EDUCATIONAL MODULES ON CLINICAL USE OF BLOOD

World Health Organization

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PREFACE

Blood transfusion is an essential part of patient care. When used correctly, it saves lives and improves health. However, blood transfusion carries a potential risk of acute or delayed complications and transfusion- transmitted infections and should only be prescribed when there are clear indications for doing so. Many countries in the world face challenges in making sufficient supplies of blood products available, while also ensuring the quality and safety of these products. National data on the use of blood products are limited, but studies suggest that blood products are often inappropriately used in both developed and developing countries. Unnecessary transfusions and suboptimal clinical practices compromise patient safety, are wasteful and limit the availability of blood products for patients who are really in need.

Appropriate use of blood and safe transfusion practice is an important element of the World Health Organization (WHO) integrated blood and transfusion safety strategies, and WHO has provided important guidance and capacity-building support to improve the clinical use of blood. In May 2010, the sixty-third World Health Assembly adopted resolution WHA63.12 on *Availability, safety and quality of blood products*, which urges Member States "to establish or strengthen systems for the safe and rational use of blood products and to provide training for all staff involved in clinical transfusion". The resolution and the subsequent *Framework to advance universal access to safe, effective and quality assured blood components in 2020–2023* also endorsed the concept of patient blood management as an integral part of transfusion medicine and recommended "effective implementation of patient blood management to optimize clinical practice of transfusion" and a holistic and patient-oriented approach to clinical care of patients who may need transfusion.

The International Society of Blood Transfusion (ISBT) is an international society where transfusion medicine professionals from across the globe come together and share knowledge to enhance transfusion practice. The ISBT Working Party for Clinical Transfusion aims at promoting good clinical transfusion practice globally through education, audits and scientific studies as well as through the development of educational tools in clinical transfusion medicine for both clinicians and transfusion specialists, medical and nonmedical. As a nongovernmental organization with official relations with WHO, ISBT has already collaborated with WHO to improve global blood safety and availability and to promote the establishment of national blood programmes based on voluntary non-remunerated blood donations.

The *Educational modules on clinical use of blood* is the update of the WHO publication *the Clinical use of blood in medicine, obstetrics, paediatrics, surgery and anaesthesia, trauma and burns* published in 2001. Publishing the Educational Modules has been undertaken as a collaboration between WHO and as part of ISBT's cooperation plan. As with the original publication, the Educational Modules is not designed to replace conventional textbooks or to provide a definitive text on the clinical use of blood. Rather, its purpose is to provide accessible learning materials that will assist prescribers of blood and other staff involved in clinical transfusion to make appropriate clinical decisions on transfusion and contribute to wider efforts to optimize clinical practice of transfusion.

Our special thanks go to the experts of the Steering Committee, the editors, content contributors and critical readers who gave their time and generously volunteered their expertise to this endeavour.

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The material developed here was updated and adapted from *Clinical use of blood in medicine, obstetrics, paediatrics, surgery and anaesthesia, trauma and burns*, published by WHO in 2001, and widely used internationally. The work of the contributors to that document is gratefully acknowledged, as is the commitment and efforts of the editors, members of the steering committee, authors and expert reviewers to this update.

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WHO's team of blood and other products of human origin would welcome comments and suggestions regarding the materials and experience with their use. Please provide any feedback to: bloodproducts@who.int.

ABBREVIATIONS

ABE	acute bilirubin encephalopathy
ACT	artemisinin-based combination therapies
ANC	absolute neutrophil counts
ANH	acute normovolaemic haemodilution
ART	antiretroviral therapy
BM	bone marrow
BMT	bone marrow transplantation
BSH	British Society for Haematology
BT	bleeding time
CBC	complete blood counts
CJD	Creutzfeldt-Jakob disease
CPDA	citrate, phosphate, dextrose and adenine
CPP	cryoprecipitate-poor plasma
DIC	disseminated intravascular coagulation
EDQM	European Directorate for the Quality of Medicines & HealthCare
ESA	erythropoietic stimulating agents
ET	exchange transfusion
FDP	fibrin degradation products
FFP	fresh frozen plasma
FNHTR	febrile non-haemolytic transfusion reactions
GVHD	graft-versus-host disease
HA	haemolytic anaemia
HBV	hepatitis B virus
HCV	hepatitis C virus
HDN	haemolytic disease of the newborn
HIC	high-income countries
HIV	Human immunodeficiency virus
HPLC	high performance liquid chromatography
ICU	intensive care units
IDA	iron-deficiency anaemia
ITP	idiopathic autoimmune thrombocytopenic purpura
ISBT	International Society of Blood Transfusion
LIC	low income countries

MSBOS	maximum surgical blood ordering schedules
NAIT	neonatal alloimmune thrombocytopenia
NSAID	non-steroidal anti-inflammatory drugs
NTDT	non-transfusion-dependent thalassaemia
PAD	preoperative autologous blood donation
PBM	patient Blood Management
PC	platelet count
PCC	prothrombin complex concentrate
PDMP	plasma-derived medicinal products
PI	pathogen inactivation
POC	point-of-care
PPF	plasma protein fraction
PT	platelet transfusions
PT	prothrombin time
RBC	red blood cells
RDT	rapid diagnostic tests
SABM	Society for the Advancement of Blood Management
SAED	serious adverse events of donation
SCA	sickle cell anaemia
SCD	sickle cell disease
SOP	standard operating procedures
SPPS	stable plasma protein solution
SSA	sub-Saharan Africa
TAXI	Transfusion and Anaemia Expertise Initiative
TBSA	total body surface area
TDT	transfusion dependent thalassaemia
TP	treponema pallidum
TRALI	transfusion-related acute lung injury
TT	thrombin time
TTP	thrombotic thrombocytopenic purpura
VWD	Von Willebrand disease
VWF	Von Willebrand Factor
WB	whole blood

INTRODUCTION

Background

The World Health Organization (WHO) has designated blood products as essential medicines because blood transfusions can save lives, and patients around the world depend on transfusions every day to keep them healthy *(1)*. In the future, a better understanding of normal physiology and disease processes may deliver more substitutes for blood products, but for many patients there are simply no current alternatives to blood transfusion.

In addition to securing adequate supplies of safe blood, there is also much work to be done in improving the safety of the clinical use of blood. This is important because blood products carry inherent biological hazards, and process-related hazards can also lead to serious or fatal consequences *(2, 3)*. Therefore, it is essential that blood is only used when needed and clinically appropriate: when the patient's condition can be improved by blood transfusion, when alternative therapies are not available and when the administration of the transfusion can be properly monitored.

However, inappropriate use of blood persists, largely through lack of education and training in the appropriate clinical use of blood, and weak systems to safely manage the whole series of processes that starts with the education and recruitment of volunteer donors; to blood donation, testing, processing and distribution; through to transfusion and follow-up of patients who have received blood products: the "vein-to-vein" transfusion process. This is wasteful, dangerous and costly.

The challenge of improving clinical transfusion practice

Improving this situation worldwide is a target of the *WHO Action framework to advance universal access to safe, effective and quality-assured blood products, 2020–2023 (4)*.

Patient blood management (PBM) plays a central role in the action framework. While various definitions exist, PBM is universally accepted as international best practice in clinical transfusion medicine. PBM is:

> a patient-focused, evidence-based and systematic approach to optimize the management of patient and transfusion of blood products for quality and effective patient care. It is designed to improve patient outcomes through the safe and rational use of blood and blood products and by minimizing unnecessary exposure to blood products. Essential elements of patient blood management include: the prevention of conditions that might otherwise result in the need for transfusion (through health promotion and screening for early detection), appropriate diagnosis and optimal treatment, including the use of alternatives to transfusion, good surgical and anaesthetic techniques, the use of alternatives to blood transfusion and blood conservation *(5)*.

WHO has made a major commitment to PBM over the past decade, including through a series of scientific and educational workshops, such as the Global Forum for Blood Safety: Patient Blood Management, held in 2011, in Dubai, United Arab Emirates, where it was noted that: "Patient blood management is essential to optimize patient outcomes and patient safety by ensuring appropriate transfusion. Therefore, efforts need to be made to implement patient blood management effectively" *(5)*.

Therefore, supporting Member States to implement and deliver PBM form part of Strategic Objective 4 of the *WHO Action framework to advance universal access to safe, effective and quality assured blood products 2020–2023*: Patient blood management. The desired outcome is that "Member States have the knowledge and capacity to develop appropriate national clinical guidelines and practice standards, and to establish effective hospital transfusion committees" *(4)*. Developing this knowledge and capacity starts with access to education about PBM, and the modules presented here form part of that wider effort.

Aims

The material provided here is intended for a global audience of health professionals. It aims to be educational in nature and to provide an up-to-date overview of key topics relevant to blood safety and the clinical practice of transfusion medicine.

Target audience

The target audience for this material is health professionals who are, or may in the future, be part of decisions to transfuse, or who administer blood transfusions. This includes medical staff and students across a range of clinical areas, nurses and midwives. It may also be useful for staff, including laboratory scientists or technicians who work in blood transfusion laboratories preparing or testing blood for transfusion, or managing inventories of blood products, or other settings where information about how blood is used may be relevant (for example, education of staff who are involved in collecting blood from donors, or management staff of blood centres or hospitals).

How this document was developed

The material developed here was updated and adapted from *Clinical use of blood in medicine, obstetrics, paediatrics, surgery and anaesthesia, trauma and burns,* published by WHO in 2001, and widely used internationally.
The current resource is presented as a series of educational modules, which may be read individually or as part of a larger set of reference material. Some of the modules are based on the original chapters, and some are newly drafted. More modules may be added in the future. Presenting the material in individual modules is intended to facilitate use, so that readers can quickly find content of interest, and so that the content in a particular area can be readily updated as needed. Importantly, the material presented here is not in the form of formal "guidelines" from WHO but is presented as an educational resource for use by health professionals.

The scope of the updated resource was determined by WHO in collaboration with the International Society of Blood Transfusion (ISBT, a nongovernmental organization in official relations with WHO), under the guidance of an international editorial group. The individual modules were drafted and/or reviewed by experts in clinical and laboratory transfusion practice and a range of clinical disciplines from around the world, including from low- and middle-income countries, and the content reflects the knowledge and experience of the contributors and reviewers. We are very grateful for their contributions.

The material is intentionally generic, so it is, as far as possible, universally applicable, and suitable for a diverse readership, including in low- and middle-income countries. No prior specialist knowledge of transfusion science or clinical practice, or access to highly specialized technologies is expected. In a document like this, it is not possible to address every aspect of physiology or every clinical scenario, especially as knowledge and practice can change rapidly. Rather, the aim is to cover the basic information that is required for understanding the principles and practice of transfusion, and the content that should be useful for the most common situations. The focus is on practical aspects, including assessment

of the patient who may require a transfusion, or the storage and handling of blood products relevant to clinical practice. Since the evidence for effective clinical practice is constantly evolving, it is important to consult up-to-date sources of information. Therefore, the reader is also referred to additional resources from WHO, ISBT and other sources. The references lists in the individual modules are sources of further information on other important aspects of blood safety, such as recruitment of voluntary non-remunerated blood donors, screening blood for transfusion-transmitted infections and maintenance of the cold chain. A key resource of systematic reviews and randomized controlled trials on all aspects of transfusion medicine can be found at: www.transfusionevidencelibrary.com.

References

1. WHO model list of essential medicines 2019 (https://www.who.int/groups/expert- committee-on-selection-and-use-of-essential-medicines/essential-medicines-lists, accessed 5 February 2021).
2. A guide to establishing a national haemovigilance system. World Health Organization.. Geneva: World Health Organization; 2016 (https://apps.who.int/iris/handle/10665/250233, accessed 23 March 2021).
3. Aide-Mémoire on clinical transfusion process and patient safety. Geneva: World Health Organization; 2010 (https://www.who.int/bloodsafety/clinical_use/who_eht_10_05_en.pdf?ua=1, accessed 5 February 2021).
4. WHO Action framework to advance universal access to safe, effective and quality- assured blood products, 2020–2023. Geneva: World Health Organization; 2020 (https://www.who.int/publications/i/item/action-framework-to-advance-uas-bloodprods- 978-92-4-000038-4, accessed 5 February 2021).
5. Global Forum for Blood Safety: Patient Blood Management 14–15 March 2011, Dubai, United Arab Emirates. Concept paper. Geneva: World Health Organization; 2011 (www.who.int/bloodsafety/events/gfbs_01_pbm_concept_paper.pdf, accessed 5 February 2021).

CHAPTER 1

GENERAL PHYSIOLOGY: BLOOD, OXYGEN AND THE CIRCULATION

Key points

1. Blood is a complex organ system composed of:
   - red blood cells, whose primary function is to transport oxygen to tissues
   - white blood cells, whose primary function is to fight infection, provide immunity and destroy foreign material that has invaded the body
   - platelets, whose primary role is to promote coagulation at the site of vascular wall injury
   - plasma, which is noncellular fluid containing many important proteins, electrolytes and other nutrients essential to maintain health
   - vascular endothelium, which is in constant contact with the blood and is essential for nutrient transport and haemostasis.

2. Blood coagulation is a complex process consisting of:
   - primary haemostasis involving platelet activation and aggregation at the site of bleeding (vascular wall)
   - secondary haemostasis, which involves the activation of two cascading plasma protein pathways to produce fibrin and create a strong clot at the site of bleeding
   - fibrinolysis, which limits the final size of the clot to prevent thrombosis extending beyond the site of injury.

   An imbalance of these mechanisms can lead to excessive bleeding (coagulopathy) or clotting (thrombosis).

3. Blood oxygen transport to tissues is dependent on:
   - sufficient diffusion of oxygen from the atmosphere into the plasma and red blood cell haemoglobin
   - an adequate arterial oxygen content comprising red blood cell haemoglobin concentration and its saturation with oxygen
   - delivery of arterial oxygen content with a cardiac output that is adequate to meet the metabolic demands of the tissues to maintain aerobic metabolism.

   Failure to meet the oxygen-based metabolic demands of tissue results in shock, which can be fatal.

1.1 Introduction

The human body consists of an integrated aggregate of bony and soft tissue structures formed into various organ systems working under a coordinated control system. This allows for a remarkable number of functions, many of which are automated and designed to preserve life. No less complex than the others, blood is a sophisticated organ system consisting of several compartments, cell types and biochemical mediators, among others, to which all other organ systems are critically linked and are dependent on. A basic understanding of the composition and function of blood is critical to an overall understanding of health and the use of blood and blood products in the treatment of disease.

Learning outcomes

After studying this chapter, the reader will be able to describe:

1. the content and function of blood and its components
2. blood physiology
3. coagulation and haemostasis
4. supply of oxygen to the body

1.2 Body fluids and compartments

The critical role of blood in providing nutrients to tissues and removing waste is dependent on a remarkable connected network of fluid-filled compartments allowing for both passive and active diffusion.

Including its presence in blood, water is the major contributor to body mass, accounting for nearly 60% of adult body mass and upwards of 80% of the body mass of children. Proteins, fats, sugars and minerals account for the remaining body mass, with a large proportion of these being distributed and dissolved in body water *(1)*.

Body fluids exist in two main compartments:

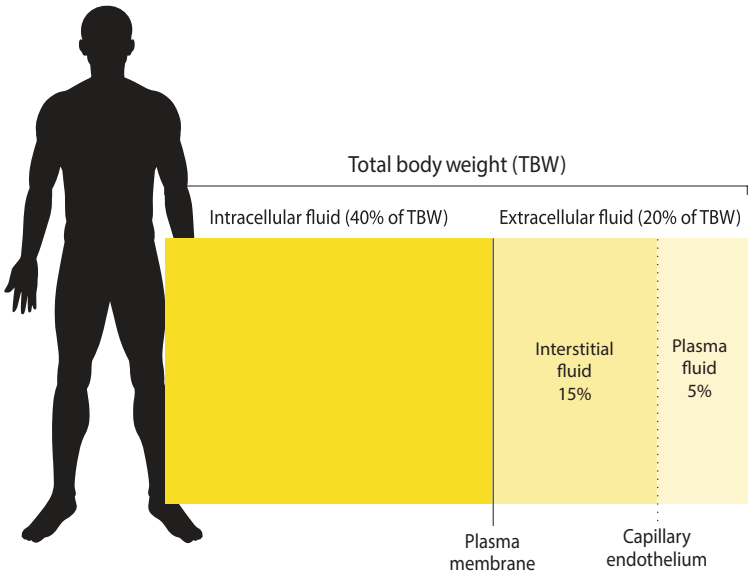
1. Intracellular fluid compartment (ICF): this is the fluid within the cells themselves, which accounts for approximately 40% of body weight.

2. Extracellular fluid compartment (ECF): the ECF is composed of two spaces:
   - intravascular space: blood and plasma confined to circulating within the vascular system, accounting for approximately 8–10% of body weight;
   - interstitial space: non-blood and non-plasma fluid existing outside the vascular system but within organs, which surrounds and bathes cells of the organs, accounting for approximately 15% of body weight.

Fig. 1.1 illustrates the structure of these compartments, including the proportions in which they generally exist and the mechanisms by which they are separated from each other.

The fluid in each of these compartments serves specific functions in maintaining health. The composition of these fluids together with differences in the membranes that separate them allow for the creation of forces that permit the essential movement of fluid constituents across membranes to meet the needs of the organs.

Figure 1.1. Structure of the body fluid compartments



These forces include:

1. Diffusion: This refers to the movement of discrete substances across compartments through concentration gradients (from high concentration to lower concentration).

2. Filtration: Hydrostatic pressure causes fluid to be filtered through a membrane.

3. Active transport: Mechanisms within a membrane exist to actively move a substance across the membrane.

4. Osmosis: This is the passive movement of water into a compartment that has a high concentration of impermeable substances, but which is freely permeable to water. The concentrations of these impermeable substances on each side of the membrane determine the extent of water movement.

Table 1.1 provides a comparison of the composition of electrolytes and the protein content within the major compartments.

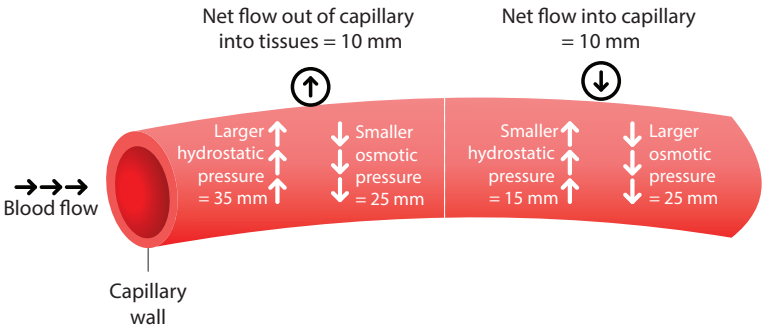
Although the plasma and interstitial compartments are quite similar, their protein content is very different. Also, as can be seen from Table 1.1, the ICF is significantly different from both components of the ECF. The major protein in the ECF is albumin. It exists mainly in the vascular space and is thus known as plasma protein. Albumin and other ECF proteins are relatively large, making cellular membranes impermeable to them. The ICF also contains high concentrations of a wider variety of proteins than are present in plasma and are for the most part too large to pass through the membrane.

