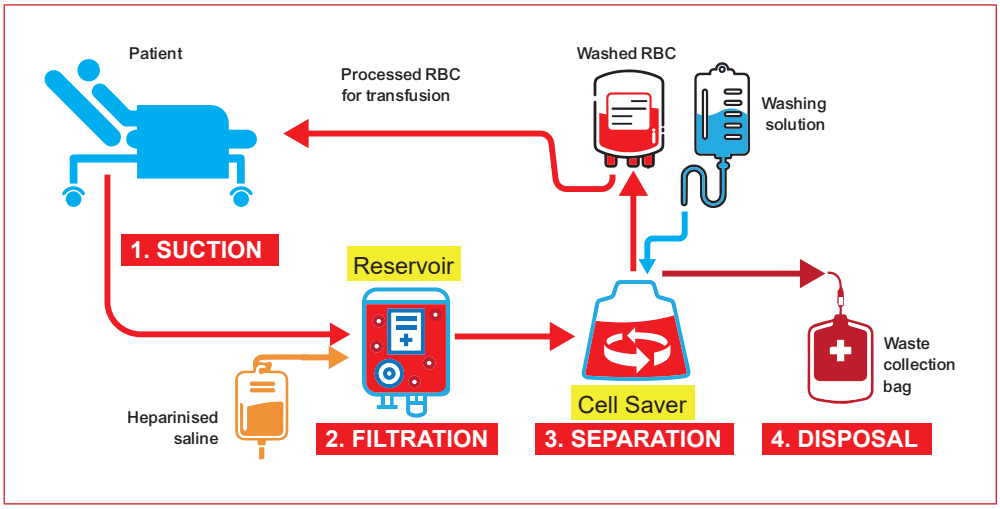
- To collect shed blood from the surgical cavity that has been closed at the completion of the surgical procedure, and then either filtered or washed in the cell saver machine before reinfused to the patient.
- Transfusion should be 6 hours for initiation of the collection.
- Aid in the prevention of post-operative anaemia.
- Continuing cell salvage beyond the operating room does not reduce transfusion requirement compared to intraoperative cell salvage alone and resulted in elevated CK levels, that suggest haemolysis.

Complications of Cell Salvage

- Air embolism
- Massive haemolysis
- Dilutional coagulopathy
- Bacterial contamination with skin commensals

**The routine use of cell salvage should be considered – Class IIa*
**Cochrane review (2010): relative reduction in risk of receiving an allogeneic RBC transfusion in 36% of cardiothoracic surgeries.*

Table 5.4: Cell salvage of autologous blood for transfusion back to the patient



5.5.7 ULTRAFILTRATION

- Ultrafiltration avoids haemodilution by eliminating fluids and low molecular weight molecules from the CPB circuit, resulting in protein-rich whole blood that can be delivered back to the patient.
- The total volume of blood during CPB can be controlled using ultrafiltration method.
- Techniques of ultrafiltration
  - modified ultrafiltration (MUF)
  - zero balance ultrafiltration (ZBUF)
  - conventional ultrafiltration (CUF)
- In the MUF technique, excess fluid is discarded after termination of CPB which is to reduce haemodilution and decrease tissue oedema.
- ZBUF technique is done during CPB, it is similar to CUF, but it replaces the lost volume with a balanced electrolyte solution, ZBUF can be used to reduce the number of inflammatory mediators.
- CUF haemo-concentrates blood by discarding excess fluid and reduces inflammatory mediators immediately upon termination of CPB, which improves haemostasis.

**Modified ultrafiltration may be considered as part of a blood conservation strategy to minimize haemodilution (Class IIb).*

- Most studies are suggestive of the beneficial effect of ultrafiltration on post-operative transfusion requirements.
- Meta-analysis[1] showed UF particularly MUF is associated with a reduction in post-operative blood transfusion.

5.5.8 PUMP BLOOD COLLECTION POST CPB

- At the time of discontinuation of cardiopulmonary bypass, the residual blood from the reservoir and the circuit is collected in the collection bag and re-transfuse back to the patient without further treatment to the residual blood.
- The quality of this blood is the same as the quality of the patient's blood at the time of discontinuation of cardiopulmonary bypass.
- This blood contains heparin, which can be removed by adding additional protamine as needed.

5.5.9 BIOCOMPATIBLE COATING OF EXTRACORPOREAL CIRCUIT (ECC)

- Biocompatible coated tubing and oxygenator mimics the natural endothelial lining of blood vessels and improves the haemocompatibility and hydrophilicity of the system, thereby reducing the risk of clot activation and contact systemic inflammatory response.
- Biocompatible coatings include ionic or covalent heparin bonding, poly(2-methoxyethylacrylate) (PMEA) and phosphorylcholine.
- However, due to its high cost, it is not widely practiced in Ministry of Health (MOH) cardiac hospitals, but it is well worth mentioning in PBM practices in cardiac surgery.

Advantages of biocompatible ECC:

- Reduce protein and platelet absorption and platelet aggregation
- Improve thrombogenicity
- Reduce bradykinin release
- Cause less platelet activation
- Reduce the release of proinflammatory cytokine

Disadvantages of non-biocompatible ECC:

- Induce a whole-body inflammatory response (blood contact with nonbiological surfaces).
- Increase postoperative morbidity due to bleeding complications and end organ dysfunction.
- Continuous interaction of blood with artificial contact lead to substantial damage of blood cells and plasma factors.
- Contact activation lead to bleeding complications and organ dysfunction.
- Plasma adheres to surface → factor XII activation → clotting initiation → activation of kallikrein (kinin bradykinin system) → fibrinolytic and complement cascades are initiated.
- Haemostatic abnormalities resulting in platelet dysfunction, hyperfibrinolytic activity, coagulation deficits, and loss of vascular integrity.
- Capillary leak syndrome, microvascular lung injury, and increased blood product use.

5.5.10 MINIMALLY INVASIVE EXTRACORPOREAL CIRCUIT (MiECC)

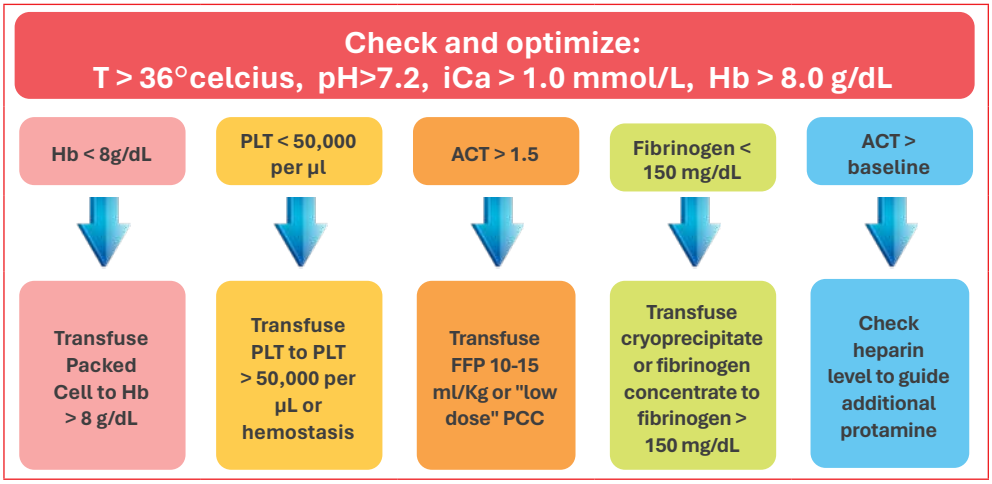
- MiECC is a closed CPB circuit without a reservoir and uses centrifugal pump.
- MiECC reduces haemodilution, postoperative bleeding, and the need for RBC transfusion while improving haematocrit.
- Thus, it improves perfusion by providing better circulatory support and end-organ protection, minimise length of ICU stay and reduce morbidity and mortality.
- It is useful in patients who are at risk of haemodilution (small adults) or who refuse autologous blood transfusion (ABT).
- Due to its high cost, it is not widely practiced in MOH hospitals, but it is well worth mentioning in PBM practices in cardiac surgery.
- The disadvantage is it has a higher risk embolism, limiting its use, due to its closed circuit feature. Furthermore, due to the absent of venous reservoir, it may increase blood transfusions in massive bleeding complications during cardiac surgery.

Intraoperative Targeted Transfusion Algorithm

Table 5.5: ROTEM/TEG Cardiac surgery Intraoperative Targeted Transfusion Algorithm

First to rule out residual heparin **ROTEM :** • INTEM CT >240s and • HEPTEM CT/INTEM CT <0.9s **TEG :** • TEG R> hTEG R x 1.25	Yes →	Give Protamine
2nd Consider thrombin formation deficit **ROTEM :** • EXTEM CT >100s • INTEM CT >240s **TEG :** • hTEG R >12min	Yes →	**PCC** 20-25 IU/kg, run over 10-15 minutes or **FFP** 10 -15 ml/kg
3rd Consider fibrinogen deficiency if: **ROTEM :** • FIBTEM A10 < 10 mm; • EXTEM A10 < 40 mm **TEG :** • MA < 40mm and FF < 8mm	Yes →	**Cryoprecipitate** **6-12 U** or **Fibrinogen concentrate** if available • 30-60 mg/kg
4th Consider thrombocytopenia **ROTEM :** • FIBTEM A10 > 10 mm • EXTEM A10 < 40 mm **TEG :** • MA < 40 mm and FF > 8mm	Yes →	**Platelet concentrate** **4 units of PLT** per 60-70 kg +/- **DDAVP** 0.3 mcg/kg
5th Consider hyperfibrinolysis **ROTEM :** • INTEM or EXTEM ml > 7% @ 30 min OR ML > 15% @ 60 min **TEG :** • LY 30 > 7.5%	Yes →	**IV Tranexemic acid** 30 -100 mg/kg or **Topical application** **Tranexemic Acid** before sternum closure
If at risk for post-operative bleeding: measure Hb, platelet count, fibrinogen level, and INR 30 min prior to separation from CPB		

Table 5.6: Targeted Transfusion Algorithm in the presence of excessive microvascular bleed



Adapted from Society of Cardiovascular Anaesthesiologists 2019 ROTEM/TEG/ Non-ROTEM/TEG based Cardiac Surgery Intraoperative Targeted Transfusion Algorithm.

- If bleeding persists despite normal ROTEM / TEG, to consider surgical re-exploration.
- The usage of PCC to treat post-op CPB bleeding is not fully established currently, as its use is regarded as off-label. However, if volume status of the patient is of concerned, PCC may be considered over FFP.

5.6 POSTOPERATIVE INTERVENTION

5.6.1 CRITERIA FOR RE-EXPLORATION FOR MEDIASTINAL BLEEDING (ADULT CARDIOTHORACIC SURGERY)

The decision to surgically re-explore is based on factors below:

1. Suspected Cardiac Tamponade
2. Persistent bleeding – when drainage:
   - > 500ml during first hour
   - > 400ml during each of first 2 hours
   - > 300ml during each of first 3 hours
   - > 1000ml in total drainage during the first 4 hours
   - > 1200ml in total drainage during the first 5 hours
3. Excessive bleeding (>300ml/h) after initial cessation of blood loss
4. Sudden massive bleeding (≥ 500mls in less than an hour) with hemodynamic instability

**Kirklin and Barret-Boyes Criteria, Interact Cardiovasc Thorac Surg. 2012 Jun; 14(6): 704-707*

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SUBMODULE 6

CRITICAL CARE

6.1 INTRODUCTION

Approximately two-third of patients admitted to Intensive Care Unit were anaemic on admission and almost all patients within the next 3 days.

The aetiology of anaemia is multifactorial. **Table 6.1** summarises iatrogenic and pathophysiological factors that are associated with the development of anaemia in critically ill patients.