Table 1.1. Composition of electrolytes and protein content within the major compartments

	Plasma (mmol/L)	Interstitial fluid (mmol/L)	Intracellular fluid (mmol/L)
Na^+	142	144	10
K^+	4	4	160
Ca^{2+}	2.5	1.25	1.5
Mg^{2+}	1	0.5	13
Cl^-	102	114	2
HCO_3^-	26	30	8
PO_4^{2+}	1	1	57
SO_4^{2-}	0.5	0.5	10
Organic acid	6	5	0
Protein	16	2	55

Oncotic pressure, or colloid osmotic pressure, is a form of osmotic pressure induced by proteins, notably albumin, in a blood vessel's plasma (blood/liquid). It displaces water molecules, thus creating a relative water molecule deficit with water molecules moving back into the circulatory system within the lower-pressure venous end of the capillaries. It has the opposing effect of both hydrostatic blood pressure pushing water and small molecules out of the blood into the interstitial spaces within the arterial end of capillaries and interstitial colloidal osmotic pressure. These interacting factors determine the partition balancing of total body extracellular water between the blood plasma and the larger extracellular water volume outside the bloodstream. Fig. 1.2 illustrates the balance of hydrostatic and oncotic forces in the capillaries, which contribute to fluid and nutrient transport to and from tissues.

Figure 1.2. Illustration of the balance of hydrostatic and oncotic forces in the capillaries



The ICF is also subject to water volume regulation, which again is mainly dependent on osmotic forces. However, unlike the ECF, which is largely protein-dependent, the ICF is mostly dependent on differences in the concentrations of sodium and potassium, which are actively controlled by pumps situated in the cell membrane.

1.3 Blood, platelets, plasma, endothelium and coagulation

Although it is not typically viewed as such, blood should be considered an organ system. Like other organ systems such as the central nervous and gastrointestinal systems, blood is made of a complex but integrated variety of cell types and has a distinct biochemistry. This allows it to provide critical nutrients to and remove waste from all other organ systems as well as to provide life-saving functions such as fighting infection and coagulation. Also, similar to other organ systems, it may malfunction for many reasons and can be subject to injury and failure.

Blood is composed of a number of cellular and acellular components including red cells, white cells, platelets and plasma proteins. Because it is in constant contact with the vascular lining and the role it plays in coagulation, the endothelium should also be considered a critical component of blood.

Red blood cells

Red blood cells (erythrocytes) account for the majority of the cellular population of circulating blood and for approximately 40–45% of total circulating blood volume. The major function of red blood cells is to take up oxygen from the lungs and carry it to tissues throughout the body. Produced in the bone marrow under the hormonal influence of erythropoietin, red blood cells have an approximate lifespan of 120 days after entering the circulatory system from the bone marrow. After this time, red blood cells are disposed of by the liver and spleen's reticular endothelial system. Red blood cells achieve their major function of uploading and offloading oxygen by making use of the iron-based molecule haemoglobin. Haemoglobin is a protein that has two pairs of peptide chains each containing an iron ring. For adult haemoglobin, one pair of these peptides is the alpha (α) chain and the other is the beta (β) chain. Each of the four chains or subunits is capable of reversibly binding with one molecule of oxygen giving a total of four molecules of oxygen for one molecule of haemoglobin.

Measured in grams per decilitre (g/dl), the typical amounts of haemoglobin in an adult male and female are approximately >13 g/dl and >12 g/dl, respectively.

White blood cells

White blood cells or leukocytes are also produced by the bone marrow, as well as the lymphatic tissue, and make up less than 1% of total circulating blood volume. However, they play the critical role of combating infection, identifying, destroying and removing invading or foreign material from the body. They also help to develop immunity and resistance in response to natural exposure to infection or from purposeful immunization.

These functions are carried out by a heterogeneous population of white blood cells. The types and percentage contribution to the white blood cell family are as follows:

- neutrophils (55–73%)
- lymphocytes (20–40%)
- eosinophils (1–4%)

- monocytes (2–8%)
- basophils (0.5–1%).

White blood cells are usually measured and reported in numbers per microlitre (µl) or cubic millimetre (mm^3).

Platelets

Produced as small fragments from megakaryocytes in the bone marrow, the major function of the platelets is to respond to damage to the vascular wall, especially damage that could result in haemorrhage. Platelets adhere to the damaged vascular wall and release a number of mediators and enzymes that participate in the coagulation process. Platelets are a major component of the resulting clot and are incorporated with fibrin where they are capable of contracting, as a mechanism to strengthen the clot. Platelets are measured as number per microlitre of blood.

The microcirculation and endothelium

An important but overlooked aspect of the blood is the role of the endothelium and microcirculation, which are critical to ensure the delivery of nutrients such as oxygen to tissues, as well as coagulation. The microcirculation with its endothelial lining is estimated to cover an area of up to 7000 m^2 *(2)*. The individual microcirculatory unit is composed of the arteriole, capillary bed and postcapillary venule. Its role is to ensure the delivery of oxygen and other nutrients to tissues in excess of their needs, as well as to remove products of metabolism. With an estimated 10^{13} endothelial cells in an adult, the endothelium is constantly exposed to blood. Thus, manipulation of the blood will inevitably affect the vascular system in some way. Injury to the endothelium can result in undesirable complications through three major mechanisms: paracellular permeability, dysfunctional haemostasis and inflammation *(3)*.

Coagulation

Coagulation is a complex but orchestrated process used by the body both to maintain vital blood flow within the vascular system to tissues and to prevent and reduce haemorrhage when the vascular system is injured. This process, which involves integrated cellular and noncellular components, is termed haemostasis. Imbalances in the system are major causes of a number of primary bleeding and clotting disorders as well as bleeding and clotting complications caused by a number of illnesses and injuries.

Coagulation and haemostasis can be divided into three major processes *(4)*:

1. *Primary haemostasis*: When injured and bleeding, the damaged endothelium of the blood vessels is the first to be involved in the process of haemostasis. This process includes vasoconstriction of the damaged vessels to reduce blood flow and the exposure of specific proteins and structures such as collagen, microfibrils and basement membranes that promote adhesion of platelets to the site. Platelet adhesion prompts the release of a number of mediators that promote further vasoconstriction and aggregation of additional circulating platelets at the site resulting in a primary platelet plug, which will grow to consist of trapped red cells.

2. *Secondary haemostasis*: Occurring in concert with primary haemostasis, the activation of an important acellular network and pathway of specific plasma proteins combined with phospholipids and calcium ions participate in clot formation. Known as the coagulation cascade, it consists of two pathways (intrinsic and extrinsic).

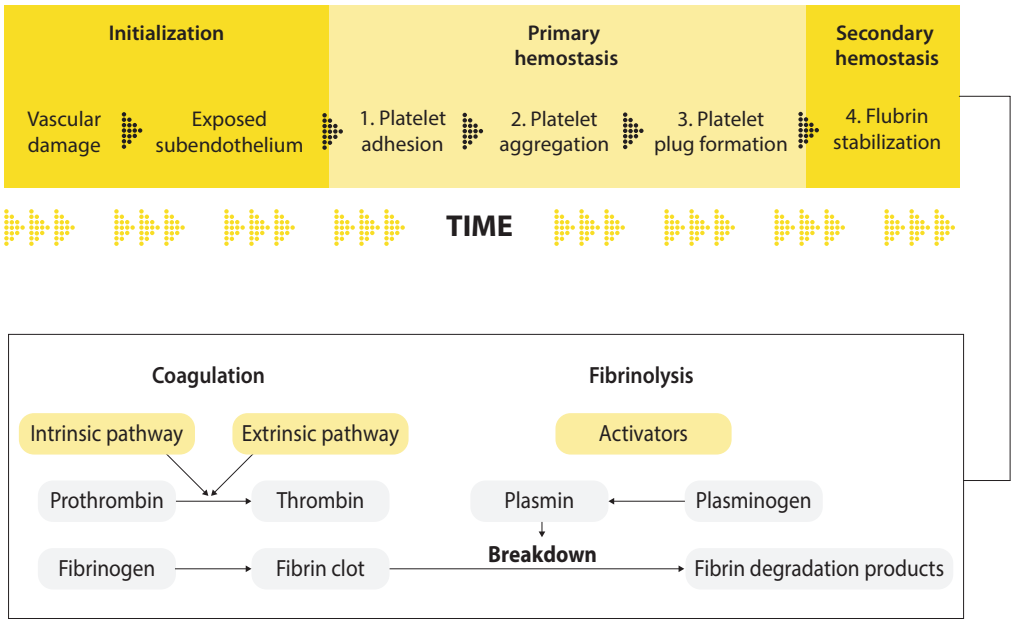
The intrinsic, or contact activation pathway, is triggered through the activation of several clotting proteins coming in contact with exposed collagen in the damaged vascular wall.

The extrinsic, or tissue factor pathway, is activated by the release of tissue factor from the damaged vascular wall. Activation of both pathways results in a cascade of enzymatic reactions leading to a final common pathway activating the protein thrombin. This causes the conversion of the soluble protein fibrinogen into insoluble fibrin, which is then incorporated into the platelet plug, strengthening it so that it becomes a fibrin clot.

3. *Fibrinolysis*: Although production of a fibrin clot is essential to produce haemostasis, it is also critical to have limitations to growth of the clot to prevent progressive thrombosis beyond the site of injury. This process of fibrinolysis or clot removal occursthrough several mechanisms including:
   - blood flowing past the clot to remove additional activated clotting factors;
   - activation of proteins designed to inactivate clotting factors; and
   - active degradation of the clot over time by specific enzymes such as plasmin.

Fig. 1.3 provides a high-level overview of the coagulation process. Although it is normally a very balanced process, major insults such as severe trauma with haemorrhage or severe inflammation, such as sepsis, can lead to drastic alterations resulting in extreme responses such as hyperfibrinolysis or thrombosis *(5, 6)*.

Figure 1.3. Overview of the coagulation process



1.4 The role of blood in supplying oxygen to the body

The primary purpose of blood and its components is to supply nutrients to tissues, remove waste from tissues, maintain haemostasis and assist in fighting infection. Critical to each of these functions is a constant supply of oxygen, which ensures life sustaining metabolism.

Basic oxygen transport

For tissues to receive oxygen, several fundamental processes must take place *(7)*.

- Oxygen is transferred from the lungs into the plasma.
- Oxygen is bound to haemoglobin in red blood cells.
- Oxygen is transported to the microcirculation where it is released to tissues for utilization.

Air contains mainly a mixture of oxygen, nitrogen and a small proportion of additional gases such as carbon dioxide. Each of these gases contribute to the total atmospheric pressure in proportion to their concentration. At sea level (760 mmHg or 101 kPA), air contains approximately 21% oxygen (160 mmHg or 21 kPA) with rest being mainly nitrogen (close to 79%).

Although the partial pressure of oxygen seems high, this level is reduced by the time air reaches the lung alveoli where diffusion of oxygen into the plasma occurs. Air humidification in the upper airways, transfer of air to the alveoli and diffusion of blood carbon dioxide from the blood plasma into the lung alveoli reduce the partial pressure of oxygen from 160 mmHg to 100 mmHg (13.3 kPa).

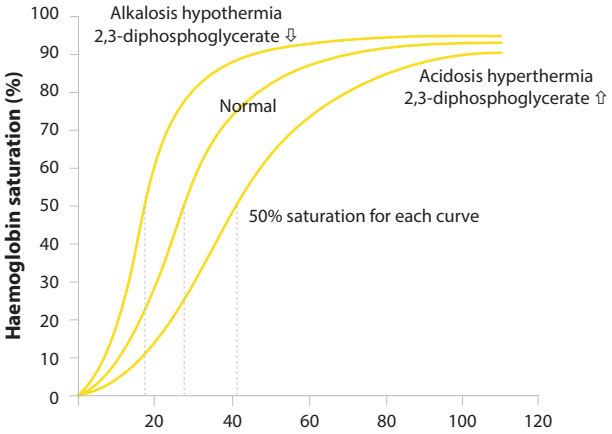
Although this is a significant drop, this partial pressure is still higher than the partial pressure of oxygen in the pulmonary capillary venous blood returning to the lung from the body, which in a resting state averages only 40 mmHg (5.3 kPA). This represents the main driving force, resulting in a rapid diffusion transfer into blood plasma from a higher-pressure gradient to a lower-pressure gradient.

In the absence of any alveolar barriers such as infection, oedema or other causes of damage, almost total equilibrium is achieved between the partial pressure of alveolar oxygen and the arterial capillary blood leaving the alveoli.

The main carrier of oxygen in the blood is the haemoglobin molecule present in red blood cells. As oxygen diffuses from the alveoli to the plasma, it rapidly crosses into the red cell, binding to haemoglobin until almost fully saturated (98 mmHg or 13 kPA). When fully saturated, each gram of haemoglobin can carry 1.36 ml of oxygen. Thus, blood would carry nearly 20 ml of oxygen in an individual with a haemoglobin level of 15 g/dl if the haemoglobin is fully saturated with oxygen. However, plasma is a very poor oxygen carrier. Only 0.3 ml of oxygen is dissolved in each 100 ml of plasma when breathing 21% oxygen.

The relationship between the partial pressure of oxygen in the plasma and haemoglobin oxygen saturation can be described using the oxyhaemoglobin dissociation curve (Fig. 1.4). This curve represents the unique cooperative oxygen binding properties of haemoglobin coupled with the concentration-driven diffusion gradients that exist between plasma and haemoglobin. The combination of these factors is responsible for the nonlinearity of the curve. Haemoglobin has a P50 of 26.7 mmHg. The P50 is the oxygen tension at which haemoglobin is 50% saturated with oxygen. Because oxygen is continuously being utilized at the tissue level, the partial pressure of oxygen in tissues is significantly lower than that entering the capillary. Oxygen will, therefore, diffuse down its pressure gradient from the capillaries into the tissue.

Figure 1.4. Oxyhaemoglobin dissociation curve



Several important factors including pH, partial pressure of CO_2, temperature and 2,3- diphosphoglycerate (2,3 DPG) can shift this curve to the left or to the right and play an important role in several disease processes. Shifting the curve to the left decreases the P50 of haemoglobin thus increasing the affinity of oxygen binding to haemoglobin. Shifting the curve to the right increases the P50 of haemoglobin thus decreasing the affinity of oxygen binding to haemoglobin, facilitating its release to tissues.

Oxygen transport to tissues

It is important to understand oxygen transport in the blood to tissues via the relationship between oxygen delivery (DO_2 in ml/min) to tissues and oxygen consumption (VO_2 in ml/min) by the tissues.

DO_2 is determined by the following equation:

arterial oxygen content (CaO_2) × cardiac output (CO)

Where CaO_2 (ml/dl blood) = (1.34 × [Hb] × SaO_2) + (0.003 × PaO_2)
1.34 = volume of oxygen bound to 1 gram of saturated haemoglobin (ml/g)
Hb = concentration of haemoglobin in g/L
SaO_2 = percentage of haemoglobin saturated with oxygen (expressed as a fraction)
0.003 = solubility coefficient of oxygen in plasma (ml/dl/mmHg or kPa). For every 1 mmHg of oxygen tension, 0.003 ml of oxygen is dissolved in 100 ml of plasma
PaO_2 = partial pressure of oxygen dissolved in arterial blood (mmHg or kPa)

Since plasma carries only 0.3 ml of oxygen per 100 cm^3 of plasma, its contribution to the total DO_2 is negligible and therefore it is often deleted from the equation.

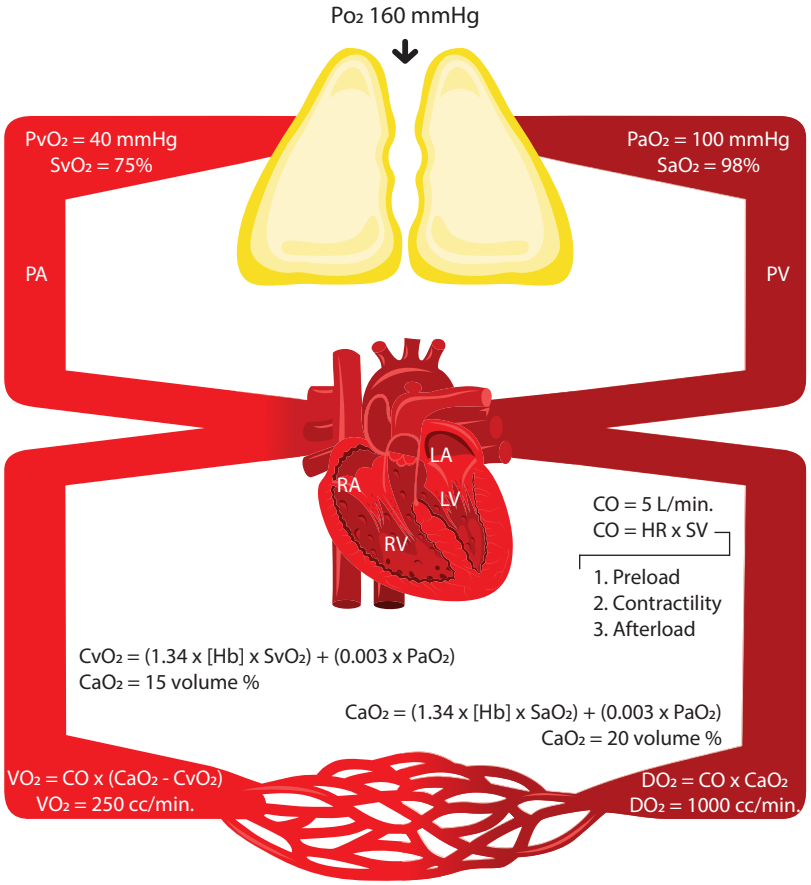
Cardiac output (cm^3 or litres per minute) is the product of heart rate and stroke volume, which are subject to a combination of mechanical, vascular and neurohormonal influences. In particular, stroke volume (the amount of blood pumped from the heart by each heartbeat) is determined by a combination of preload (amount of blood entering the heart), afterload (the arterial resistance the heart must pump against) and contractility (how forcefully the heart contracts).

VO_2 is determined by the following equation:

$CO \times (CaO_2 - CvO_2)$

where CvO_2 is calculated similarly to CaO_2 except that mixed venous haemoglobin saturation from the pulmonary artery (reflecting return from the body as a whole) is used in the calculation. On average and under resting conditions, the adult body will consume approximately 200–250 cm^3 oxygen per minute. This represents approximately 25–30% extraction of the available oxygen, resulting in a mixed haemoglobin oxygen saturation of 70–75% when arterial haemoglobin oxygen saturations are 95–99%. Fig. 1.5 shows an overview of whole-body oxygen transport.

Figure 1.5. Overview of whole-body oxygen transport



CaO_2: Arterial oxygen content
CvO_2: Mixed venous oxygen content
CO: Cardiac output
DO_2: Oxygen delivery
Hb: Concentration of haemoglobin
HR: Heart rate
PaO_2: Partial pressure of oxygen dissolved in arterial blood
PvO_2: Mixed venous oxygen pressure
SaO_2: Arterial oxygen saturation
SV: Stroke volume
SvO_2: Mixed venous oxygen saturation
VO_2: Oxygen consumption

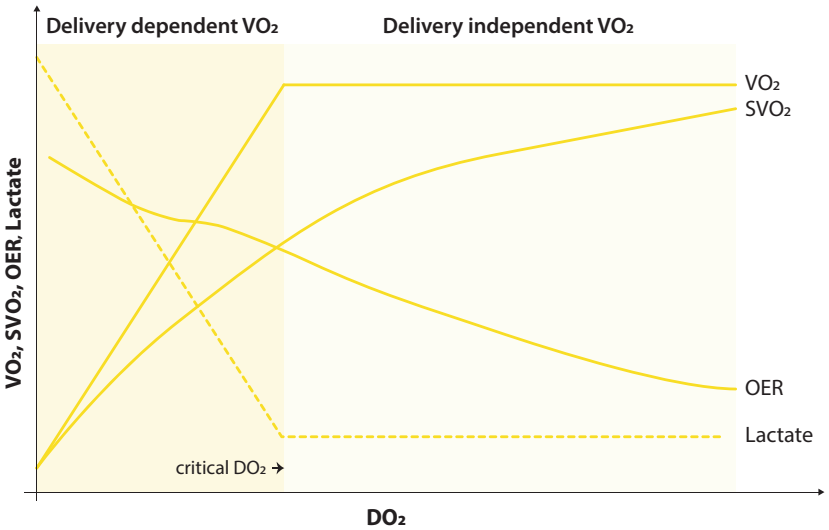
Using the equations above, it becomes clear how certain pathologies individually or in combination can contribute to detrimental decreases in DO_2. This is useful in determining which components can or should be manipulated using transfusion medicine. There are, of course, limits to how much each component of DO_2 can be altered. For example, increasing haemoglobin above 15 g/dl to increase CaO_2 will at some point reach a limit due to rheological challenges at the level of the microcirculation as well as how much volume the heart can handle before it fails. Table 1.2 lists major influencers of DO_2 and VO_2, which can alter the balance favourably or unfavourably depending on the situation.

Table 1.2. Major influencers of the balance of oxygen delivery (DO_2) and oxygen consumption (VO_2)

⇧ VO_2	⇩ DO_2	⇧ DO_2	⇩ VO_2
Stress	⇩ SaO_2	⇧ SaO_2	Hypothermia
Pain	⇩ Haemoglobin	⇧ Haemoglobin	Anaesthesia
Hyperthermia	⇩ Cardiac output	⇧ Cardiac output	
Shivering			

These principles form the basis for understanding shock, which is a major cause of death and frequently requires transfusion for its treatment. Shock is traditionally defined as tissue DO_2 below tissue oxygen metabolic needs or demands. Fig. 1.6 demonstrates the biphasic relationship between DO_2 and VO_2. As DO_2 decreases, VO_2 may remain constant due to an increasing ratio of oxygen that is extracted at the level of the tissue (oxygen extraction ratio, OER), which is mirrored by a decrease in haemoglobin oxygen saturation (SvO_2) in the tissues. However, as DO_2 continues to decrease, there will eventually come a point where the OER cannot meet tissue VO_2 demands resulting in a state of DO_2-dependent VO_2. At this point (critical DO_2), there is a transition from aerobic to largely anaerobic metabolism and VO_2 is directly dependent on DO_2. It is at this point that an oxygen deficit begins to accumulate, as signalled by increased levels of anaerobically produced lactate. Because oxygen deficit is the change in VO_2 from baseline, this deficit is equal to the difference between baseline VO_2 and the VO_2 at a particular time point after reaching critical DO_2. This quantified deficit over time is the oxygen debt *(8)*.

Figure 1.6. The biphasic relationship between oxygen delivery (DO_2) and oxygen consumption (VO_2)



The degree (depth and duration) of oxygen debt has clear consequences, as oxygen debt has been linked to the degree of reperfusion injury, inflammation and acidosis. These events in turn are responsible for the development of endothelial injury and the coagulopathy that can occur in the setting of severe haemorrhagic and other forms of shock as well as the incidence of organ failure *(9)*.

References

1. Pain RW. Body fluid compartments. Anaesth Intensive Care. 1977;5:284–94.
2. Aird WC. Endothelium as an organ system. Crit Care Med. 2004;32(5 Suppl):S271–9.
3. Aird WC. Endothelium and haemostasis. Hamostaseologie. 2015;35:11–6.
4. Versteeg HH, Heemskerk JW, Levi M, Reitsma PH. New fundamentals in hemostasis. Physiol Rev. 2013;93:327–58.
5. White NJ, Ward KR, Pati S, Strandenes G, Cap AP. Hemorrhagic blood failure: Oxygen debt, coagulopathy, and endothelial damage. J Trauma Acute Care Surg. 2017;82(6S Suppl 1):S41– S49.
6. Hess JR, Brohi K, Dutton RP, Hauser CJ, Holcomb JB, Kluger Y, et al. The coagulopathy of trauma: a review of mechanisms. J Trauma-Inj Infect Crit Care. 2008;65:748–54.
7. Pittman RN. Regulation of tissue oxygenation. San Rafael (CA): Morgan & Claypool Life Sciences; 2011.
8. Barbee RW, Reynolds PS, Ward KR. Assessing shock resuscitation strategies by oxygen debt repayment. Shock. 2010;33:113–22.
9. Bjerkvig CK, Strandenes G, Eliassen HS, Spinella PC, Fosse TK, Cap AP, et al. "Blood failure" time to view blood as an organ: how oxygen debt contributes to blood failure and its implications for remote damage control resuscitation. Transfusion. 2016;56 Suppl 2:S182–9.

CHAPTER 2

ANAEMIA

Key points

1. The prevention, early diagnosis and treatment of anaemia, and conditions that cause anaemia, are important in minimizing the need for transfusion.

2. Anaemia develops as a result of one or more of the following:
   - increased red blood cell loss
   - decreased or inadequate production of normal red blood cells
   - increased destruction of red blood cells.

3. Anaemia becomes clinically important when it contributes to a reduction in oxygen supply making it inadequate for the patient's needs.

4. The principles of treatment of anaemia are:
   - Treat the underlying cause of the anaemia.
   - Establish the clinical consequences of the anaemia (patient reserves, decompensation).
   - Optimize all the components of the oxygen delivery system to improve the oxygen supply to the tissues.
   - Blood transfusion should only be considered in patients with symptomatic anaemia.

2.1 Introduction

When an individual becomes anaemic, a variety of physiological changes take place. Central to these changes are the body's own compensatory responses to anaemia that, within limits, help preserve the oxygen supply to the tissues.

The main purpose of this module is to explore these compensatory mechanisms that, when reinforced by appropriate treatment of the anaemia, may be sufficient to make blood transfusion unnecessary.

Learning outcomes

After reading this chapter, the reader will be able to:

1. Define anaemia in an individual and distinguish between a normal haemoglobin range and a reference haemoglobin range.
2. List some commonly used methods of determining the red cell or haemoglobin content of the blood.
3. Identify the factors that affect the haemoglobin concentration in a patient and that may alter one's interpretation of it.
4. Outline the main causes of anaemia.
5. Describe the effects of anaemia and the ensuing compensatory responses, with particular emphasis on acute and chronic blood loss.
6. State the principles of the treatment of anaemia.
7. Outline the measures that can be used to prevent anaemia in a population.
8. Understand the recommendations for red cell transfusion thresholds for the individual patient.

2.2 Definitions

Anaemia

Anaemia is defined as a haemoglobin concentration in blood that is below the expected value, considering age, sex, pregnancy and ethnicity.

This definition therefore requires a comparison to be made between the individual's haemoglobin concentration and the expected value. To determine the patient's expected haemoglobin concentration, it is necessary to refer to one of the following haemoglobin ranges:

- the normal haemoglobin range; or
- a reference haemoglobin range.

The normal haemoglobin range

The normal haemoglobin range is the 95% distribution of haemoglobin concentrations found in a representative, large group of fit and healthy individuals (Fig. 2.1). In principle, therefore, it might be considered as a worldwide standard indicator of good health, varying only with age, sex, pregnancy, ethnicity or altitude of residence.

Figure 2.1. Haemoglobin range

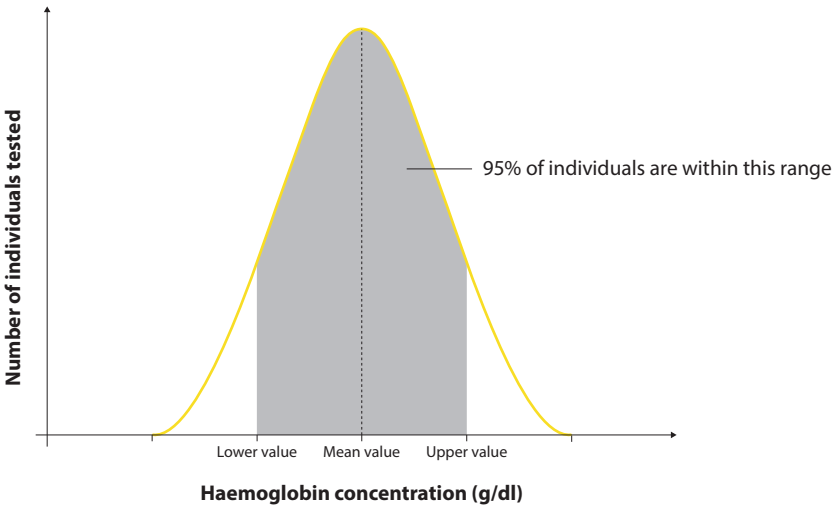


Fig. 2.1 shows the normal 95% ranges and criteria for defining an individual as anaemic, proposed by the World Health Organization (WHO), but it is important to remember that some individuals who are apparently normal and healthy will have values outside the range (<5% of the normal individuals). Published values for "normal" haemoglobin levels indicate, for example, that many adult females should be considered normal, even though their haemoglobin levels are below 12 g/dl (Table 2.1).

Table 2.1. Criteria for anaemia, based on normal haemoglobin (Hb) range at sea level, proposed by WHO

Age and sex	Normal Hb (g/dl)	Anaemic if Hb range less than: (g/dl)[a]	
Birth (full-term)	13.5–18.5	13.5	(Hct 34.5)
Children: 2–6 months	9.5–13.5	9.5	(Hct 28.5)
Children: 6 months–5 years	11.0–14.0	11.0	(Hct 33.0)
Children: 5–12 years	11.5–15.5	11.5	(Hct 34.5)
Children: 12-14 years	12.0–15.0	12.0	(Hct 36.0)
Adult males	13.0–17.0	13.0	(Hct 39.0)
Adult females: non-pregnant	12.0–15.0	12.0	(Hct 36.0)
Adult females: pregnant			
First trimester: 0–12 weeks	11.0–14.0	11.0	(Hct 33.0)
Second trimester: 13–28 weeks	10.5–14.0	10.5	(Hct 31.5)
Third trimester: 29 weeks–term	11.0–14.0	11.0	(Hct 33.0)

Hct = haematocrit.

[a] These values define anaemia. They are often used as thresholds for investigation and treatment, but are not indications for transfusion.

Reference haemoglobin ranges

A reference haemoglobin range is the distribution of haemoglobin concentrations found in a specific well-defined population, called the reference population. It is developed by sampling the haemoglobin values from a group of individuals who are representative of that population (see Table 2.2 for examples).

Table 2.2. Examples of reference ranges for non-pregnant females

Reference range for nonpregnant females	Range (g/dl)	Mean (g/dl)
Delhi, India	6.3–14.8	10.5
Burkina Faso	9.4–15.0	12.2

If the reference population is composed predominantly of healthy individuals, the reference range will be similar to the normal haemoglobin range. However, the reference range values will be lower than the normal range if the reference population has a high prevalence of disorders affecting the haemoglobin concentration, such as iron deficiency, malaria or inherited haemoglobinopathies.

Reference haemoglobin ranges are useful for identifying anaemia in certain populations and for targeting them with appropriate public health measures. When repeatedly obtained for the same population, reference ranges will also help to assess the effectiveness of these measures.

Reference haemoglobin ranges should not be used as a basis for investigation and treatment of an individual patient. The normal haemoglobin range should be used for this purpose.

2.3 Measuring haemoglobin concentration and haematocrit

Haemoglobin concentration

In addition to the clinical features of anaemia, an accurate haemoglobin measurement on a patient's blood sample is essential when deciding whether the patient needs a blood transfusion.

Many of the laboratory methods for determining haemoglobin concentration are technically capable of providing results of sufficient quality for clinical use. However, regardless of the method, reliable results depend on good laboratory practice, appropriate staff training, use of standard operating procedures, and regular calibration and maintenance of the equipment. The correct use of internal controls and, if possible, external quality assessment samples is also important.

Table 2.3 summarizes some of the methods commonly used for haemoglobin measurement

Table 2.3. Methods for haemoglobin measurement

Methods	Comments
Using a spectrophotometer or photoelectric photometer:	All require some type of optical equipment with battery or mains power supply, maintenance, calibration, spares and user training
Haemoglobin cyanide	
Oxyhaemoglobin	
Direct reading haemoglobinometers	–
Copper sulfate method	Only useful for screening blood donors

Haematocrit or packed cell volume

An alternative method of estimating the red cell content of the blood is to measure the haematocrit or packed cell volume (PCV). The PCV is determined by centrifuging a small sample of blood in an anticoagulated capillary tube and measuring the volume of packed red cells as a percentage of the total volume.

An equivalent measurement, the haematocrit, can be calculated by automated haematology analyses from the red cell indices.

For clinical purposes, the terms "haematocrit" and "PCV" are used interchangeably.

The relationship between haematocrit and haemoglobin concentration in a given sample is influenced by the size and haemoglobin content of the red cells. A useful conversion factor is that haematocrit (%) is approximately equal to three times the haemoglobin concentration. Haematocrit values are shown in Table 2.1.

2.4 Clinically important anaemia

It is relatively simple to define a patient as being anaemic by comparing his or her haemoglobin concentration with a normal range. However, to judge whether the anaemia is clinically important, a detailed assessment of the individual patient's signs and symptoms is needed.

The oxygen supply to the tissues also depends on:

- the degree of saturation of haemoglobin; and
- the cardiac output.

Alterations in the haemoglobin concentration should therefore not be interpreted in isolation, but should be seen in the context of changes or disorders affecting the other variables of oxygen supply.

2.5 Interpreting haemoglobin values

The haemoglobin value is a measurement of concentration and is the amount of haemoglobin present in a fixed volume of the patient's blood. It is normally expressed as grams per decilitre (g/dl) or grams per litre (g/L).

In this chapter, all haemoglobin values are expressed in g/dl. The haemoglobin value itself is dependent on:

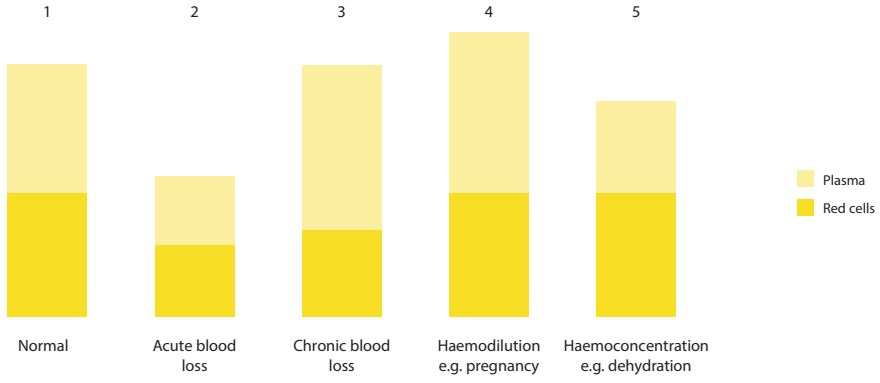
- total amount of circulating haemoglobin in the red cells; and
- blood volume.

A variation in either of these factors will affect the haemoglobin concentration. During pregnancy, for example, apparent anaemia may simply be the result of an increase in plasma volume, without a reduction in the total amount of haemoglobin present. This is called haemodilution. Since the overall capacity of blood to carry oxygen is unchanged, it is not necessarily a pathological state.

Haemodilution: reduced haematocrit (packed cell volume). Acute haemodilution is caused by red cell loss and replacement by crystalloid or colloid infusion.

Conversely, where there is a reduction in the plasma volume without any alteration in the total amount of haemoglobin present, a higher than expected haemoglobin concentration will be apparent. This is known as haemoconcentration and can occur, for example, in a person with severe dehydration. The haemoglobin concentration therefore needs to be considered together with other information about the patient's condition to avoid misinterpretation (see Fig. 2.2).

Figure 2.2. Alteration of haemoglobin in relation to plasma



Red cell volume	N	L	L	N	N
Plasma volume	N	L	H	H	L
Hb level	N	N/L	L	L	N/H

N, normal; H, high; L, low.

Column 1 represents a normal patient.
Column 2 illustrates a patient who loses blood rapidly over a short period of time (haemorrhage). Both red cells and plasma are lost together, but the haemoglobin concentration may initially remain fairly normal.
Column 3 shows the effect of a slow (or chronic) blood loss over weeks or months. Normal compensatory responses have operated to expand the plasma volume in order to maintain the total blood volume, but the haemoglobin concentration is reduced because red cells have been lost.
Column 4 illustrates the effect of haemodilution. This picture would be seen in a patient who had received intravenous replacement fluids or as a normal feature in pregnancy.
Column 5 shows the consequences of dehydration, resulting in haemoconcentration. There is no loss of red blood cells (RBCs), but blood volume is reduced. The haemoglobin concentration is therefore above normal.