Table 6.1: Causes for Anaemia in Critically Ill

Pathophysiological Causes for Anaemia	Iatrogenic Causes for Anaemia
Inflammation leading to; • Impaired erythropoiesis • Reduction of RBC maturation and life span	Frequency and volume of phlebotomies
Endogenous kidney dysfunction with low erythropoietin concentration	Haemolysis due to extracorporeal therapies e.g., CRRT and ECMO
Altered iron metabolism	Blood volume discarded
Nutritional deficiency of iron, folate, vitamin B12	Invasive procedures
Fluid shift due to sepsis	Coagulation disorders due to pharmacotherapy
Major haemorrhages	Impaired / insufficient enteral feeding
Occult bleedings	Fluid resuscitation in septic patient
Coagulation disorder due to thrombocytopenia and liver synthesis disorder	Surgical interventions

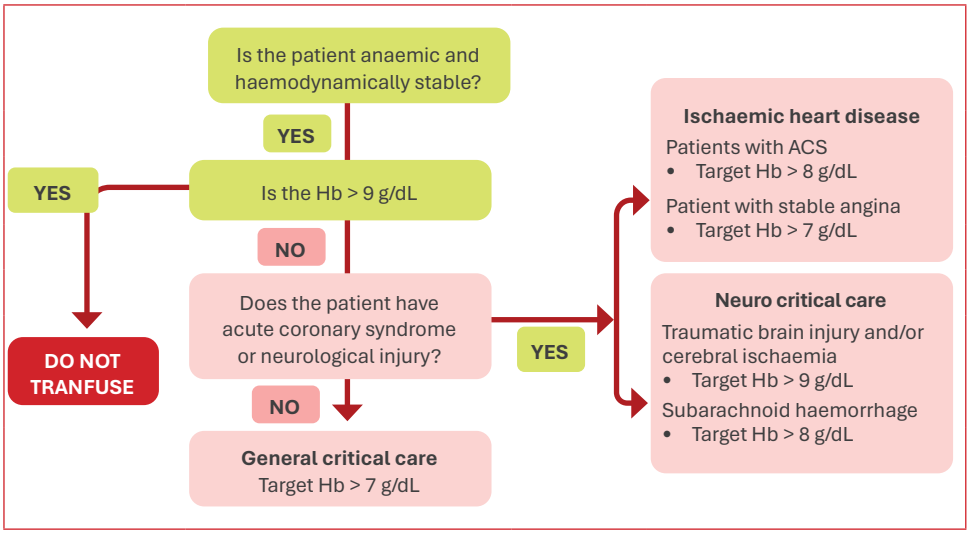
6.2 POINTS OF PRACTICE RECOMMENDATIONS FOR RED BLOOD CELL TRANSFUSION

- In critically ill patients, a restrictive transfusion strategy (transfusing less blood; transfusing at a lower haemoglobin threshold) should be employed.
- RBC transfusion should not be based on Hb concentration alone, but also be based on assessment of clinical status.
- When indicated, transfuse a single unit of RBC, followed by clinical reassessment to determine the need for further transfusion.
- RBC transfusion should not be used as a strategy to assist weaning from mechanical ventilation when the Hb is >7 g/dL.

Table 6.2: Point of practice recommendations for RBC

General intensive care
• A transfusion threshold of 7 g/dL or below, with a target Hb range of 7–9 g/dL, should be the default for all critically ill patients, unless specific co-morbidities or acute illness-related factors modify clinical decision-making.
• Transfusion triggers should not exceed 9 g/dL in most critically ill patients.
• RBC transfusion should not be used as a strategy to assist weaning from mechanical ventilation when the Hb is > 7 g/dL.
Sepsis
• A restrictive transfusion threshold (7 g/dL) is recommended compared to a liberal transfusion threshold (9 g/dL) in critically ill adults with sepsis and septic shock.
Ischaemic heart disease
• In patients suffering from Acute Coronary Syndrome (ACS) the Hb should be maintained at > 8 g/dL
• Anaemic critically ill patients with stable angina should have a Hb maintained > 7 g/dL
Neurocritical care
• In patients with Traumatic Brain Injury (TBI) the target Hb should be 7–9 g/dL
• In patients with TBI and evidence of cerebral ischaemia the target Hb should be > 9 g/dL
• In patients with subarachnoid haemorrhage the target Hb should be 8–10 g/dL
• In patients presenting to the ICU with an acute ischaemic stroke the Hb should be maintained above 9 g/dL.

Table 6.3: RBC algorithm for critical care in general critical care, ischaemic heart disease and neurocritical care.



Be less confident using Hb trigger of 7 g/dL (but target Hb 7 – 9 g/dL) if:

- Patient is elderly with significant cardiorespiratory co-morbidities

Be more confident using Hb trigger of 7 g/dL if:

- Patient is < 55 years
- The severity of illness is relatively low

6.2.1 ALTERNATIVE TO RBC TRANSFUSION

- Recombinant erythropoiesis-stimulating agents should not be routinely used in critically ill anaemic patients.
- In the absence of clear evidence of iron deficiency, routine iron supplementation is not recommended during critical illness.

6.2.2 BLOOD SAMPLING TECHNIQUES & FREQUENCY OF PHLEBOTOMY

- The introduction of blood conservation devices should be considered to reduce phlebotomy-associated blood loss.
- Paediatric blood sampling tubes can be effective for reducing iatrogenic blood loss.
- Avoid or reduce routine blood investigations ordered in a stable patient.

6.2.3 BLOOD COMPONENT TRANSFUSION

6.2.3.1 Fresh Frozen Plasma and Cryoprecipitate

- The routine use of FFP, Cryoprecipitate in critically ill patients with coagulopathy is not advised. The underlying causes of coagulopathy should be identified.
- The administration of FFP may be independently associated with adverse events, including Acute Respiratory Distress Syndrome and Acute Lung Injury. The decision to transfuse these products to an individual patient should consider the relative risks and benefits.
- Assessment of bleeding risk is complex and requires careful consideration of patients' clinical status and laboratory parameters.
- Patients with an INR ≤ 2 may not benefit from the administration of FFP and can generally undergo invasive procedures within the ICU without any serious bleeding; higher INRs may be tolerated in certain clinical situations.

6.2.3.2 Platelet

- In critically ill patients, in the absence of acute bleeding, the administration of platelets may be considered appropriate at a platelet count of < 10 x 10^9/L. Higher count (< 20 x 10^9/L) may be considered in patients with severe sepsis or haemostatic abnormalities.
- Prophylactic platelet transfusion should be considered for patients having elective central venous catheter placement with a platelet count less than 20 x 10^9/L.
- Patients with a platelet count > 50 x 10^9/L can generally undergo invasive procedures within the ICU without any serious bleeding; lower platelet counts may be tolerated in certain clinical situations.

Table 6.4: Suggested indication for platelet transfusion

Platelet Count threshold	Indication for Platelet Transfusion
< 10 x 10^9/L	Prophylaxis in non-bleeding
< 20 x 10^9/L	• Prophylaxis in non-bleeding with severe sepsis, haemostatic abnormalities • Central venous catheter placement
< 50 x 10^9/L	Invasive procedures within the ICU

6.2.4 ANTIFIBRINOLYTIC

- In acutely bleeding critically ill trauma patients, Tranexamic acid (TXA) should be administered within 3 hours of injury.
- In critically ill patients with upper gastrointestinal bleeding, consider the use of Tranexamic acid.

6.2.4.1 Tranexamic acid (TXA)

- TXA is most effective when administered promptly, ideally within 3 hours of the injury. Delayed TXA administration is less efficacious and may carry potential risks.
- The recommended administration of Tranexamic acid (TXA, 1g bolus followed by a 1g infusion over an 8-hour period) in accordance with the dosage regimen employed in the CRASH-2 trial, a large multicenter randomized controlled trial.

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SUBMODULE 7

MEDICAL

7.1 GENERAL TRANSFUSION IN MEDICAL

7.1.1 RECOMMENDATIONS / PRACTICE POINTS

a. Red Blood Cell (RBC) Transfusion

Recommendation / Practice Points	
PP1	• The decision for RBC transfusion in general medical patients should not be based on Hb concentration alone. • It must be decided together with the clinical status of the patient.
PP2	Where indicated, single unit policy of RBC transfusion should be considered, followed by clinical reassessment to determine the need for additional transfusion.

PP3	• Threshold Hb level for rough guide is as follows:
	  • Hb concentration < 7 g/dL: RBC transfusion is likely to be appropriate and may not be required in well-compensated patients or where other specific treatment is available.
	  • Hb concentration of 7-10 g/dL: The decision for RBC transfusion should be based on clinical assessment (to treat symptoms & signs)
	  • Hb concentration >10 g/dL: RBC transfusion is likely to be unnecessary and is usually inappropriate.

PP4	• Underlying cause of anaemia should be treated. • Iron therapy is indicated to treat patients with iron deficiency anaemia regardless of whether transfusion is required or not.

b. Fresh Frozen Plasma (FFP) Transfusion

Recommendation / Practice Points	
PP1	• The routine use of FFP in medical patients with coagulopathy (including liver impairment patients) is not recommended. • Coagulation test correlate poorly with bleeding risk in liver impairment[1,2].
PP2	The underlying causes of coagulopathy should be assessed & treated as necessary.
PP3	The decision for FFP transfusion in patients with coagulopathy should consider the risks and benefits for each patient, tailored based on case basis.

c. Cryoprecipitate / Fibrinogen Concentrate Transfusion

Recommendation / Practice Points	
PP1	The routine use of Cryoprecipitate / Fibrinogen Concentrate in medical patients with coagulopathy is not recommended.
PP2	The underlying causes of coagulopathy or DIC should be assessed & treated as necessary.
PP3	• The decision for Cryoprecipitate / Fibrinogen Concentrate transfusion in patients with coagulopathy / DIC should consider the risks and benefits for each patient. • Cryoprecipitate / Fibrinogen Concentrate transfusion should be based on case basis and specialist opinion is advised for the management of DIC.

d. Platelet Transfusion

Recommendation / Practice Points	
PP1	The causes of the thrombocytopenia should be established & treated as necessary.
PP2	Platelet transfusion can be considered for the prevention and treatment in bleeding patients with thrombocytopenia or platelet dysfunction.
PP3	Not all causes of thrombocytopenia require platelet transfusion and can be contraindicated in certain conditions like Thrombotic Thrombocytopenic Purpura (TTP) and Heparin Induced Thrombocytopenia (HIT).
PP4	Long term platelet prophylaxis should be avoided to prevent the risk of platelet alloimmunization and platelet refractoriness.

7.2 CARDIOVASCULAR

7.2.1 ACUTE CORONARY SYNDROME

Anaemia in ACS is independently associated with MI and recurrent ischaemia.

Anaemia is independently associated with all-cause mortality in ACS.

7.2.1.1 Recommendations / Practice Points

Recommendation / Practice Points	
PP1	In patients with ACS and a Hb concentration < 8 g/dL, RBC transfusion may be associated with reduced mortality and is likely to be appropriate.
PP2	In patients with ACS and a Hb concentration of 8–10 g/dL, the effect of RBC transfusion on mortality is uncertain and may be associated with an increased risk of recurrence of MI.
PP3	Any decision to transfuse should be made with caution and based on careful consideration of the risks and benefits.
PP4	In ACS patients with a Hb concentration > 10 g/dL, RBC transfusion may not be recommended because of an association with increased mortality.

7.2.2 CHRONIC HEART FAILURE (CHF)

In all patients with heart failure, there is an increased risk of transfusion-associated circulatory overload. This needs to be considered in all transfusion decisions. Where indicated, transfusion should be of a single unit of RBC followed by reassessment of clinical efficacy and fluid status.

7.2.2.1 IV iron in CHF patient

Recommendation / Practice Points	
PP1	**Prevention of circulatory overload** Identification and treatment of iron deficiency (absolute and functional) is recommended to improve functional or performance status. This is consistent with the 2011 update to the *Guidelines for the Prevention, Detection and Management of Chronic Heart Failure in Australia, 2006*. 138

7.2.2.2 ESA in CHF patient

Recommendation / Practice Points	
PP1	**Reducing mortality** Ngo et al (2010) found that ESAs significantly reduce mortality (5.9% vs 10.4%; 95% CI 0.61; 95% CI 0.37, 0.99)
PP2	**Functional / performance status** Ngo et al (2010) found that ESAs, compared with control, significantly improve Six-Minute Walk Test (6MWT) distance (MD 69.33 m; 95% CI 16.99, 121.67) and NYHA functional class (MD -0.73; 95% CI -1.11, -0.36) (Table 3.78).
PP3	**Thromboembolic Phenomenon** Ngo et al (2010) There was no significant difference between ESA and no ESA for the incidence of stroke (1.8% vs 1.3%; RR 1.57; 95% CI 0.52, 4.70), myocardial infarction (2.2% vs 3.7%; RR 0.69; 95% CI 0.31, 1.55), or other thromboembolic events (1.0% vs 1.8%; RR 0.65; 95% CI 0.22, 1.88).