2.6 Causes of anaemia

Anaemia is not a diagnosis in itself, but an indication of one or more causes of a reduced haemoglobin concentration. A simple classification of the processes that can lead to anaemia is shown in Table 2.4.

Table 2.4. Causes of anaemia

Increased red cell loss (high reticulocytes)	
Blood loss	
Acute blood loss	Trauma, surgery, obstetric haemorrhage, gastrointestinal haemorrhage etc.
Chronic blood loss	Low-grade bleeding from gastrointestinal, urinary or reproductive tracts due to parasitic infestation, malignancy, inflammatory disorders etc.
Increased red cell destruction (haemolysis)	
Haemolysis due to corpuscular factors	Red cell membrane defects (congenital spherocytosis)
	Red cell enzyme defects (G6PD deficiency, pyruvate kinase deficiency)
	Haemoglobinopathies (thalassaemias, HbS)
	Acquired intracorpuscular defects (PNH)
Haemolysis due to extracorpuscular factors	Red cell antibodies (ABO, Rh and other red cell incompatibilities; auto-antibodies)
	Chemicals (drugs, venoms, arsenic, lead)
	Mechanical (heat/burn wounds, artificial heart valves, DIC, malignant hypertension)
	Hypersplenism
	Infections (i.e. malaria, *Clostridium*)
Decreased production of normal red blood cells (hypoproliferative anaemia)	
Normochromic, normocytic anaemia (bone marrow suppression of erythropoiesis)	
⇩ Erythropoietin	Chronic renal failure
	Hypothyroidism
	Chronic inflammatory disease
Bone marrow failure	Metastatic carcinomas (prostate, breast, lung, kidneys)
	Malignancies of the haemopoietic tissues (lymphomas, multiple myeloma, leukaemias)
	Exposure to drugs (e.g. chloramphenicol), toxic chemicals (e.g. lead), radiation or chemotherapy
	Other causes (aplastic anaemia, myelofibrosis, myelodysplastic syndrome)
Decreased production of normal red blood cells (hypoproliferative anaemia)	
Hypochromic, microcytic anaemia (decreased haemoglobin synthesis)	
⇩ Haem synthesis	Iron deficiency
	Anaemia of chronic disease
	Porphyrin synthesis abnormalities e.g. sideroblastic anaemias
Globin synthesis abnormalities	Thalassaemias

Hyperchromic, macrocytic anaemia (low reticulocytes)	
Megaloblastic anaemia Vitamin B12 deficiency	Insufficient dietary intake (vegetarians, vegans)
	Malabsorption
	Absence of intrinsic factor (pernicious anaemia, gastrectomy, damage to gastric epithelium by corrosive chemicals or malignant infiltration)
	Increased utilization by bacteria in areas of overgrowth (blind-loop syndrome)
	Pathology of ileum (tuberculosis, lymphoma, tropical sprue)
Folate deficiency	Insufficient dietary intake (alcoholism, poor diet in general)
	Malabsorption (Crohn's disease, intestinal lymphoma, phenytoin therapy)
	Increased folate requirements (pregnancy, haemolytic anaemias, exfoliative dermatitis)
	Administration of folate antagonists (trimethoprim, methotrexate, zidovudine)
Non-megaloblastic anaemia (normal vitamin B12 and folate, bone marrow examination for further diagnosis)	Myelodysplastic syndrome
	Aplastic anaemia
	Direct marrow injury destroying haemopoietic tissue

G6PD, glucose-6-phosphate dehydrogenase; HbS, haemoglobin S; PNH, paroxysmal nocturnal haemoglobinuria; DIC, disseminated intravascular coagulation.

Source: Namibian guidelines for the appropriate clinical use of blood and blood products (GACUB).

Iron deficiency anaemia is the most common cause of anaemia worldwide. It is important to understand the basic mechanisms of iron metabolism as this is fundamental to the prevention, diagnosis and treatment of anaemia.

Iron metabolism

Iron is an essential nutrient required by every human cell. Most of the body's iron is contained in the haemoglobin. Iron is absorbed in the intestines, transported in the blood by a carrier protein (transferrin) and stored as ferritin (in cells such as those of the bone marrow, gut, liver and spleen). Humans do not have an effective mechanism for excreting iron, otherthan through loss of blood and small amounts through shedding of skin and intestinal cells.

The physiological adjustment of the iron balance in an individual depends on small alterations in intestinal absorption and on sufficient iron in the diet (see Table 2.5).

Table 2.5. Iron absorption

Sex	Normal daily iron loss (mg/day)	Maximum iron absorption (mg/day)
Men	1	1–2
Menstruating women	1.5	1–2
Pregnant women	2	1–2

The total body iron content of a normal adult is about 4–5 g of which approximately 2.5 g is in the red cells. Iron forms part of the oxygen-binding site of haemoglobin and is therefore fundamental to the body's oxygen supply. As the red cells are broken down at the end of their normal lifespan, the iron that is released and recycled provides most of the body's requirements. Only small quantities of iron are absorbed from the gastrointestinal tract (duodenum and

jejunum) in non-iron-deficient people. Hepcidin, a peptide hormone, is the key regulator of iron metabolism and is mainly synthesized in the liver. This hormone reduces extracellular iron in the body by several mechanisms:

- It lowers dietary iron absorption by reducing iron transport across gut mucosal cells (enterocytes).
- It reduces iron exit from macrophages, the main site of iron storage.
- It reduces iron release from the liver.

In all three instances regulation is accomplished by reducing the transmembrane iron transporter ferroportin. During conditions in which the hepcidin level is abnormally high, such as inflammation, serum iron level falls due to iron being trapped within the macrophages and liver cells, and decreased gut iron absorption. This typically leads to anaemia because of the inadequate amount of serum iron that is available for developing red cells. When the hepcidin level is abnormally low, as in haemochromatosis, iron overload occurs due to increased ferroportin-mediated iron efflux from storage and increased iron absorption in the gut.

A typical adult's daily food intake in a developed country contains 10–15 mg of iron, of which 1–2 mg/day (5–10%) is normally absorbed. This is sufficient to meet the replacement needs of healthy adult males and of females who are not menstruating. However, when iron requirements are increased for any reason, the body's limited stores can be rapidly depleted. Chronic or acute bleeding depletes iron stores; for example, a blood loss of 500 ml removes 250 mg of iron. Without treatment, iron reserves take many months to replenish.

Adaptation to anaemia

Chapter 1 described how the respiratory and circulatory systems interact with the RBCs to maintain the supply of oxygen to the tissues. When blood is lost or anaemia occurs for other reasons, these systems adapt to compensate and maintain, as far as possible, the supply of oxygen to essential organs and tissues.

The clinical condition of the patient will depend on:

- ability to mount these compensatory responses
- degree of red cell insufficiency
- whether anaemia has occurred rapidly (over hours) or gradually (over months).

Transfusion of red cells, or less commonly of whole blood, is often used in the treatment of anaemia and blood loss. However, transfusion can often be avoided because the body's own compensatory mechanisms may be able to maintain adequate oxygen delivery while other treatments take effect. These compensatory responses are described below.

2.7 Anaemia due to acute blood loss

In patients with acute blood loss, or haemorrhage, there is both a reduction in the total amount of haemoglobin in the circulation and a loss of blood volume, or hypovolaemia. In contrast, the blood volume is normally well-maintained in patients with chronic anaemia (see Fig. 2.2).

Effects of acute blood loss

As discussed in Chapter 1, the supply of oxygen to the tissues depends on the transfer of oxygen from the lungs to the blood, its storage in the form of saturated haemoglobin, and its transport and delivery to the tissues. An adequate level of haemoglobin and an efficient circulation are required to transport it.

Haemorrhage can interfere with all of these processes by causing reductions in:

- oxygen transfer from the lungs to the red cells
- oxygen storage by the red cells
- oxygen transport and delivery to the tissues.

Reduced oxygen transport

The loss of blood volume from the circulation, or hypovolaemia, causes a reduction in the venous return to the heart. In turn, this reduces the cardiac output and blood pressure. Blood flow to the tissues therefore decreases and the transport of oxygen to them is impaired.

Reduced oxygen storage

The loss of RBCs reduces the total amount of haemoglobin in the circulation, which, in turn, reduces the overall oxygen-storage capacity of the blood.

Remember that a haemoglobin measurement conducted in the early stages of acute haemorrhage may not be significantly lower than normal and is not a reliable guide to the amount of blood loss. This is because both plasma and RBCs are lost from the circulation simultaneously. It is only when the plasma volume is restored, either by compensatory mechanisms or fluid therapy, that the haemoglobin concentration (or haematocrit) will begin to fall (see Fig. 2.2).

Reduced oxygen transfer

The reduction in cardiac output causes mismatching of the pulmonary blood flow and ventilation in the lung (alveolar dead space), resulting in a decrease in the partial pressure of oxygen in the pulmonary capillaries. As the partial pressure falls, the degree of saturation of the remaining haemoglobin in the circulation also falls. This reduces the oxygen-carrying capacity of the blood still further.

The consequence of a major uncontrolled haemorrhage is therefore oxygen starvation of the tissues and organs of the body, or tissue hypoxia.

Compensatory responses to acute blood loss

No tissue is able to sustain prolonged periods of hypoxia and the body therefore responds immediately to any significant blood loss with several compensatory mechanisms:

- restoration of plasma volume
- restoration of cardiac output

- circulatory compensation
- stimulation of ventilation
- changes in the oxygen dissociation curve
- hormonal changes
- synthesis of plasma proteins.

Restoration of plasma volume

As cardiac output and blood pressure fall, the hydrostatic pressure in the capillaries supplying the tissues of the body also falls. The balance between the oncotic and hydrostatic pressures in the capillaries is therefore altered, allowing an influx of water into the plasma from the interstitial fluid. This mechanism helps to restore the circulating plasma volume. At the same time, water also moves from the intracellular compartment into the interstitial fluid.

Restoration of cardiac output

The fall in cardiac output and pressure in the heart and major vessels is detected by pressure receptors (baroreceptors), which activate the sympathetic nervous system via the vasomotor centre in the brain. The sympathetic nerves act on the heart, increasing both its rate and force of contraction, helping to restore the cardiac output.

Circulatory compensation

The sympathetic nerves also act on the vessels supplying the tissues and organs of the body during acute haemorrhage. They cause vasoconstriction of arterioles, particularly in tissues and organs that are not immediately essential to life, such as skin, gut and muscle, which reduces the blood flow to them. This has the following effects:

- preserving blood flow to the essential organs: brain, kidney and heart; and
- restoring the arterial blood pressure.

In addition, the sympathetic nerves cause constriction of the veins, or venoconstriction, which transfers blood from the veins into the circulation. Since venoconstriction increases the venous return to the heart, it is another important mechanism for restoring the cardiac output during haemorrhage.

Stimulation of ventilation

A reduced blood flow with oxygen starvation causes many tissues and organs to convert to anaerobic metabolism, which produces large quantities of lactic acid. The resulting metabolic acidosis, together with the lowered partial pressure of oxygen in blood, is detected by chemoreceptors in the aorta and carotid arteries. These chemoreceptors stimulate the respiratory centre in the brain, which responds by increasing the depth and rate of ventilation to restore the partial pressure of oxygen in blood.

Changes in the oxygen dissociation curve

During haemorrhage, the oxygen dissociation curve shifts to the right, largely as a result of acidosis. The effect of this is to reduce haemoglobin's affinity for oxygen in the tissue capillaries, thereby encouraging the release of oxygen and increasing its availability to the tissues.

Hormonal responses

The secretion of several hormones is increased in response to haemorrhage but, unlike the other compensatory mechanisms, their effects are usually only apparent after several hours or days.

1. Vasopressin (antidiuretic hormone or ADH) is released from the pituitary gland in response to a fall in blood volume. Its principal action is to reduce the amount of water excreted by the kidneys. This concentrates the urine and thus conserves body water. Vasopressin also causes vasoconstriction, which may help to increase the blood pressure.

2. Aldosterone production from the adrenal gland is also increased during haemorrhage, triggered by the renin–angiotensin system. Aldosterone acts on the kidney, causing retention of sodium in the body. Together with the water-retaining properties of vasopressin, this helps to restore the volume of the extracellular fluid and, in particular, to re-expand the circulating blood volume.

3. Erythropoietin production from the kidney increases in response to hypoxia during haemorrhage. Red blood cell output in the bone marrow is therefore stimulated. This is not an immediate response but, over several days, it will lead to the replacement of cells that have been lost.

4. Other hormones that are also released during severe haemorrhage, include:
   - adrenal steroids
   - catecholamines: e.g. adrenaline and noradrenaline.

All have important roles in enabling the body to compensate and respond to the potentially life-threatening situation.

Synthesis and movement of plasma proteins

Haemorrhage also results in the loss of plasma proteins and platelets from the vascular system. This can lead to alterations in the oncotic pressure of plasma. Although there is rapid mobilization (within 6–12 hours) of preformed albumin into the circulation during acute blood loss, complete restoration of plasma protein levels (by synthesis in the liver) may take several days. The dilution of coagulation proteins and platelets as a result of massive blood loss and fluid replacement can contribute to blood clotting problems.

Clinical features of acute blood loss

The clinical features of haemorrhage in an individual are largely determined by the volume and rate of blood loss. However, they also depend on the patient's capacity to mount the compensatory responses described above.

Patients differ in their capacity to compensate for a given blood loss. The clinical picture may therefore vary.

Haemorrhage occurring in an elderly or anaemic patient, particularly in if they have co- existing cardiorespiratory disease, often becomes clinically apparent at an earlier stage than it would in a previously healthy patient.

The clinical picture of acute blood loss can therefore range from minimal signs or symptoms of hypovolaemia, often detected by a small rise in heart rate when only small amounts of blood are lost, through to haemorrhagic shock when massive uncontrolled bleeding occurs (see Box 2.1).

Box 2.1. Clinical features of major haemorrhage

Haemorrhagic shock

- Thirst
- Cool, pale, sweaty skin
- Tachycardia
- Decreased pulse pressure
- Reduced blood pressure
- Increased respiratory rate
- Restlessness or confusion
- Reduced urine output

2.8 Anaemia due to chronic blood loss

In cases of chronic blood loss, such as gastrointestinal loss due to hookworm, there is a continuing loss of blood from the circulation over a long period. Anaemia thus develops gradually. There is generally no reduction in the circulating blood volume and normovolaemia is maintained (see Fig. 2.2, column 3).

Effects of chronic blood loss

The body can initially compensate for chronic red cell loss by increasing RBC production. However, iron is lost with the red cells and this eventually depletes the body's iron stores. Since iron is an essential component of haemoglobin, its deficiency causes a reduction in the level of haemoglobin in the RBCs being produced.
Chronic blood loss therefore typically gives rise to an iron deficiency anaemia due to impaired production of haemoglobin. The red cells are small (microcytic) and contain little iron (hypochromic). Since the red cells contain less haemoglobin, the oxygen- carrying capacity of blood is reduced.

Compensatory responses to chronic blood loss

The body responds to chronic blood loss with the following compensatory mechanisms:

- cardiovascular compensation
- changes in the oxygen dissociation curve
- changes in blood viscosity
- hormonal responses.

Cardiovascular compensation

As the oxygen- carrying capacity of blood falls, the amount of oxygen available to the tissues also falls. The tissues respond by dilating their blood vessels (vasodilation) to increase the blood supply and thus maintain the delivery of sufficient amounts of oxygen. The increased tissue blood flow results in an increased venous return, which, in turn, increases the cardiac output.

Chronic blood loss, and chronic anaemias in general, are therefore largely compensated for by a raised cardiac output. However, in the case of severe chronic anaemia, the heart may be unable to sustain the high output demanded of it and heart failure can occur.

Changes in the oxygen dissociation curve

The other major compensatory response that occurs in chronic anaemia is a shift of the oxygen dissociation curve to the right. This has the effect of reducing haemoglobin's affinity for oxygen in the tissue capillaries, thereby encouraging the release of oxygen and increasing its availability to the tissues. This shift is primarily due to an increase in the RBC metabolite 2,3- diphosphoglycerate.

Changes in blood viscosity

As the RBC mass decreases in a person with anaemia, the viscosity of blood is decreased. This results in an improved capillary blood flow, which enhances the delivery of oxygen to the tissues. Cardiac output also tends to increase as a consequence of reduced blood viscosity.

Hormonal responses

Many of the same hormonal responses as are seen in acute blood loss also occur in patients with chronic blood loss, although the degree of compensation required is considerably less. Thus, red cell production is stimulated by erythropoietin, provided there is sufficient iron available for haemoglobin synthesis, and blood volume is maintained by the action of vasopressin and aldosterone.

Clinical features of chronic blood loss

Provided that the patient's compensatory mechanisms are effective, few clinical symptoms or signs of chronic anaemia may be evident until a relatively low haemoglobin concentration is reached, or the patient decompensates for another reason. However, the clinical features of anaemia will become apparent at an earlier stage when there is:

- limited capacity to mount a compensatory response: for example, in patients with significant cardiovascular or respiratory disease
- increase in demand for oxygen: for example, associated with infection, pain, fever or exercise
- further reduction in the oxygen supply: for example, in a patient with blood loss or pneumonia.

2.9 Chronic anaemia due to other causes

In many instances, anaemia may result from either:

- decreased production of either RBCs or haemoglobin

- increased destruction of RBCs.

The underlying causes of these anaemias include:

- nutritional deficiencies
- infections
- malignancy
- autoimmune diseases
- inherited disorders of red cells: for example, haemoglobinopathies
- aplastic anaemia and myelodysplasia.

Generally, anaemia caused by these conditions develops relatively slowly and thus may be compensated for by many of the same mechanisms that operate during chronic blood loss. However, severe acute anaemia may have medical causes such as haemolysis or splenic sequestration of red cells.

The clinical picture of all chronic anaemias is due to a combination of:

- the anaemia itself, that is, the diminished oxygen-carrying capacity of blood; and
- features of the underlying condition.

Acute-on-chronic anaemia

The term "acute-on-chronic anaemia" is often used to describe a further sudden fall in haemoglobin concentration in a patient who is already chronically anaemic. This situation is often a clinical emergency, especially in young children, and the management may include the need for red cell transfusion.

2.10 Principles of the treatment of anaemia

Anaemia is abnormal and indicates the presence of some form of pathology that requires investigation and treatment.