7.3 NEPHROLOGY

7.3.1 NON-TRANSFUSION INTERVENTIONS FOR PATIENTS WITH CHRONIC KIDNEY DISEASE (CKD)

7.3.1.1 Treatment with Iron agents

Background

Iron supplementation can potentially reduce the severity of anaemia in Chronic Kidney Disease (CKD) patients with iron deficiency. It has a potential to reduce anaemia intervention either decrease in ESA dose or red blood cell (RBC) transfusion.It is widely used in CKD patients to treat iron deficiency, prevent its development in Erythropoietin Stimulating Agent (ESA) treated patients, raise haemoglobin levels in the presence or absence of ESA treatment as well as reduce ESA doses in patients receiving ESA treatment.

A decision to provide an individual patient with iron therapy should be based on an assessment that an increase in Hb level is desirable with intention to avoid transfusions or reduce anaemia related symptoms. The potential adverse effects of iron supplementation have been considered and are appropriately outweighed the expected treatment benefit.

7.3.1.2 Treatment with ESAs

Background

The introduction of recombinant human erythropoietin (rHuEPO) into clinical practice is a major cornerstone in the treatment of anaemia of patients with CKD. It is intended to replace the insufficient endogenous erythropoietin (EPO) production related to CKD progression. The immediate benefit of rHuEPO in CKD patients with anaemia was clear. reduction in the need for regular blood transfusions was another major benefit, resulting in less frequent transmission of blood-borne viral diseases, and less transfusion related hemosiderosis [5,6,7].

Nevertheless, all correctable causes of anaemia in CKD patients such as absolute iron deficiency, hyperparathyroidism and any inflammatory states should be addressed and treated appropriately prior to ESA initiation.

7.3.1.3 Recommendations / Practice Points

Recommendation	
R1	Evaluate the potential benefits of avoiding blood transfusions, ESA therapy, and anaemia-related symptoms against the risks of harm in individual patients when initiating iron supplementation.
R2	For adult CKD patients with anaemia not on iron or ESA therapy, a trial of IV or oral iron can be considered to a targeted haemoglobin if TSAT is ≤ 30% and ferritin is ≤ 500 ng/ml (≤ 500 mg/l)
R3	For non-dialyzed CKD patients, consider IV iron dosed to a target ferritin of 400-600 microg/L in minimizing the need for another anaemia management[8].
R4	For dialyzed CKD patients, consider protocolized IV iron supplementation unless ferritin is > 700 microgram/L or TSAT is > 40%[9].
R5	In adult CKD patients with concurrent absolute or functional iron deficiency the use of ESA is less effective at maintaining a targeted haemoglobin.
R6	ESA therapy to a haemoglobin target of 10–11 g/dL in adult CKD patients with anaemia, reduces RBC transfusion.
R7	Evaluate the potential benefits of reducing blood transfusions and anaemia-related symptoms against the risks of harm in individual patients (e.g., stroke, vascular access loss, hypertension) when initiating ESA.
R8	ESA therapy not considered in adult non dialysis CKD patients with haemoglobin concentration of ≥ 10.0 g/dL.
R9	Initiate ESA therapy in adult dialyzed CKD patients when the haemoglobin is between 9.0–10.0 g/dL.
R10	ESAs not to be used to maintain Hb concentration > 11.5 g/dL in adult CKD patients,
R11	ESAs are not used to increase the Hb concentration above 13 g/dL in adult CKD patients due to increased morbidity.
R12	In CKD patients with anaemia, target haemoglobin is between 10.0 – 11.5 g/dL.

7.4 GASTROENTEROLOGY

7.4.1 INTRODUCTION

In patients with acute bleeding, a restrictive transfusion approach is effective to reduce mortality and improve other clinical outcomes compared with a liberal transfusion approach. RBC transfusion should be based on assessment of the patient's clinical status and not by a Hb concentration alone. Where indicated, transfusion of a single unit of RBC is recommended, followed by clinical reassessment to determine the need for further transfusion.

In adults with liver cirrhosis, serial large-volume paracentesis (LVPs) are mainstays in the treatment of diuretic-resistant ascites, both for patients awaiting liver transplantation and for those who are not transplantation candidates. At this moment, the risk attributable to the paracentesis is unclear due to the difficulty in adjusting for underlying severity of illness and comorbidities in these patients and in knowing whether they were truly diuretic resistant.

7.4.2 RECOMMENDATION / PRACTICE POINTS

a. Acute Gastrointestinal loss

Recommendation/ Practice Points	
PP1	For Well Compensated patient (follow general transfusion guideline)
PP2	In critically bleeding patients, refer to patient blood management – critical bleeding/ massive transfusion

b. Inflammatory Bowel Disease (IBD)

Recommendation/ Practice Points	
PP3	IV iron may be required in patients who are intolerant of oral iron or to avoid aggravation of intestinal inflammation

c. Ascites in adult with liver cirrhosis

Recommendation/ Practice Points	
PP4	• The necessity of plasma expansion after large-volume paracentesis remains controversial. • Suggestion for albumin solution to be given (6-8g per litre of fluid removed) when ≥ 5 litres of ascites are removed *(Grade 2B)*. • Suggestion against using albumin if <5 litres ascites are removed *(Grade 2C)*.

7.5 HAEMATOLOGY

7.5.1 CHEMOTHERAPY AND HEMATOPOIETIC STEM CELL TRANSPLANT

Introduction

The prevalence of anaemia in cancer patients can exceed 90% for those receiving certain treatments. It often has a negative impact on quality of life (QOL). Anaemia also can be a dose-limiting toxicity that prevents patients from realizing the full benefit from newer antineoplastic therapies (ANTs). Cancer-associated anaemia is caused by 1 or more of 3 primary mechanisms: (1) ineffective erythropoiesis, (2) haemolysis or (3) blood loss.

Intensive combination chemotherapy regimens for acute leukaemia and aggressive lymphoma, with or without haemopoietic stem cell (HSC) rescue, typically suppress the production of blood cells by the bone marrow for 7 to 14 days, during which the patient is likely to require prophylactic or therapeutic transfusions of red cells and platelets.