The compensatory mechanisms in response to anaemia, described in this section, often enable patients to tolerate relatively low haemoglobin concentrations. This is particularly the case in patients with chronic anaemia that has developed slowly over weeks or months. However, if these compensatory mechanisms fail to maintain the oxygen supply to the tissues, decompensation occurs and, without treatment, death will rapidly ensue.

Once decompensation has occurred, the only effective treatment is to raise the oxygen- carrying capacity of the blood by means of a blood transfusion. However, the primary aim should be to treat the anaemia by other means before this point is reached.

Blood transfusion should only be considered when the anaemia is symptomatic. Recommendations on haemoglobin transfusion thresholds are most helpful in deciding whether a patient needs a RBC transfusion. Section 2.11 provides a summary of RBC transfusion thresholds for different patient populations.

The management of anaemia will vary according to its cause, time course and the degree of compensation. This requires a detailed assessment of the individual patient. However, the general principles of the treatment of anaemia are:

- Treat the underlying cause.
- Optimize all the components of the oxygen delivery system to improve the oxygen supply to the tissues.

Treating the underlying cause of the anaemia

Treatment aimed at the underlying cause of the anaemia will often prevent any further reduction in oxygen-carrying capacity. For example, in a patient with chronic anaemia due to an infestation, eliminating the parasite will prevent further deterioration in the haemoglobin concentration.

Improving the oxygen supply to the tissues

Remember that a patient's haemoglobin concentration is only one of the critical factors that determines the overall supply of oxygen to the tissues. The oxygen supply also depends on:

- degree of saturation of haemoglobin with oxygen; and
- cardiac output.

Therefore, treatment aimed at optimizing all the factors that influence the oxygen supply system will improve the availability of oxygen to the tissues.

In the case of acute haemorrhage, for example, the oxygen supply will be improved by:

- restoring the cardiac output with intravenous fluid replacement therapy;
- increasing the inspired oxygen concentration to raise the saturation of haemoglobin; and
- transfusion, if necessary, to raise the haemoglobin concentration.

In a patient with chronic iron deficiency anaemia, elevating the haemoglobin level with simple oral iron therapy will improve the supply and availability of oxygen to the tissues. The route of administration of iron treatment will depend on the type of anaemia, as oral treatment will not be effective in patients with chronic inflammation, also known as anaemia of chronic disease. In those cases, parenteral iron treatment is a relatively safe and effective alternative.

2.11 Principles of the prevention of anaemia

One of the most important tools for achieving the most appropriate clinical use of blood and blood products is the implementation of effective public health programmes and hospital patient blood management programmes (see Chapter 9) to prevent the conditions that make transfusion necessary.

Government involvement will be helpful to establish preventive measures that will help to avoid blood transfusions. Governments can help in the effective organization of the primary health care system and by supporting implementation of patient blood management programmes within hospitals.

In many developing countries, most transfusions are given to children under the age of 5 years and to women of childbearing age. These groups should be a particular target for preventive measures through the provision of adequate and accessible maternal and child health services.

The prevention of anaemia in a population will often include the following activities.

1. Health education on:
   - nutrition
   - hygiene, sanitation, clean water supplies
   - prevention of malaria: for example, the use of bednets impregnated with insecticide
   - road safety.

2. Supplementation programmes: the administration of iron and/or folate supplements to targeted groups – should be approached with caution in malarious areas *(1)*.

3. Dietary modification: for example, enhancing iron absorption by increasing dietary vitamin C, and decreasing simultaneous tea intake.

4. Control of viral, bacterial and parasitic infections, including through:
   - immunization programmes
   - improvements in sanitation and water supplies
   - eradication of sources of infection: for example, hookworm, mosquitoes
   - treatment of infection or infestation: for example, deworming.

5. Food fortification: fortification with iron of centrally-processed staple foods, such as bread, milk, salt, rice, sugar and fish products may be appropriate in some countries.

2.12 Red blood cell transfusion thresholds

Several high-quality trials on RBC transfusion thresholds have recently been conducted among haemodynamically stable, hospitalized adult patients. More than 40 randomized controlled trials, involving more than 20 000 patients, have compared restrictive transfusion thresholds (transfusing RBCs only when the haemoglobin level reaches 7–8 g/dl) with liberal transfusion thresholds (transfusing RBCs only when the haemoglobin level reaches 9–10 g/dl).

Based on recent systematic reviews of the literature on transfusion thresholds and clinical transfusion guidelines, the following recommendations can be made *(2–6)*.

- Haemoglobin concentration of <**7 g/dl** should be used as the transfusion threshold for hemodynamically stable hospitalized adult patients, including critically ill patients.
- Haemoglobin concentration of **7.5 g/dl** should be used as the transfusion threshold for those undergoing cardiac surgery *(4)*.
- Haemoglobin concentration of **8 g/dl** should be used as the transfusion threshold for those undergoing orthopaedic surgery, and those with underlying stable cardiovascular disease.
- Patients admitted with an acute upper gastrointestinal bleed may have a lower mortality when a transfusion threshold haemoglobin concentration of **7 g/dl** is adopted.

There is insufficient evidence to recommend an optimal transfusion threshold in patients with:

- acute coronary syndrome (small trials showed a trend towards lower mortality when using a liberal transfusion threshold);
- severe thrombocytopenia, being treated for haematological or oncological disorders who are at risk for bleeding;
- chronic transfusion-dependent anaemia;
- acute neurological disorders such as stroke and traumatic brain injury.

Blood transfusions in haemodynamically stable patients are generally recommended when the haemoglobin level is below 7 g/dl and should not normally be recommended for those whose haemoglobin level is above 10 g/dl, except in exceptional circumstances (see Table 2.6) *(5,6)*.

RBC transfusions in paediatric patients are most common in critically ill children and those undergoing cardiac surgery. A recent consensus recommendation based on trial evidence and expert opinion regarding RBC transfusions in these paediatric patients concluded the following *(7):*

- A haemoglobin concentration of <7 g/dl should be used as the transfusion threshold for haemodynamically stable, critically ill children.
- A transfusion threshold of haemoglobin concentration between 7 and 10 g/dl should be considered in critically ill children with acute brain injury.
- RBC transfusions should be given to attain a haemoglobin concentration of 10 g/dl in critically ill children with sickle cell disease before surgical procedures necessitating general anaesthesia.
- A haemoglobin concentration of < 7–8 g/dl should be used as the transfusion threshold for haemodynamically stable, critically ill children with cancer diagnoses or those undergoing haemopoietic stem cell transplant.
- RBC transfusions to maintain a haemoglobin concentration of 7–9 g/dl should be given to hemodynamically stable, critically ill paediatric patients with uncorrected congenital heart disease.

- No RBC transfusion should be given if the haemoglobin concentration is > 9 g/dl in haemodynamically stable paediatric patients undergoing cardiac surgery for stage 1 palliation or stage 2 and 3 procedures in single ventricle physiology.

- No RBC transfusion should be given if the haemoglobin concentration is ≥ 7 g/dl in haemodynamically stable paediatric patients with congenital heart disease undergoing biventricular repair.

Table 2.6. AABB Guidelines (2016): transfusion recommendations for haemodynamically stable patients without active bleeding

Haemoglobin concentration	Transfusion recommended?
Hb < 6 g/dl	Recommended except in exceptional circumstances
Hb 6–7 g/dl	Generally likely to be indicated
Hb 7–8 g/dl	May be appropriate in patients undergoing orthopaedic or cardiac surgery, and in those with stable cardiovascular disease, after evaluating the patient's clinical status
Hb 8–10 d/dl	Generally not indicated, but should be considered for some populations (e.g. patients with symptomatic anaemia, ongoing bleeding, acute coronary syndrome with ischaemia, and haematology/oncology patients with severe thrombocytopenia who are at risk of bleeding)
Hb > 10 g/dl	Generally not indicated except in exceptional circumstances

References

1. Supplementation programmes: the administration of iron and/or folate supplements to targeted groups with caution in malarious areas [online] (http://www.who.int/elena/titles/review_summaries/iron-children-malaria/en/, accessed 24 January 2021).
2. Carson JL, Stanworth SJ, Alexander JH, Roubinian N, Fergusson DA, Triulzi DJ et al. Clinical trials evaluating red blood cell transfusion thresholds: An updated systematic review and with additional focus on patients with cardiovascular disease. Am Heart J. 2018;200:96–101.
3. Carson JL, Stanworth SJ, Roubinian N, Fergusson DA, Triulzi D, Doree C et al. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Database Syst Rev. 2016;10:CD002042.
4. Mazer CD, Whitlock RP, Fergusson DA, Hall J, Belley-Cote E, Connolly K et al. Restrictive or liberal red-cell transfusion for cardiac surgery. N Engl J Med. 2017;377:2133–44.
5. Carson JL, Guyatt G, Heddle NM, Grossman BJ, Cohn CS, Fung MK et al. Clinical practice guidelines from the AABB: Red blood cell transfusion thresholds and storage. JAMA 2016;316:2025–35.
6. Mueller MM, Van Remoortel H, Meybohm P, Aranko K, Aubron C, Burger R, et al; ICC PBM Frankfurt 2018 Group. Patient blood management: recommendations from the 2018 Frankfurt Consensus Conference. JAMA. 2019;321:983–97. doi: 10.1001/jama.2019.0554.
7. Valentine SL, Bembea MM, Muszynski JA, Cholette JM, Doctor A, Spinella PC et al. Consensus Recommendations for RBC Transfusion Practice in Critically Ill Children From the Pediatric Critical Care Transfusion and Anemia Expertise Initiative. Pediatr Crit Care Med. 2018;19:884–98.

CHAPTER 3

COLLECTION, TESTING AND STORAGE OF BLOOD PRODUCTS

Key points

1. Safe blood products, used correctly, can be life-saving. However, even where product quality standards are very high, transfusion carries some risks.
2. Blood must be collected from healthy donors who are at low risk for infections that are transmissible by blood transfusion. The donated blood must be carefully assessed against well-recognized standards, to protect the safety of the recipient and that of the donor.
3. No blood or blood product should be administered unless all nationally required tests for transfusion-transmissible infections have been performed and shown to be non-reactive.
4. Each product must be tested and labelled to show its product type, storage requirements, expiry date, any modifications, and other relevant information such as ABO group and Rh D group (where applicable).
5. Whole blood may be transfused to replace red cells in the case of acute bleeding when there is also a need to correct hypovolaemia.
6. One unit of donated blood may be separated into components, including red cell concentrates, plasma, cryoprecipitate and platelet concentrates, to meet the needs of more than one patient.
7. Plasma can transmit most of the infectious agents present in whole blood and can cause other reactions; there are limited indications for its transfusion.
8. Plasma derivatives are made by a pharmaceutical manufacturing process from large volumes of plasma comprising many individual blood donations. They must be tested to minimize the risks of transmitting infections and should also undergo pathogen inactivation to ensure that they are safe.
9. Factors VIII and IX and other coagulation factors are also made by recombinant DNA technology. These are often favoured because of their reduced risk of transmitting infectious agents that are not eliminated by inactivation procedures applied to plasma-derived products.

3.1 Introduction

The term "blood product" refers to any therapeutic substance prepared from human blood, including whole blood, other blood components for transfusion, and plasma-derived medicinal products (PDMPs).

Whole blood can be separated into a variety of blood components for different clinical indications. However, many countries have no facilities for component separation and whole blood remains a widely used product in most developing countries. The use of whole blood may be a safe and sustainable way of meeting most urgent transfusion requirements. However, where resources are available, the use of blood components offers many advantages.

This section describes the methods of production of various blood products and summarizes their characteristics and indications for use. Readers should be familiar with each of the blood products used in their hospital, whether whole blood, blood components or plasma derivatives, or a combination thereof.

Since blood transfusion involves the transplant of tissue from the donor to the recipient, there are risks to the recipient of transfusion-transmitted infections and of immunological responses to foreign cells or plasma proteins.

Transmission of infectious diseases can be prevented both by careful selection of blood donors (following international and national guidelines) and by testing for the main transfusion-transmitted agents. Pathogen reduction technologies are also available for some blood products.

You should only prescribe blood products when there are clear indications for doing so. Used correctly, they are life-saving, but inappropriate use can endanger life.

Learning outcomes

After reading this chapter, the reader will be able to:

1. Describe the main characteristics of each blood product in current use in the hospital.
2. Prescribe the most appropriate blood product available for each patient requiring transfusion.
3. Explain the main factors that may influence the availability and use of blood products.
4. Verify the implementation of measures for reducing the risk of transmission of infectious diseases and for the correct testing of blood products according to national requirements.

3.2 Definitions, summary of blood product content and storage requirements

Definitions of the different blood products are given in Table 3.1.

Table 3.1. Blood products: definitions

Name	Definition
Blood product	Any therapeutic substance prepared from human blood
Whole blood	Unseparated blood collected into an approved container containing an anticoagulant-preservative solution
Blood component	1. A constituent of blood, separated from whole blood, such as: • Red cell concentrate • Red cell concentrate, in additive solution • Plasma • Platelet concentrate
	2. Plasma or platelets collected by apheresis[a]
	3. Cryoprecipitate, prepared from fresh frozen plasma
Plasma-derived medicinal products (PDMPs)	Human plasma proteins prepared under pharmaceutical manufacturing conditions, such as: • Albumin • Coagulation factor concentrates • Immunoglobulins

[a] Apheresis: a process of collecting single blood components (plasma, platelets or red cells) directly from the donor and returning the remainder to the donor. This is performed using specially designed equipment.

Blood product content and storage requirements

The product descriptions and properties provided below are examples based on typical practice around the world using modern collection and preparation methods. Specifications do vary, and factors influencing characteristics of blood components include:

- donor haematocrit and other factors
- collection method, volume, kit, anticoagulant and additive solution
- separation method (for example, manual versus semi-automated versus automated)
- product modifications (for example, leukodepletion).

You should consult and be familiar with the specifications for products available in your country and hospital, including their availability, storage, handling and use.

The blood product content and storage requirements are summarized in 3.2(a) and (b).

3.2 (a): Blood product content and storage requirements

Product description and examples of typical properties	Whole blood	Red cells	Red cells, in additive solution	Red cells, buffy coat removed, in additive solution	Red cells, leukocyte- depleted, in additive solution
Volume	450 ± 50 ml	280 ± 50 ml	180–230 ml red cells; 100–110 ml additive solution added	180–230 ml red cells after removal of plasma and buffy coat; 100–110 ml additive solution added	180–230 ml red cells after removal of plasma and after filtration for leukocyte removal; 100– 110 ml additive solution added
Anticoagulant	63 ml	Mostly removed with plasma	Mostly removed with plasma	Mostly removed with plasma	Mostly removed with plasma
Additive solution	Usually none	NA	100–110 ml of an additive solution (SAG-M, AS1, 3 or 5)	100–110 ml of an additive solution (SAG-M, AS1, 3 or 5)	100–110 ml of an additive solution (SAG-M, AS1, 3 or 5)
Haemoglobin	> 45 g	> 45 g	> 45 g	> 43 g	> 43 g
Haematocrit	35–45%	65–75%	50–70%	50–70%	50–70%
Plasma	200–300 ml	50–70 ml	10–20 ml	10–20 ml	10–20 ml
Leukocytes	The original amount	The original amount	The original amount	$<1.2 \times 10^9$ per unit	$<1 \times 10^6$ white cells per unit
Storage conditions	+ 4 ± 2 °C in controlled conditions	+ 4 ± 2 °C in controlled conditions	+ 4 ± 2 °C in controlled conditions	+ 4 ± 2 °C in controlled conditions	+ 4 ± 2 °C in controlled conditions
Storage duration	Up to 35 days if anticoagulant contains adenine (CPDA-1), or up to 21 days if collected in CPD	Same as whole blood	Up to 42 days	Up to 42 days	Up to 42 days
Unit of issue	1 unit	1 unit	1 unit	1 unit	1 unit
Characteristics	NA	NA	NA	NA	Leukodepletion greatly reduces the risk of CMV transmission

SAG-M, saline adenine glucose mannitol; AS, additive solution; CPDA-1, citrate phosphate dextrose adenine-1; CPD, citrate phosphate dextrose.

3.2 (b): Product description and examples of typical properties

	Fresh frozen plasma (FFP) from whole blood	FFP from apheresis	Platelet concentrate, recovered, single unit	Pooled unit	Plateletpheresis
Description	Plasma separated from whole blood within 6–8 hours of collection and frozen to –25 °C or colder within 1 hour	Plasma collected by apheresis and then frozen to –25 °C or colder within 1 hour	Unit of platelets derived from a single whole blood donation	Platelets prepared from pooling multiple (typically 4–6) whole blood-derived donor units	Platelet concentrate obtained by platelet apheresis from a single donor
Volume	200–250 ml	700–800 ml	50–60 ml	> 40 mL per 60×10^9 of platelets	> 40 mL per 60×10^9 of platelets
Content	Normal plasma levels of non-labile clotting factors, albumin and immunoglobulin; factor VIII and other labile coagulation factors levels at least 70% of normal fresh plasma levels	Same as FFP from whole blood	Minimum platelet content 55–60 $\times 10^9$ platelets suspended in plasma	Minimum platelet content 200×10^9 platelets suspended in plasma or in additive solution	Minimum platelet content 200–300×10^9 platelets suspended in plasma or in additive solution
Storage	–25 °C or colder for up to 1 year	–25 °C or colder for up to 1 year	20–24 °C (with constant agitation) for up to 5 days	Up to 5 days 20 °C–24 °C (with constant agitation) unless collected in specialized platelet bags validated for longer storage (7 days) and associated with bacterial detection strategies	Same as pooled unit
Unit of issue	1 unit	1 unit	May be supplied either as a single unit or pooled	1 unit prepared from multiple (typically 4–6) whole blood-derived buffy coats or platelet concentrates	1 unit
Characteristics	NA	NA	$<1.2 \times 10^9$ red cells $<0.2 \times 10^9$ leukocytes	$< 1 \times 10^9$ leukocytes. If leukodepleted, the unit must contain $<1 \times 10^6$ white cells per unit	$<0.3 \times 10^9$ leukocytes. If leukodepleted, the unit must contain $<1 \times 10^6$ white cells per unit

Source: Council of Europe Guide for the preparation, use and quality assurance of blood components (*1*) and from the Circular of information for the use of human blood and blood components produced by AABB, the American Red Cross, America's Blood Centers and the Armed Services Blood Program (*2*).

3.3 Whole blood

Whole blood is obtained from blood donors by venesection. During donation, blood is collected, under constant agitation, into a sterile, disposable, plastic bag which contains an anticoagulant- preservative solution. This solution usually contains citrate, phosphate, dextrose and often adenine (citrate phosphate dextrose adenine solution, CPDA). The functions are summarized in Table 3.3.

There are variations in the volume of blood collected and in the type of anticoagulant-preservative solution used in different regions of the world. Multiple bag sets are available if collected blood needs to be divided in smaller aliquots for paediatric transfusion.

During storage, metabolism continues in the red cells and in platelets, while some plasma proteins lose their biological activity. The biochemical and metabolic effects of storage are summarized in Table 3.3 and Box 3.1.

Table 3.3. Functions of anticoagulant-preservative solution in blood collection bag

Solutions	Functions
C: Sodium citrate	Binds with calcium ions in blood in exchange for the sodium salt so the blood does not clot
P: Phosphate	Supports metabolism of the red cells during storage to ensure adenosine triphosphate (ATP) generation
D: Dextrose	Maintains the red cell metabolism and provides energy sources
A: Adenine	Maintains red cell ATP

Box 3.1. Effects of storage on whole blood

- Reduction in the pH (blood becomes more acidic)
- Rise in plasma potassium (K) concentration (accumulation of extracellular K^+)
- Progressive reduction in the red cell content of 2,3 disphosphoglycerate (2,3 DPG), which may reduce the release of oxygen at tissue level until 2,3 DPG is restored
- Reduction in Factor VIII of 10–20% within 24 hours from donation. Other coagulation factors and inhibitors (such as FVII, FIX, FXI, FXII, FXIII, fibrinogen and antithrombin) are relatively stable or slightly decreased during storage (*3*).

Note that none of the randomized clinical trials to date have shown harm to the recipients following the transfusion of red blood cells (RBCs) stored for longer periods compared to RBCs stored for shorter periods.

Advantages

- Whole blood requires only simple and inexpensive single collection bags.
- No special equipment is needed for processing.
- For patients with haemorrhage, whole blood supplies red cells, platelets, volume and stable coagulation factors.

Disadvantages

- For patients at risk of circulatory overload, whole blood has a higher volume than red cell concentrates as it also contains an entire unit of plasma.
- When transfusing high volumes of non-identical ABO whole blood, plasma compatibility must also be taken into account; commonly low-titre O whole blood is used for recipients of multiple non-ABO identical whole blood units (*4, 5*).

Indications

- red cell replacement in patients with acute blood loss with hypovolemia
- exchange transfusion
- patients needing red cell transfusions where red cell concentrates or suspensions are not available

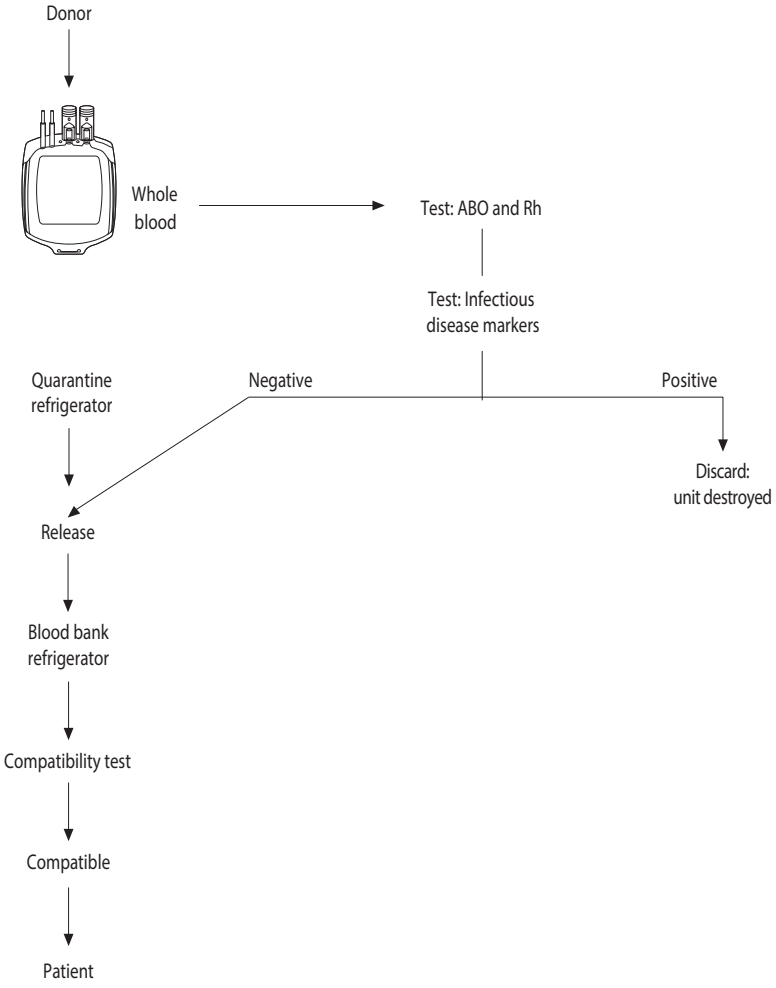
Contraindications

There is a risk of volume overload associated with incipient cardiac failure in an anaemic recipient who requires only RBC transfusion.

Administration

- Generally, ABO identical and Rh compatible blood is preferred, unless low-titre group O whole blood is used.
- Complete transfusion within 4 hours of commencement.
- Never add medication to a unit of blood.

Figure 3.1. Production of whole blood



3.4 Components prepared from whole blood

Whole blood must be collected, tested and processed to a high safety standard as shown in Fig. 3.1. Whole blood may be suitable for transfusion in many clinical situations, such as red cell replacement in a patient with acute blood loss where there is also hypovolaemia. However, the separation of whole blood into its components – red cells, platelets and plasma – is preferable for a rational use of the blood, since generally only specific components are required in the treatment of patients.

Blood component preparation begins with centrifuging the blood bag in a refrigerated centrifuge or, if no centrifuge is available, by allowing the blood to separate under gravity overnight in a refrigerator at a temperature between +2 °C and +6 °C. The plasma is then removed by transferring it into a second empty plastic bag, which is supplied connected to the primary whole-blood bag to ensure sterility, leaving all the red cells in the original blood collection bag (see Fig. 3.2).

These components may be processed further, for example, by addition of an additive solution to red cells (to prolong red cell storage).

Alternatively, they may be processed by buffy coat removal and leukocyte depletion. Both these practices are used because leukocytes present in donated blood play no therapeutic role in transfusion and may cause adverse transfusion reactions. In particular, leukocyte depletion has a number of potential benefits for transfusion recipients, including reduced risk of: platelet refractoriness, febrile non-haemolytic transfusion reactions and cytomegalovirus (CMV) transmission.

"Pooling" (e.g. by combining platelets or buffy coats separated from 4–6 donations to produce a therapeutic dose of platelets for an adult patient) is another option

The process of separation requires specialized plastic bags, equipment and an effective quality control system. A higher level of expertise and more work is also necessary to ensure the quality of the components produced.

An infectious agent present in the donated blood may be transmitted to all recipients of the components prepared from a single donation.

Red cell concentrate

Red cell concentrate (also called packed red cells or concentrated red cells) is the simplest red cell component. Since it is not subjected to further manipulation, the red cell concentrate also contains white cells from the donated blood.

Advantages

Red cell concentrate is simple and inexpensive to prepare (Fig. 3.2).

Disadvantages

Red cell concentrate has a high ratio of red cells to plasma (high haematocrit), which increases viscosity, thereby increasing the time required for transfusion through a small gauge needle or cannula.

The white cells are a cause of febrile non-haemolytic transfusion reactions in some patients. Units can be leukoreduced to decrease the likelihood of this complication.

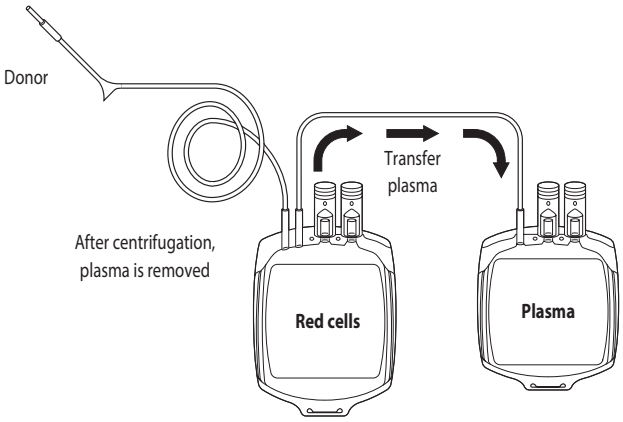
Indications

This product is indicated for replacement of red cells in patients with clinically significant anaemia where other measures (e.g. iron therapy) are unavailable or will not achieve their effect in a timely way.

Administration

The procedure for administration is the same as for whole blood.

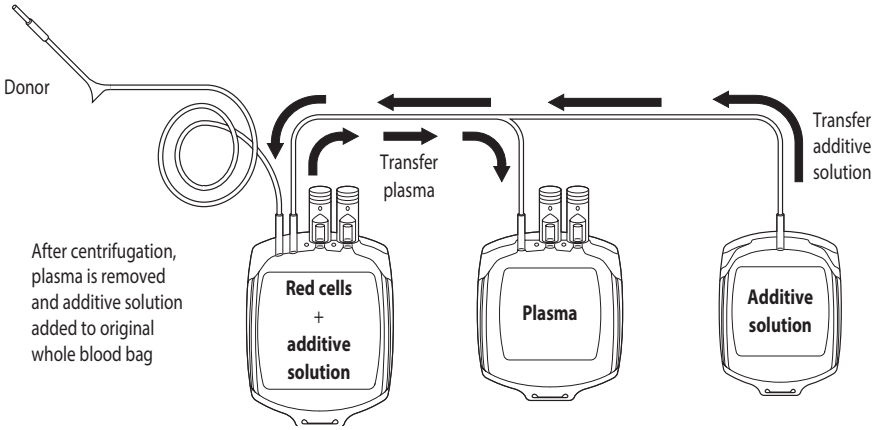
Figure 3.2. Preparation of red cell concentrate



Red cell concentrate, in additive solution

Red cell concentrate in additive solution is prepared by removing the plasma into a second empty plastic bag, as described above. An additive solution formulated for the optimal preservation of the red cells is then transferred from a third plastic bag into the original bag (see Fig. 3.3).

Figure 3.3. Preparation of red cell concentrate



Advantages

- lower haematocrit, which reduces viscosity and is therefore easier to infuse
- better preservation of the red cells during storage, giving a longer shelf-life than for whole blood or red cell concentrate
- smaller volume compared to whole blood
- frees up plasma for transfusion to other patients or for production of plasma-derived medicinal products.
- Residual plasma is minimal, therefore major (red blood cells) ABO compatibility applies. Group O is the universal donor as far as ABO group is concerned.

Disadvantages

Costs are higher as a special blood collection set containing at least three interconnected packs is required.

Indications

The indications are the same as for red cell concentrate.

Administration

The administration procedure is the same as that for whole blood. Better flow rates are achieved than with red cell concentrate or whole blood.

Buffy coat-removed red cells

The removal of the white cells from whole blood requires controlled centrifugation so that the red cells settle to the bottom of the blood bag. The white cells (and most of the platelets) remain in a layer called the 'buffy coat', which forms an interface between the red cells and the plasma.

If facilities are available, specialized bag systems and equipment can be used to remove the buffy coat, which can be further processed to obtain pooled platelet concentrates.

Advantages

- The red cell unit contains only about 10% of the white cells present in red cell concentrate.
- There is less risk of transfusion reactions due to leukocyte antibody (and the transmission of intracellular infection) when the red cells are transfused.
- The buffy coat can be used to prepare platelet concentrates.

Disadvantages

- Costs are higher as special blood packs and equipment are required.
- More skills and specialized operator training are needed.

Leukocyte-depleted (filtered) red cells or whole blood

Special leukocyte filters can be used to remove three or more orders of magnitude of the original number of white cells. Pre-storage and post-storage filters are available. Pre-storage filters are already part of the collection bags system. Post-storage filters are utilized at the time of transfusion and are part of the administration set.

Pre-storage filtration is the standard of practice in many countries, but, if closed and sterile systems for filtration are not available, bedside (post-storage) leukoreduction can be used.

Advantages

- reduces development of antibodies to white cells and platelets
- reduces febrile non-haemolytic acute transfusion reactions

- filtered blood containing less than 1×10^6 white cells per unit reduces the transmission of cytomegalovirus (CMV) infection.

Disadvantages

- Cost are higher as special blood bags and equipment (pre-storage filtration) or special filters (post-storage filtration) are required.
- More skills and specialized operator training are needed.
- It is difficult to perform quality control to verify that leukodepletion has been achieved.

Indications

- to prevent white cell alloimmunization in patients receiving repeated transfusion but, to achieve this, all blood components given to the patient must be leukocyte-depleted;
- to reduce risk of CMV transmission in vulnerable patents; and
- to treat patients who have experienced febrile reactions to red cell transfusion.

Contraindications

It is not sufficient to prevent graft-versus-host disease: for this purpose, blood components should be irradiated (radiation dose: 25–30 Gy).

Administration

The procedure for administration is the same as that for whole blood.

Special precautions (see manufacturer's instructions) are necessary for the use of the bedside filters, if leukocyte-depleted red cells or whole blood are not available.

Plasma

The main clinical indication for plasma transfusion is the treatment of coagulation disorders in patients with bleeding due to reduced levels of several clotting factors.

Plasma is separated from whole blood by centrifugation, by allowing the red cells to settle under gravity in a blood bank refrigerator or by automated extraction methods. It can also be collected from donors by plasmapheresis (see section 3.4).

Several different plasma preparations are available as described below.

Fresh frozen plasma (FFP)

Plasma must be frozen at –25 °C or colder (within 6–8 hours after separation). When plasma is stored at a temperature of 2–6 °C, the labile clotting activity of Factor VIII will decline by 10–20% within 48 hours, while other coagulation factors and inhibitors (such as FVII, FIX, FXI, FXII, FXIII, fibrinogen and antithrombin) can remain relatively stable or only slightly decreased for 48– 72 hours or more (*6*). FFP can be stored for 1 year or longer if low temperatures can be maintained (below –25 °C).

Quarantine FFP (donor retested plasma)

Quarantine FFP, also termed "donor retested plasma", is a plasma product that can be released only once the donor has been retested, with negative results, at least for infectious agents that are regularly screened under blood bank conditions. The time period must be chosen to exclude the risk associated with the window period (usually from 3 to 6 months).

Pathogen-reduced plasma

Where facilities exist, plasma from donated blood can be subjected to procedures leading to pathogen reduction and/or inactivation to ensure a safer product (see also section 3.6).

Other plasma preparations

Several "liquid" preparations of plasma (i.e. not frozen) are now used in emergency situations in order to save the time needed for thawing frozen plasma and to give prompt treatment to patients with severe haemorrhage. These products include thawed plasma (ready for use), plasma frozen within 24 hours after collection (FP24), "never frozen" plasma and cryoprecipitate-poor plasma (CPP). FP24, CPP and thawed plasma contain decreased amounts of labile coagulation factors; nevertheless, they have been successfully used in the management of major haemorrhage (*6*).

Indications for plasma transfusion

- replacement of multiple coagulation factor deficiencies in patients who are bleeding (or at serious risk of bleeding) as in:
  - warfarin anticoagulant overdose (if prothrombin complex concentrates are not available),
  - replacement of coagulation factors in patients receiving large-volume transfusions,
  - severe liver disease with acute bleeding,
  - acute disseminated intravascular coagulation (DIC),
  - thrombotic thrombocytopenic purpura (TTP)

Dosage

The initial dose is 15–20 ml/kg.

Administration

- Plasma must normally be ABO compatible to avoid the risk of haemolysis in the recipient. However, the practice of issuing thawed group A plasma for the initial resuscitation of trauma patients of unknown ABO group has recently been demonstrated to be safe and effective (*7*).

- Before use, plasma needs to be thawed between 30 °C and 37 °C (higher temperatures will inactivate clotting factors and other proteins). Approved devices such as water baths or other equipment must be properly maintained and used according to the manufacturer's instructions.

- Once thawed, plasma should infused within 4–6 hours or stored in a refrigerator at a temperature between +2 °C and +6 °C.

- Infuse using a standard blood infusion set as soon as possible after thawing.

- Labile coagulation factors may degrade; however, all other factors are stable at +2 to +6 °C for at least 5 days after thawing.

Precautions

- Volume/circulatory overload is a frequent and potentially lethal adverse event.
- Allergic reactions are common. Most are minor but severe or life-threatening allergic or anaphylactic reactions occasionally occur.
- Transfusion-related acute lung injury (TRALI) may also occur if donors are not screened for human leukocyte antigen (HLA) antibodies. Women who had pregnancies and previously transfused donors are at higher risk of carrying HLA antibodies in their plasma.

Contraindications

Plasma is not recommended as a replacement fluid to correct hypovolaemia in the non-bleeding patient because it carries the same risk as whole blood of transmitting human immunodeficiency virus (HIV), hepatitis viruses B and C, and other transfusion-transmissible infections.

There is no evidence that plasma offers any additional clinical benefit over crystalloid replacement fluids or colloid fluids in the treatment of hypovolaemia (except for major haemorrhage in trauma patients, where crystalloids are inferior to plasma (*8*)).

Cryoprecipitate

Cryoprecipitate is a component prepared from fresh frozen plasma by re-suspending the precipitate formed during controlled thawing (+2 to +6 °C) in 10–20 ml of plasma supernatant. Cryoprecipitate contains about half of the Factor VIII and fibrinogen from the donated whole blood-derived plasma unit: e.g. Factor VIII: 80–100 IU/unit; fibrinogen: 150–300 mg/unit. It is usually supplied as a single donor unit or a bag of 4–6 single donor units that have been pooled.

Infection risk is the same as for plasma, but a normal adult dose can involve exposure to plasma from up to six different donors.

It can be stored at –25 °C or colder for up to 1 year.

Indications

- Cryoprecipitate may be used as an alternative to Factor VIII concentrate in the treatment of inherited deficiencies, i.e. of Von Willebrand Factor (von Willebrand's disease) and of Factor VIII (hemophilia A), only if recombinant or pathogen inactivated factor concentrates are unavailable.
- It can be used as a source of Factor XIII.
- It may be used as a source of fibrinogen in patients with acquired coagulopathies: for example, disseminated intravascular coagulation (DIC), critical bleeding requiring massive transfusion.

Administration

- When possible, use ABO-compatible product.
- After thawing, infuse as soon as possible through a standard blood administration set.
- Cryoprecipitate must be infused within 6 hours of thawing and 4 hours of pooling.