Allogeneic (donor) HSC transplantation after myeloablative chemo-radiotherapy often requires much longer periods of transfusion support, particularly when recovery is complicated by delayed engraftment, acute graft-versus-host disease (GvHD) or severe sepsis.

By incorporating guidance from both the World Health Organization and CTCAE, we can construct a definition for cancer-associated anaemia that reconciles shortcomings **(Refer Table 7.1)**.

Table 7.1: Definition and criteria for grading cancer-associated anaemia

Anaemia Grade	CTCAE + WHO Criteria	
	Women	Men
Grade 1	Hb 11.9-10.0 g/dL	Hb 12.9-10.0 g/dL
Grade 2	Hb 9.9-8.0 g/dL	Hb 9.9-8.0 g/dL
Grade 3	Hb ≤ 7.9 g/dL	Hb < 7.9 g/dL
Grade 4	Life-threatening consequences requiring urgent intervention, such as RBC transfusion	Life-threatening consequences requiring urgent intervention, such as RBC transfusion

By using World health Organization (WHO) criteria and the CTCAE (v5.0) grading system for anaemia, a definition for cancer-associated anaemia was established: grade 1 anaemia was defined as Hb ≤ 11.9 g/dL for women with cancer and Hb ≤12.9 g/dL for men with cancer. Severity of anaemia increases with increasing grade up to grade 5 (death).

7.5.1.1 Red Cell Transfusion

The ideal red cell 'transfusion trigger' for patients undergoing intensive cytotoxic therapy is uncertain. These patients have much in common with patients in critical care in which there is evidence to support a restrictive red cell transfusion policy.

Recommendation	
R1	• Prophylactic RBC Transfusion: Refer General Transfusion/ Critical Care • A restrictive RBC transfusion threshold of 7–8 g/dL haemoglobin is recommended for adult patients who are hemodynamically stable. • A restrictive RBC transfusion threshold of 8 g/dL is recommended for patients with existing cardiovascular disease
R2	ESAs may be offered to patients with chemotherapy-associated anaemia whose cancer treatment is not curative in intent and whose haemoglobin has declined to less than 10 g/dL.; (Evidence quality: high; Strength of recommendation: strong)
R3	ESAs should not be offered to patients with chemotherapy-associated anaemia whose cancer treatment is curative in intent. (Evidence quality: intermediate; Strength of recommendation: strong)
R4	Iron replacement may be used to improve haemoglobin response and reduce RBC transfusions for patients receiving ESA with or without iron deficiency. Baseline and periodic monitoring of iron, total iron binding capacity, transferrin saturation, or ferritin levels is recommended. (Evidence quality: intermediate; Strength of recommendation: weak)
R5	HSCT recipients are at risk of ta-GvHD and should receive irradiated cellular blood products. These cellular blood products can be irradiated with either gamma rays (25Gy) or X Rays.

7.5.1.2 Prophylactic Platelets Transfusion

Recommendation / Practice Points	
R1	Prophylactic platelet transfusions should be given to patients receiving intensive chemotherapy, with a transfusion trigger of 10×10^9/L
R2	One adult therapeutic dose (ATD) should be given once daily to adults and children > 15 kg in weight.
R3	It is standard practice to increase the platelet transfusion threshold to 20×10^9/L in patients who are febrile and/or receiving antibiotic therapy for suspected bacterial or fungal infection
R4	A therapeutic platelet transfusion policy in patients undergoing lower risk procedures such as autologous HSC transplantation may be appropriate, but further research is required before this can be routinely recommended.
R5	Platelet prophylaxis is not required for bone marrow aspiration or trephine biopsy, but local pressure should be applied
R6	For patients requiring lumbar puncture, central-line insertion, percutaneous organ biopsies and most invasive surgeries the platelet count should be increased to $> 50 \times 10^9$/L
R7	HSCT recipients are at risk of ta-GvHD and should receive irradiated cellular blood products. These cellular blood products can be irradiated with either gamma rays (25Gy) or X Rays.
PP1	Thrombopoietic agents may benefit patients with chemotherapy induced thrombocytopenia (CIT). Further studies with well-characterized bleeding and platelet thresholds are warranted to explore the possible benefits of thrombopoietic agents for CIT.

7.5.2 MYELODYSPLASTIC SYNDROMES

Introduction

Patients with myelodysplastic syndromes (MDS) often need extended periods of red blood cell or platelet transfusion support, with the goal to manage symptoms of anaemia and thrombocytopenia, respectively, and improve quality of life.[15]

Haemoglobin < 90g/L in men and < 80g/L in women was independently associated with worse overall survival and with both non leukemic and cardiac causes of death.

Bleeding due to thrombocytopenia is variably reported as the cause of death in 5% to 24% of patients with MDS in different studies.[16]

In accordance with the principles of Patient Blood Management (PBM), restrictive transfusion approaches are often practiced.1 Questions of optimal schedule and dosage are still being explored in clinical trials. The decision to transfuse must address potential hazards balanced against the anticipated benefits while explaining the anticipated benefits and risks to the patient. Tolerance of the anaemia and specific outcomes like falls, cognitive impairment, risk of autonomy loss and hospitalization are cornerstones of decision making. Measures to prevent of transfusion-associated circulatory overload (TACO) should be undertaken.

Therapeutic approaches for MDS include those directed at ameliorating the underlying bone marrow disease or managing the resulting cytopenias. These options include growth factors such as erythropoiesis-stimulating agents (ESAs), Thrombopoietin receptor agonist (TPO) or granulocyte colony-stimulating factor plus novel agents including molecularly targeted therapies are coming into clinical practices.