Platelet concentrates

Platelets are separated from whole blood by centrifugation either by the platelet-rich plasma method (soft spin centrifugation) or by the buffy coat method (hard spin centrifugation). Products are often pooled to produce a therapeutic dose of platelets for an adult. This requires at least 200×10^9 platelets, corresponding to platelets from 4–6 whole blood units.

In all cases, temperature-controlled centrifuges and special equipment are needed for platelet separation and pooling.

Pooling increases the risk of transmission of infection. A dose of platelets can be collected from a single donor by plateletpheresis (see section 3.4), thus avoiding exposure of the patient to platelets from several donors.

As for red blood cell products, and for the same reasons, platelet concentrates can be further processed through a leukodepletion filter, to reduce white blood cells to less than 1×10^6/unit.

Indications

- Platelet concentrates are indicated for the treatment of bleeding due to:
  - thrombocytopenia,
  - platelet function defects.

- They are also indicated for prevention of bleeding due to severe thrombocytopenia, such as in bone marrow failure (with platelet count < 10 000/ml and no comorbidities).

- Not indicated in:
  - idiopathic autoimmune thrombocytopenic purpura,
  - thrombotic thrombocytopenic purpura (TTP),
  - untreated DIC.

Note that platelet concentrates are indicated for prophylaxis of bleeding in surgical patients only if they are known to have preoperative functional platelet defects (acquired or congenital). Platelet transfusions are only indicated in major surgery and platelet count less than 50×10^9/L (100×10^9/L in very limited cases, for example, in neurological surgery).

Dosage

A dosage of 1 unit of platelet concentrate/10 kg body weight: in a 60 or 70 kg adult, 4–6 single donor units containing at least 55×10^9 platelets each should raise the platelet count by $20–40 \times 10^9$/L, unless causes for refractoriness are present (for example, splenomegaly, fever, DIC, sepsis, HLA or platelet-specific antibodies).

Administration

- If not pooled in sterile conditions, platelet concentrates should be infused as soon as possible after pooling (generally within 4 hours) because of the risk of bacterial contamination. If pooled in sterile conditions, storage is the same as for an apheresis product.

- Platelet concentrates should be infused slowly, over at least 2 hours in a non-bleeding patient, to avoid administering a large bolus of cytokines quickly, as a febrile reaction can occur.

- Platelet concentrates must not be refrigerated before infusion as this might impair platelet function, although there is an evolving literature on the use of cold stored platelets in patients with massive bleeding.

- Four to six units of platelet concentrates (which may be supplied pooled) should be infused through a fresh standard blood administration set (special platelet infusion sets are not required).

- Platelet concentrates that are ABO-compatible should be given whenever possible, although minor and major ABO-mismatched platelet transfusions are often administered to adult recipients.

- Platelet concentrates prepared from RhD-positive donors should be avoided for RhD- negative children and women of childbearing potential. In emergency settings, if RhD- compatible platelets are not available, the decision should be made in consultation with the treating team. RhD immunoglobulin prophylaxis may be considered.

Complications

Febrile non-haemolytic and allergic reactions are not uncommon, especially in patients receiving multiple transfusions.

3.5 Component collection by apheresis

Apheresis is an alternative method of producing blood components. It is a sterile process in which a donor is connected to a specialized device by which blood is withdrawn and a specific component, usually plasma or platelets, is mechanically separated and collected. The red cells and other components of the blood that are not required are then reinfused back into the donor.

- Plasmapheresis is the collection of donor plasma by apheresis.

- Plateletpheresis is the collection of donor platelets by apheresis.

The advantage of apheresis is that relatively large amounts of plasma or platelets can be collected from a single donor. Since the red cells are returned to the donor's circulation, this avoids loss of red cells and possible consequent iron depletion and anaemia, and the process can be repeated at frequent intervals.

Plasma collected by apheresis

Plasma obtained by apheresis has the same indications, contraindications and storage condition as plasma separated from whole blood.

Platelet concentrates collected by apheresis

Platelet concentrates collected by apheresis are generally equivalent to the same dose of pooled platelet concentrates prepared with 4–6 whole blood platelet units.

If a specially typed, compatible donor is required for the patient (human platelet antigen (HPA) or HLA matched), several doses may be obtained from the selected donor.

Dosage

One unit of platelet concentrate collected from a single donor by apheresis is usually equivalent to one therapeutic dose for adult patients.

Administration
The procedure for administration is the same as for whole blood platelets.

Most of the plasma can be removed either in pooled platelet concentrates or in platelet concentrates from apheresis and platelets can be resuspended in additive solutions. This allows the reduction of risks associated with plasma transfusion such as TRALI or plasma ABO incompatibility

3.6 Plasma-derived medicinal products

Fractionation of plasma into plasma-derived medicinal products (PDMPs) is a pharmaceutical manufacturing process in which large quantities of plasma, obtained from whole blood separation or plasmapheresis, are pooled together and processed into specific products. These products include:

- albumin;
- coagulation factors, such as Factor VIII/von Willebrand Factor, Factor IX and fibrinogen; and
- immunoglobulins.

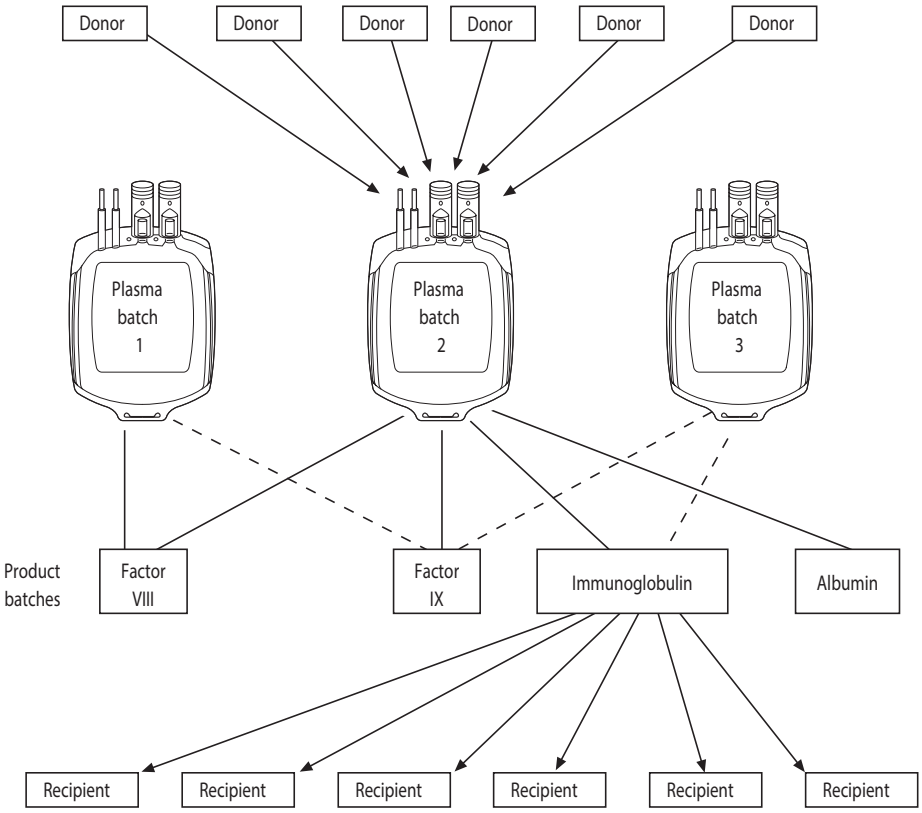
It is usual for a single vial of a PDMP, manufactured by a large fractionation plant, to derive from plasma from as many as 30 000 different blood donations, as shown in Fig. 3.4. A single manufacturing batch of this product may be sent to many countries around the world and be transfused to hundreds of individual patients.

The risk of transfusion-transmitted infection can be avoided only by scrupulous quality control and good manufacturing practice throughout plasma fractionation. This requires consistent use of effective methods to exclude, remove or inactivate any contaminants at all stages of the process, from blood donor selection through to final viral inactivation of the product.

Processes for heat treatment or chemical treatment and/or monoclonal antibody purification, or ultrafiltration of plasma and/or derivatives to reduce the risk of transmitting viruses are currently highly effective against many viruses that have lipid envelopes. Examples include: HIV-1 and 2, hepatitis B and C, and human T-cell lymphotropic virus type 1 (HTLV-I) and HTLV-II.

Inactivation of non-lipid enveloped viruses such as hepatitis A and human parvovirus B19 is less effective and it is common pharmaceutical practice to test plasma units for these viruses also.

Figure 3.4. Plasma derivatives expose many recipients



Human albumin solutions

Description

Human albumin solutions are prepared by fractionation of large pools of donated human plasma.

Preparations

- Different preparations are available in different countries. Typical concentrations of albumin in licensed products are 4%, 5%, 20% and 25%. A 25% preparation contains 250 mg/ml of albumin.

- Stable plasma protein solution and plasma protein fraction are also available, with similar albumin content to albumin 5%.

Infection risk

There is no risk of transmission of viral infections if human albumin solutions are correctly manufactured.

Indications

- It is used as a replacement fluid in therapeutic plasma exchange: use albumin 5%.

- It is also indicated for the treatment of diuretic-resistant oedema in hypoproteinaemic patients, for example, in those with nephrotic syndrome or ascites: use albumin 20% with a diuretic.

- Although 5% human albumin is currently licensed for a wide range of indications (for example, volume replacement, burns and hypoalbuminaemia), there is no evidence that it is superior to crystalloid replacement fluids for acute plasma volume replacement.

Contraindications

Human albumin solution should not be used as intravenous nutrition as it is very expensive and is not a viable source of essential amino acids.

Administration

There are no compatibility requirements and no filter is needed.

Precautions

Administration of albumin, especially concentrated albumin, may cause acute expansion of intravascular volume with a risk of pulmonary oedema (transfusion-associated circulatory overload).

Coagulation factors

Factor VIII concentrate

Description

Purified Factor VIII is prepared from large pools of donor plasma. Factor VIII ranges from 0.5–20 IU/mg of protein. Preparations with a higher activity are available. Licensed products are heated and/or chemically treated to reduce the risk of transmission of viruses.

Unit of issue

Factor VIII concentrate is issued in vials of lyophilized protein labelled with different content, usually from 500 to 1000 IU of Factor VIII.

Infection risk

The currently available virus-inactivated products do not appear to transmit HIV, HTLV and hepatitis C, which have lipid envelopes. The inactivation of non-enveloped viruses such as hepatitis A and parvovirus B19 is less effective, but in commercial products only plasma found to be negative for these viruses by nucleic acid testing (NAT) is used for fractionation.

Storage

Lyophilized derivatives should be stored as indicated in the manufacturer's instructions.

Indications

Factor VIII concentrate is used in the treatment of hemophilia A.

Intermediate purity preparations that contain clinically meaningful quantities of von Willebrand Factor can be used for the treatment of von Willebrand's disease.

Administration
Factor VIII concentrate should be reconstituted and infused according to manufacturer's instructions.

Alternatives
Factor VIII prepared using recombinant DNA technology is commercially available. It is clinically equivalent to Factor VIII derived from plasma and does not carry the risk of transmitting pathogens derived from plasma donors. Recombinant replacement products, where available, should be the first choice in treating patients.

Factor IX concentrates

Description
It is available as preparations containing purified concentrate of Factor IX. Purified Factor IX is prepared from large pools of donor plasma. Licensed products are heated and/or chemically treated to reduce the risk of transmission of viruses.

Unit of issue
Factor IX concentrates are issued as vials of lyophilized protein labelled with content, usually about 350–600 IU Factor IX.

Infection risk
The risks of infection are the same as for Factor VIII.

Storage
Preparations of factor IX should be stored according to the manufacturer's instructions.

Indications
Factor IX is used in the treatment of haemophilia B (Christmas disease). It is also indicated for the immediate correction of very prolonged prothrombin time (reversal of warfarin-related haemorrhage).

Administration
The administration is the same as for Factor VIII.

Alternatives
- Prothrombin complex concentrates (also containing Factor IX) can be used to treat haemophilia B when purified Factor IX is not available.
- Factor IX produced in vitro by recombinant DNA methods is available for treatment of haemophilia B. It offers the same advantages as recombinant Factor VIII.

Prothrombin complex concentrates

Description
Prothrombin complex concentrates are available as preparations containing concentrated Factors II, IX and X (PCC3 – three factor) or Factors II, VII, IX, X (PCC4 – four factor). Factors are at 25- fold higher concentration than in FFP.

Unit of issue
Each PCC vial contains 500 units of Factor IX.

Infection risk
The infection risk is the same as for Factor VIII.

Storage
Prothrombin complex concentrates should be stored according to the manufacturer's instructions.

Indications
- Prothrombin complex concentrates are indicated in the first-line management of life- threatening haemorrhage in unstable patients on anticoagulants (for example, warfarin).

- Prothrombin complex concentrate (4 factor preferred) is also used in the reversal of rivaroxaban or apixaban in patients with acute major bleeding.

Contraindications
Prothrombin complex concentrate is contraindicated in patients with disseminated intravascular coagulation and heparin-induced thrombocytopenia.

Precautions
Do not give after 6–7 hours from onset of haemorrhage (as this paradoxically increases risk of bleeding). PCC lasts for less than 1 day and vitamin K should be given concurrently for a sustained effect.

Immunoglobulin preparations

Normal human immunoglobulin (NHIG) and so-called "specific" immunoglobulin (IgG) products containing higher levels of antibody against specific organisms are used, often together with vaccines (active immunization), to protect against infection. This is called passive immunization. Further information on the use of vaccines and IgG (active and passive immunization) should be available from your Ministry of Health.

IgG preparations are manufactured by fractionation of donated human plasma.

Immunoglobulin for intramuscular use

Description
An immunoglobulin preparation is a concentrated solution of the IgG antibody component of plasma.

Preparations
Standard or normal IgG is prepared from large pools of donors and contains antibodies against infectious agents to which the donor population has been exposed.

Infection risk
Transmission of virus infections has not been reported with intramuscular IgG.

Indications

- Hyperimmune or specific IgG: from patients with high levels of specific antibodies to infectious agents: for example, hepatitis B, rabies, tetanus.
- Prevention of specific infections.
- Treatment of immunodeficiency states.

Administration

These preparations must not be given intravenously as severe reactions occur.

Anti-RhD immunoglobulin (anti-D RhIG)

Description

Anti-D RhIG is prepared from plasma containing high levels of anti-RhD antibody from previously immunized persons.

Indications

It is indicated for prevention of haemolytic disease of the newborn in Rhesus-negative mothers who give birth to RhD-positive babies or RhD-negative recipients of RhD-positive blood products in certain circumstances. It is also used for treatment of immune thrombocytopenic purpura in special cases.

Immunoglobulin for intravenous use (IVIg)

Description

The description is the same as for the intramuscular preparation, but with subsequent processing to make the product safe for IV administration.

Indications

- primary immunodeficiency states
- clinically significant acquired hypogammaglobulinaemia
- idiopathic autoimmune thrombocytopenic purpura and some other immune disorders
- Kawasaki disease
- Guillain-Barré syndrome and certain other neurological conditions.

There are also different human-specific intravenous immune globulin (IVIG) preparations, which include human varicella-zoster IgG and cytomegalovirus IgG.

Immunoglobulin preparations for subcutaneous use are also licensed in many countries. Their advantages over IVIG include ease of administration and fewer side-effects. They can be administered at home and they offer more patient convenience.

3.7 Testing for infectious agents and pathogen reduction

Blood donors may carry infectious agents in their blood, sometimes over prolonged periods and without necessarily demonstrating any clinical symptoms or signs of disease (*9–11*). Virtually all infectious agents that are present in blood can be transmitted by transfusion. However, due to their clinical and epidemiological relevance, only a few infectious agents are routinely screened for in donated blood before transfusion.

Screening for transfusion-transmissible infections

Because of the risk of transfusion-transmitted infection, blood should be collected only from donors who have been selected in accordance with established screening criteria (*12*). Every unit of donated blood must be screened at least for the following infections (*13*):

- HIV-1 and HIV-2 (anti-HIV-1, anti-HIV-2) antibody
- hepatitis B surface antigen (HBsAg)
- hepatitis C (HCV) antibodies
- *Treponema pallidum* antibodies (syphilis).

Where possible, these tests should also include screening for:

- Chagas disease, for donors living in countries where the seroprevalence is significant
- malaria, where donors are exposed to risks of infection.

Screening for other infectious agents should comply with national policies that should reflect the prevalence of the infection in the potential blood donor population.

No blood or blood product should be released for transfusion until these and all other nationally required tests are shown to be non-reactive.

Human immunodeficiency virus (HIV)

Acute "seroconversion" illness

After exposure and infection, viraemia may not be detectable for a few days. Thereafter, high titres of virus (i.e. RNA or antigen) are detectable for several weeks. Subjects then may remain infectious for life.

The "window period"

The period between infection and detectable evidence of virus by donation screening (whether viral nucleic acid, antigen or antibody) is often called the "window period". Blood donated in this period is infectious.

With early anti-HIV antibody tests, antibodies against HIV-1 and HIV-2 became detectable only approximately 21 days after exposure to infection. Viral RNA and an HIV-1 viral protein, designated p24 antigen, are detectable 7 days earlier than the antibodies.

Current-generation serological tests combine the detection of antibodies and HIV-1 p-24 antigen and therefore have the potential to further reduce the window period, at least for HIV-1.

Where resources are available, a molecular test (NAT) for the direct detection of HIV-1 RNA or DNA is included in the screening test panel to further reduce the risk of transmission of this virus, mainly during the window period. RNA testing shortens the window period during which the disease is present but not detectable.

Epidemiology

There are wide variations in the prevalence of HIV infection between and within countries, and even within localized areas. Global estimates of HIV-positive individuals are of little help in assessing the risks of transmission by blood transfusion in a given locality and the prevalence of infection in each potential donor population group should therefore be determined.

Prevention

Prevention initially relies on the selection of low-risk voluntary non-remunerated blood donors and the exclusion of unsuitable donors. Screening tests for HIV are required to enable infected donated blood to be identified and discarded. Confidentiality and the further management of seropositive blood donors through referral for counselling and treatment are essential.

Human T-cell lymphotropic virus type I (HTLV-I) and II

The prevalence of HTLV-I infection is high in some parts of the world, notably parts of the Caribbean and the southern part of Japan. The virus can cause neurological disorders and a rare form of adult T-cell leukaemia. There is usually a delay of many years between infection and the development of illness, but it is likely that only a small proportion of those infected become ill. HTLV-I is transmissible by the transfusion of cellular blood components.

The link between HTLV-II infection and disease is less clear.

Prevention

Donated blood should be screened for HTLV-I and II where there is evidence of HTLV risk in the donor population or an indication of disease. HTLV is a cell-associated virus, so leukodepletion of blood components also provides some protection.