7.5.2.1 Recommendations/Practice Points

Recommendation / Practice Points	
R1	Supportive care should be offered to all patients with MDS and symptomatic cytopenias (1A)
R2	Red cell transfusions should be given to improve symptomatic anaemia (1A)
R3	Policies for transfusion, including haemoglobin thresholds for red cell transfusion, should take clinical factors into consideration, including patient-related factors (1A).
R4	Patients with IPSS Low and Intermediate-1 (or IPSS-R very low, low or intermediate with a score up to 35) MDS with symptomatic anaemia, or asymptomatic anaemia and Hb < 100 g/l should be considered for a trial of therapy with an ESA (1A).
R5	Patients with stable MDS not receiving intensive chemotherapy and without signs of bleeding should not be offered prophylactic platelet transfusions (1A).
R6	Thrombopoietin receptor agonists (TPO) may be used to reduce bleeding events in thrombocytopenic patients with low or intermediate-1 risk MDS (1A).
PP1	The haemoglobin concentration should not be allowed to rise above 120 g/l (2C).
PP2	Luspatercept may be considered in MDS with ring sideroblasts (MDS-RS) patients of very low, low or intermediate-risk IPSS-R risk status who require ≥2 units of red blood cells per eight weeks and have previously failed ESA therapy.
PP3	All suitable lower-risk patients (IPSS low and intermediate-1; IPSS-R low and very low) should be considered for iron chelation therapy at the time they have received 20 units of red cells, or when the ferritin is more than 1000 lg/l (1B).

Table 7.2: Goals of RBC and platelet transfusion in MDS

	Goal of transfusion	Measured by	Desired Outcomes
Red cell transfusion	• Improve acute and chronic symptoms of anaemia (fatigue, dyspnea, chest pain, palpitations, effects on cognitive function). • Minimize major complications of (severe) anaemia • Improve functional outcomes	• Haemoglobin and hematocrit • Functional measures using standardized tool (eg, fatigue score, walk distance, grip strength) or self-report	• Control of symptoms • Better functional status in activities of daily living • Increased ability to participate in work or social and community interests
Platelet Transfusion	• Improve symptoms of thrombocytopenia (patient experience of skin bruising and other bleeding) • Minimize major complication of (severe) thrombocytopenia • Improve functional outcomes	• Platelet count • Bleeding assessments (eg, standardized tool or self-report)	• Improve health-relataed QoL

7.5.3 TRANSFUSION IN THALASSAEMIA

Introduction

Thalassaemia is an inherited haemoglobin disorder and one of the commonest diseases attributable to single defective genes.

The aim of blood transfusion in thalassaemia is to deliver a safe and effective transfusion regimen whilst minimising the burden of transfusion therapy on everyday life. An effective transfusion regimen will result in:

- Good growth and development
- Good energy levels
- Sufficient suppression of intra and extramedullary haematopoiesis

Novel pharmacological therapies that ameliorate the transfusion need especially targeting the ineffective erythropoiesis are in the various state of development.

7.5.3.1 Transfusion Dependent Thalassaemia

Introduction

Transfusion combined with chelation therapy for transfusion-dependent thalassemia (TDT) has been successful in extending life expectancy, decreasing comorbidities and improving quality of life.

Table 7.3: Criteria for initiating transfusion therapy

Recommended Criteria
Confirmed diagnosis of thalassaemia
Laboratory criteria: • Haemoglobin level (Hb) < 70 g/l on 2 occasions, > 2 weeks apart (Excluding all other contributory causes such as infections)
Clinical criteria irrespective of haemoglobin level: • Significant symptoms of anaemia • Poor growth / failure to thrive • Complications from excessive intramedullary haematopoiesis such as pathological fractures and facial changes • Clinically significant extramedullary haematopoiesis

Transfusion recommendation

This overall approach to transfusion has been shown to promote normal growth, to allow normal physical activities, to adequately suppress bone marrow activity and to minimize transfusional iron accumulation in most patients.

Recommended/ Practice Points	
R1	Lifelong regular blood transfusions
R2	Administered every two to five weeks to maintain the pre-transfusion haemoglobin level 95-105 g/l.
R3	Higher target pre-transfusion haemoglobin level of 110-120g/l may be appropriate for patients with heart disease, clinically significant extramedullary hematopoiesis or other medical conditions, and for those patients who do not achieve adequate suppression of bone marrow activity at the lower haemoglobin level.
R4	Keep the post-transfusion haemoglobin below 140-150 g/l (IIA)
R5	Use leucodepleted packed red cells. Pre-storage filtration is strongly recommended but blood bank pre-transfusion filtration is acceptable.
PP1	All patients should have their RBC phenotyped. Phenotype specific packed red cells should be considered in certain high risk blood groups.
PP2	Luspatercept may reduce transfusion requirement in the non-transfusion-dependent thalassemia.

7.5.3.2 Non-Transfusion Dependent Thalassaemia

Introduction

Non-transfusion-dependent thalassaemia (NTDT) refers to all thalassaemia disease phenotypes that do not require regular blood transfusions for survival. Ineffective erythropoiesis and peripheral haemolysis in NTDT patients lead to a multitude of subsequent patho-physiologies and clinical complications throughout the course of the disease.

Transfusion therapy has been shown to be protective against complications such as thrombosis, extramedullary haematopoiesis, PHT, heart failure, cholelithiasis and leg ulcers in patients with NTDT.

Recommended/ Practice Points	
R1	Haemoglobin level should not be an indicator for initiation of transfusion therapy, except in patients with considerably severe anaemia (haemoglobin level < 5 g/dL)
R2	Occasional blood transfusions should be considered in NTDT patients within any setting with anticipated acute stress, haemoglobin drop, or blood loss; such as: • Pregnancy • Surgery • Infections
R3	More frequent transfusions should be considered in the following settings, with reassessment for tapering or withdrawal when a sustained clinical benefit is achieved: • Declining haemoglobin level in parallel with profound enlargement of the spleen (at a rate exceeding 3 cm/year in periods of maximal growth and development) • Growth failure (height is more indicative of growth pattern than weight) • Poor performance at school • Diminished exercise tolerance • Failure of secondary sexual development in parallel with bone age • Signs of bony changes • Frequent haemolytic crisis (haemoglobin H disease) • Poor quality of life

Recommended/ Practice Points	
R4	Transfusions may be considered for the primary prevention (in high-risk populations) management or secondary prevention of the following complications: • Thrombotic or cerebrovascular disease • Pulmonary hypertension with or without secondary heart failure • Extramedullary haematopoietic pseudotumors • Leg ulcers
R5	Use leucodepleted packed red cells. Pre-storage filtration is strongly recommended but blood bank pre-transfusion filtration is acceptable.
PP1	All patients should have their RBC phenotyped. Phenotype specific packed red cells should be considered in certain high risk blood groups
PP2	Luspatercept may reduce transfusion requirement in the non-transfusion dependent thalassaemia

7.5.4 TRANSFUSION IN AUTOIMMUNE HAEMOLYTIC ANAEMIA (AIHA)

Introduction

AIHA is a haematologic disorder that may arise as an idiopathic condition or in conjunction with other illnesses such as connective tissue disease. It can be classified into Warm AIHA, Cold AIHA, Mixed AIHA and Drug-induced AIHA.

In patients with AIHA, autoantibody in the patient's serum usually reacts with all normal red blood cells making it almost impossible to find compatible blood. The autoantibody may mask the presence of a red cell alloantibody capable of causing a haemolytic transfusion reaction.

Transfusion in AIHA

Beside specific management depending on types of AIHA to minimize red cells haemolysis, red cells transfusion may be required for certain cases.

Recommended/ Practice Points	
PP1	Red cells transfusion should be limited to life-threatening anaemia, patients in decompensated state or severe bleeding.
PP2	Avoid transfusion in haemodynamically stable patients to minimize the risk of developing transfusion-related alloantibody.
PP3	• If no cross-matched compatible red cells are available, red cells with lesser agglutination reaction with the patient's serum (least incompatible) is chosen in cross matching. • In cases with difficulty to find compatible or least incompatible blood, crossmatched with antigen compatible red cells may benefit to the patient. In this case, pre-transfusion red cell phenotyping for clinically significant antibodies (e.g. Rh, Kidd, Duffy and MNSs) will be required.
PP4	During transfusion, red cells should be administered slowly and monitored closely.

7.6 COMMUNITY DWELLING ELDERLY

Non-transfusion interventions for elderly patients with anaemia

- Prevalence of anaemia increases with age.
- Not significant to reduce mortality, improve functional status and prevent thromboembolic events.
- In view of multifactorial etiologies, thorough investigations lead to correct diagnosis and management.

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SUBMODULE 8

NURSING

8.1 PATIENT BLOOD MANAGEMENT IN MASSIVE BLEEDING; NURSING ROLES AND RESPONSIBILITY

8.1.1 INTRODUCTION

The blood transfusion process is a complex procedure. Prompt action, close monitoring and safe transfusion guidelines measure are needed in management of massive bleeding to be implemented by the nurses to ensure safe transfusion. This will enhance the recovery process and shorten the hospital stay. Thus, will help to save cost associated with blood management.

Before blood transfusion, it is essential that the nurses ensure:

- Right blood group
- Right Blood Product
- Right Patient
- Right Duration
- Right Place (acute setting)
- Right Vascular Access

8.2 PRACTICAL ASPECTS FOR NURSING CARE IN MASSIVE BLOOD TRANSFUSION

a. Pre Transfusion:

i. Nurses should ensure that:

- The emergency blood crossmatch form filled as mentioned per required and sent.
- The Consent form is signed by the patient or qualified representative.
- The blood and blood product volume is prescribed by Doctor in patient notes.
- Appropriate preparation blood box is used for transportation.

ii. Baseline monitoring

- Vital signs should be taken and recorded accurately.
  (Heart rate, temperature, respiratory rate and blood pressure)

iii. Administration sets and filters

- Use standard in-line blood filters as in the guideline for blood. Smaller filter for platelets and fresh frozen plasma in special condition (micro aggregate filters).
- The set should not be used for more than 4 hours, due to bacterial contamination.
- IV set must be primed with Normal Saline 0.9% or prior blood product transfusion.
- If administration set has previously been used for the transfusion of red cells it **SHOULD NOT** be used for transfusing platelet.

iv. Duration and infusion rate

- The transfusion volume and rate should be administered by nurses as prescribed by the doctor.

b. During Transfusion:

i. Patient monitoring

- Monitor patient's vital sign; heart rate, temperature, respiratory rate and blood pressure should be checked and recorded:
- Every 15 minutes, 30 minutes and hourly throughout the transfusion period.
- After completion of the transfusion.

ii. Patient should be observed continuously for signs and symptoms of transfusion related reactions such as;

- Apnea or tachypnea
- Tachycardia, bradycardia or arrhythmia
- Cyanosis
- Significant change in systolic blood pressure
- Significant change in temperature
- Haemoglobinuria
- Rashes

iii. Adverse transfusion reaction

- **If any adverse** transfusion reaction suspected or detected, infusion should be stopped immediately.
- Inform doctor **STAT.**
- Post transfusion specimens of blood, urine and balance transfused blood bag should undergo a transfusion reaction evaluation in the blood bank.

c. Post Transfusion

i. Document volume of all blood and blood product transfused in the Intake & Output chart and nursing notes.

ii. Ensure blood investigation for laboratory assessment such as FBC, PT/ APTT, INR and fibrinogen is taken.

iii. To return unused blood and blood products to blood bank immediately if there is no appropriate storage available.

iv. Patient's vital sign: heart rate, temperature, respiratory rate and blood pressure should be checked and recorded: after completion of the transfusion.

8.3 GENERAL CONSIDERATION

- Each hospital should comply to their own local Massive Transfusion Protocol (MTP).
- The ward shall ensure that only validated blood warmers are used.
- Blood transfusion checklist should be used and completed in every blood and blood product transfusion.

REFERENCE

1. *Transfusion Practice Guidelines for Clinical Laboratory Personal (4th ed).* Ministry of Health Malaysia

LIST OF ABBREVIATIONS

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ID	Iron Deficiency
PPH	Post Partum Hemorrhage
MTP	Massive Transfusion Protocol
ESA	Erythropoietin Stimulating Agent
POCT	Point of Care Testing
RBC	Red Blood Cell
TEG	Thromboelastography
ROTEM	Rotational Thromboelastometry
TRALI	Transfusion Related Acute Lung Injury
TACO	Transfusion-Associated Circulatory Overload
ATG	Anti Thymocyte Globulin
IUT	Intraunterine Transfusion
Rh	Rhesus
PCC	Prothrombin Complex Concentrate
HCT	Hematocrit
UFH	Unfractionated Heparin
LMWH	Low Molecular Weight Heparin
HTK	Histidine-Tryptophan-Ketoglutarate

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