Hepatitis B virus

The hepatitis B virus (HBV) carrier state is highly prevalent in many areas of the world, in some areas affecting more than 10% of the potential blood donor population.

Infection with HBV may lead to clinical or subclinical infection. Transmission by blood may be followed by acute hepatitis, followed either by resolution or by chronic hepatitis. The longer-term consequences may be cirrhosis and primary liver cancer. The likelihood of progression to chronic infection is related to age at the time of infection: 80–90% of infants infected during the first year of life develop chronic infections and 30–50% of children infected before the age of 6 years will develop chronic infections. Less than 5% of otherwise healthy persons who are infected as adults will develop chronic infection and 20–30% of adults who are chronically infected will develop cirrhosis and/or liver cancer (*9*).

Prevention
All donated blood should be screened for HBsAg prior to transfusion.

Where resources are available a molecular test (NAT) for the detection of HBV DNA is included in the screening test panel to further reduce the risk of transmission of this infectious agent.

WHO recommends vaccination against HBV for neonates and it is included in the immunization schedule of infants worldwide. The number of HBV carriers is therefore expected to progressively decrease.

Hepatitis C virus

Hepatitis C virus (HCV) infection is usually asymptomatic. About half the affected patients develop chronic hepatitis and a substantial proportion eventually develop severe liver damage.

Prevention
All donated blood should be screened for anti-HCV antibodies.

Where resources are available, a molecular test (NAT) for the detection of HCV RNA is included in the screening test panel to further reduce the risk of transmission of this infectious agent.

Hepatitis E virus

Hepatitis E virus (HEV) infection gives rise to a broad spectrum of disease ranging from asymptomatic or mild infections that resolve spontaneously, to less common acute severe infections, especially in pregnancy. Serious persistent chronic HEV infections may occur, mainly in immunocompromised individuals, and transfusion transmission has been documented in these cases (*10*). If laboratory screening is implemented, only recipients at significant risk from HEV infection require blood and/or components screened for the presence of HEV RNA.

Syphilis

Syphilis is caused by infection with the bacterium Treponema pallidum (TP). It is essentially a sexually (venereal) transmitted disease, and it can be spread by close contact with mucus- membrane lesions. TP can be transmitted by blood transfusion. A positive syphilis test does not necessarily mean that TP is present in the donor's blood, nor does it suggest active infection. But, in many contexts it is also considered a marker of high-risk sexual behaviour; hence, donors with a positive result for a syphilis test should not be accepted to donate blood.

Prevention
All donated blood must be screened for serological evidence of TP infection. Positive donors are then excluded from donations. A further safeguard is that the storage of donated blood for 72 hours at 2 °C to 6 °C virtually eliminates the risk of infection as the organism is very sensitive to low temperatures.

Chagas disease

Chagas disease, caused by Trypanosoma cruzi, is transmissible by transfusion. Current estimates suggest that about 6 to 7 million people are infected in Latin American countries.

Trypanosoma is transmitted by triatomine insects. The vector lives in low-standard housing in both urban and rural areas. Blood transfusion is the second most common cause of transmission. Persistent parasitaemia in infected blood donors can lead to infected donations over a long period (*11*). The infection is subclinical in the indeterminate phase, but then leads to a chronic phase, which results in irreversible changes, including cardiomyopathy, mega-oesophagus and megacolon.

Prevention

Efforts to eliminate Chagas disease have been successful in reducing the number of infections in recent decades. This has been achieved by vector control and the testing of donated blood to exclude infected units.

Malaria

All blood components can carry the Plasmodium parasite and therefore have the potential to transmit malaria. In non-endemic countries, transfusion-transmitted malaria is rare (less than one case per million units of blood transfused). However, the mortality rate is high, often because the diagnosis is not suspected.

Prevention

In endemic areas laboratory screening of all donated blood for malaria parasites by means of microscopy or rapid tests is not sufficiently sensitive to identify all asymptomatic carriers, while antibody tests are not yet sufficiently specific for use in the routine screening of all blood donations.

In endemic areas, prevention of transfusion-transmitted malaria might be achieved by either:

1. prophylaxis with antimalarial medications in the recipient of the blood, if the index of suspicion is high; or

2. pretreatment of the donor with antimalarial medications, if indicated.

In many circumstances, neither of these options may be very practical. Therefore, where prophylaxis is not available or routinely used, it is important to maintain a high index of suspicion and to treat symptoms of malaria in recipients of blood early with the locally-recommended antimalarial regimen.

In non-endemic areas, strict donor selection criteria should be used to exclude donors who have recently been in an area where malaria is endemic or who have had malaria. In these contexts, serological tests for the detection of anti-Plasmodium antibodies are utilized to identify previous exposure to plasmodia and exclude potential asymptomatic malaria carriers from donation.

Cytomegalovirus (CMV)

Globally, a very high proportion of blood donors have antibodies to CMV. Transfusion-transmitted CMV is usually only a concern in pregnant women and immunocompromised patients, in particular:

- premature infants, especially those weighing less than 1200–1500 g who are born to CMV antibody-negative mothers; and

- CMV antibody-negative bone marrow recipients who receive CMV seronegative grafts.

Prevention

Immunocompromised patients, CMV antibody-negative pregnant women, premature infants and CMV antibody-negative bone marrow recipients receiving CMV seronegative grafts should receive donations that do not contain detectable antibody to CMV or blood products that have been leukoreduced and contain $<5 \times 10^6$ white blood cells. In many countries, leukoreduced blood components are considered equivalent to seronegative units for transfusion transmitted CMV prevention.

West Nile Virus, Zika virus and other arboviruses

Arboviruses are pathogens that are normally transmitted by insects or ticks. Some of them have an animal reservoir and many are endemic in tropical areas. During recent decades, some viruses transmitted by mosquitoes have caused epidemics in countries where they were not previously present. Many of these viruses can be transmitted by transfusion by asymptomatic carriers and they are able to cause severe disease in non-immune patients, in particular in immunologically vulnerable ones.

Among these viruses West Nile virus, Zika virus and Chikungunya virus have emerged as a new threat in some previously nonendemic countries. Owing to the acute nature of these infections and the high rate of asymptomatic infections, clinical history and serological tests are relatively insensitive to identify virus carriers.

For these reasons, in countries where resources are available and these infections are transmitted in the community, all donations are tested with a molecular test (NAT) to detect these viruses and reactive units are discarded. In countries or areas where these and other arbovirus infections are not present, specific deferral periods (usually 28 days) are mandated for asymptomatic donors who have travelled from endemic areas. Longer deferral periods (usually 6 months) are mandated in the case of suspected or documented infections.

Creutzfeldt-Jakob disease (CJD) and variant CJD (vCJD)

CJD is a rare and fatal degenerative neurological disorder. The disease has been transmitted from humans to humans by infected extracts of pituitary growth hormone, by grafted cornea and dura mater tissue, and by contaminated neurosurgical instruments. The infectious agent was identified as a prion, a variant form of a protein present in the brain capable of triggering a severe disease.

A new variant of CJD (vCJD), occurring in younger patients, was first reported in 1995. Consumption of contaminated meat was recognized to be the most important risk factor.

The control of this new disease was mostly achieved by public health measures aimed at reducing the risk of animal infection and at the detection and elimination of contaminated cattle from human and animal food chains.

Experimental studies of vCJD have shown the potential infectivity and the transmissibility of infection by blood products. Only a few cases of apparent transfusion transmission of vCJD infectivity have been identified so far.

Prevention

Risk minimization strategies in response to the threat of vCJD include leukodepletion, geographically-based donor deferrals and deferral of transfusion recipients in endemic areas as blood donors.

On the basis of current scientific knowledge, it is also essential to exclude the following groups from donating blood:

- donors who have been treated with extracts derived from human pituitary glands (growth hormone and gonadotrophin);
- donors with a familial history of CJD, Gerstmann-Straussler-Scheinker disease and fatal familial insomnia; and
- donors who have received a human cornea or dura mater graft.

Prevention of bacterial contamination and bacterial testing of platelets

Pre-donation health screening, validated skin disinfection and collection methods together with strict adherence to sterility procedures during blood component handling are essential to reduce the contamination of blood components. Diversion of the first few millilitres of blood to a sampling pouch is a further measure to reduce the introduction of contaminants potentially present in the donor's skin.

Platelet concentrates, however, still have the highest risk of bacterial proliferation because they are stored at 20–24 °C, which allows replication of a wide variety of microorganisms. For this reason, prompt detection of bacterial contamination may improve biological safety of this component.

Different methods of rapid bacterial growth detection on samples of platelet concentrates are in use in some contexts to identify and to exclude contaminated platelet units. These include culturing platelet samples for 18–24 hours before they are transfused and rapid solid-phase tests that detect Gram-positive and negative bacterial cell wall constituents.

Inspection of products

Blood establishments and hospital blood banks should develop and implement procedures to ensure that blood components are visually inspected upon receipt, prior to issue and prior to transfusion. Haemolytic red cell concentrates (bright cherry red colour in the supernatant) are unsuitable for transfusion. Bacterial contamination can be suspected in red cell concentrates that are dark purple to black in colour, those that show increased opacity, those in which clotting and fibrin are present, those showing grey discoloration, and when there are excessive and unusual air bubbles in platelets and plasma. Units suspected of being contaminated with bacteria are not acceptable for transfusion.

Pathogen reduction technologies

Of the three pillars of blood safety (donor selection, blood testing and pathogen inactivation), pathogen inactivation techniques, leading to the availability of pathogen-reduced blood components, are the most recently introduced and are used in some countries for plasma and platelet preparations (*14*). Pathogen inactivation (PI) is a proactive strategy to mitigate the risk of transfusion-transmitted infections. These technologies have the potential to reduce the transmission of a broad spectrum of microorganisms, including bacteria, viruses and parasites. PI technologies for the treatment of single plasma units and platelet concentrates are commercially available and have been successfully implemented in many countries worldwide.

Risks associated with transfusion that are potentially avoidable or reducible by PI technologies can be either infectious or non-infectious. The former are related to already known but re-emerging and/or newly emerging infectious agents, among which arboviruses have emerged as a major transfusion safety concern over the past 15 years. Another benefit

of some PI technologies is the potential to eliminate the risk of transfusion-associated graft-versus-host disease, because the process also prevents engraftment and replication in the recipient of donor lymphocytes present in the blood components.

All current PI technologies have limitations in their efficacy. The amatosalen and ultraviolet A (UVA)-based system is ineffective for non-enveloped viruses such as hepatitis A, hepatitis E and parvovirus B19. The riboflavin/UV-based system has only weak effects against bacteria and some viruses. The UVC light-based system is highly effective against bacteria and most transfusion- relevant viruses, but only moderately effective against HIV. Also, these technologies are different for chemical and biological characteristics, activity in specific components, metabolite generation and adverse reactions (toxicity).

Despite these weaknesses, PI systems have the potential to add an additional and significant layer of safety to blood transfusion. A distinct product is solvent-detergent-plasma, a pooled standardized pharmaceutical. Pooling has the disadvantage that one single plasma unit can contaminate a whole pool, but the advantages are represented by dilution and possible neutralization of antibodies and allergens, which eliminates transfusion-related acute lung injury (TRALI) and significantly reduces allergic reactions.

Limitations

- PI technologies for the most commonly used blood component, i.e. red cells, are still under development and not yet available for clinical utilization.

- Different epidemiological situations in different countries may or may not justify the introduction of these methods. As a result, implementation of PI technologies needs to be considered by each country, in relation to the risks of transfusion.

- The cost–benefit needs to be assessed because the introduction of PI technologies will increase the cost of blood component preparation. Many countries cannot afford the extra costs (note that NAT testing and universal leukodepletion is not yet a standard of care in most countries).

- There is a potential for adverse effects in recipients. These vary depending on the method selected but may include exposure to agents including to neoantigens that could cause DNA damage and alloimmunization. Long-term clinical outcome data on transfusion recipients exposed to PI-treated products will be needed.

References

1. Guide for the preparation, use and quality assurance of blood components, twentieth edition. Brussels: Council of Europe; 2020 (https://www.edqm.eu/en/blood-guide, accessed 1 February 2021).
2. Circular of information for the use of human blood and blood components. AABB, the American Red Cross, America's Blood Centers, and the Armed Services Blood Program [online] (https://www.aabb.org/tm/coi/Documents/coi1017.pdf, accessed 1 April 2021).
3. Acker JP, Marks DC, Sheffield WP. Quality assessment of established and emerging blood components for transfusion. J Blood Transfus. 2016;2016:4860284. doi: 10.1155/2016/4860284.
4. Strandenes G, Berséus O, Cap AP, Hervig T, Reade M, Prat N et al. Low titer group O whole blood in emergency situations. Shock. 2014;41 (Suppl 1):70–5. doi:10.1097/SHK.0000000000000150.
5. Yazer MH, Jackson B, Sperry JL, Alarcon L, Triulzi DJ, Murdock AD. Initial safety and feasibility of cold-stored uncrossmatched whole blood transfusion in civilian trauma patients. J Trauma Acute Care Surg. 2016;81:21–6. doi: 10.1097/TA.0000000000001100.
6. Watson JJ, Pati S, Schreiber MA. Plasma transfusion: history, current realities, and novel improvements. Shock. 2016;46:468–79.
7. Dunbar NM, Yazer MH. Biomedical Excellence for Safer Transfusion (BEST) Collaborative and the STAT Study Investigators. Safety of the use of group A plasma in trauma: the STAT study. Transfusion. 2017;57:1879–84. doi: 10.1111/trf.14139.
8. Barelli S, Alberio L. The role of plasma transfusion in massive bleeding: protecting the endothelial glycocalyx? Front Med (Lausanne). 2018;18;5:91. doi: 10.3389/fmed.2018.00091.
9. Hepatitis B [online]. Geneva: World Health Organization; 2018 (https://www.who.int/news- room/fact-sheets/detail/hepatitis-b, accessed 1 February 2021).
10. Bi H, Yang R, Wu C, Xia J. Hepatitis E virus and blood transfusion safety. Epidemiol Infect. 2020;148:e158. doi:10.1017/S0950268820001429.
11. Leiby DA, Herron RM, Jr, Garratty G, Herwaldt BL. Trypanosoma cruzi parasitemia in US blood donors with serologic evidence of infection. J Infect Dis. 2008;198:609–13.
12. Blood donor selection: guidelines on assessing donor suitability for blood donation. Geneva: World Health Organization; 2012 (https://www.who.int/bloodsafety/publications/bts_guideline_donor_suitability/en/, accessed 1 February 2021).
13. Screening donated blood for transfusion-transmissible infections: recommendations. Geneva: World Health Organization; 2010 (https://www.who.int/publications-detail- redirect/screening-donated-blood-for-transfusion-transmissible-infections-recommendations, accessed 1 February 2021).
14. Schenkle P. pathogen inactivation technologies for cellular blood components. Transfus Med Hemother. 2014;41:309–325.

CHAPTER 4

CLINICAL TRANSFUSION PROCEDURES

Key points

1. Providing the right blood component to the right patient at the right time is a team effort involving many members of the health care staff.

2. Clear communication strategies, established policies, written standardized procedures and staff training are key to safe transfusion practice.

3. Details of the following are outlined:
   - pretransfusion laboratory testing requirements;
   - blood storage and transportation requirements; and
   - blood administration procedures.

4. The indications and processes for blood component modification are discussed.

Learning outcomes

After studying this chapter, the reader will be able to describe:

- principles of safe clinical transfusion practice, including patient identification, component selection and monitoring during transfusion

- principles of laboratory compatibility testing

- principles of blood component selection, including requirements for modified components.

4.1 Introduction: getting the right blood to the right patient at the right time

Once the decision to transfuse has been made, everyone involved in the transfusion process shares the responsibility to ensure the right blood gets to the right patient at the right time. Box. 4.1 summarizes the main steps in this process and outlines the tasks performed by the various health professionals involved in transfusion.

National guidelines on the clinical use of blood should always be followed in all hospitals where transfusions take place. A local transfusion committee should monitor clinical blood use and review transfusion reactions. It should also ensure that national guidelines are followed and oversee appropriate training.

Initial training and ongoing competency assessment for all staff involved in transfusion and covering the entirety of the transfusion process is a quality systems requirement. Audit of all processes according to a regular audit schedule also contributes to quality improvement by highlighting necessary changes to procedures or training.

In addition, clinical audit to ensure that blood utilization policies are followed is an important quality improvement tool. Guidelines with audit templates are available.

Each hospital should ensure that the following are in place:

- a blood request form;
- a maximum blood ordering schedule (MSBOS) for common surgical procedures;
- guidelines on clinical and laboratory indications for the use of blood, components and alternatives to transfusion;
- defined responsibilities for medical, blood bank and nursing staff and midwives, as well as assistants and students;
- standard operating procedures (SOPs) for each stage in the clinical transfusion process;
- clinical and laboratory audit with feedback of results contributing to ongoing practice changes.

All staff involved in the transfusion process should be trained and should follow SOPs. Development of SOPs requires local input by the transfusion service or blood bank and ideally they are prepared in collaboration with medical and nursing staff. These are often based on national or international standards and adapted for local use. The written procedures should be available to all staff involved in the transfusion process.(*1*,*2*,*3*,*4*)

Responsibility for keeping SOPs up to date and available for training staff to use them should be defined by hospital management, along with the programme for training of clinical staff in administering blood and monitoring patients during and following transfusion.

Box 4.1. Steps in the clinical transfusion process

Getting the right blood to the right patient at the right time

1. Assess the patient's clinical need for blood and when it is required. (*clinical/physician*) 4.1
2. Inform the patient or guardian about the proposed transfusion treatment and document consent and indication for transfusion. (*clinical/physician*) 4.2.1
3. Determine the urgency of transfusion. (*clinical/physician*) 4.2.2
4. If blood is needed urgently, contact the blood bank by telephone or use the approved method for urgent requests. (*clinical*) 4.2.3
5. Select the blood component and quantity required. Use a blood ordering schedule as a guide to transfusion requirements for common surgical procedures. (*clinical/physician*) 4.2.4
6. Complete the blood request form accurately and legibly. (*clinical*) 4.2.6
7. Verify the patient's identity at the bedside. (*clinical/laboratory*) 4.2.5
8. Obtain and correctly label a blood sample for compatibility testing. (*clinical/laboratory*) 4.2.7
9. Send the blood request form and blood sample to the blood bank. (*laboratory/clinical*) 4.3
10. Perform pretransfusion tests and select compatible units. (*laboratory*) 4.3
11. Deliver blood components by designated staff (maintaining approved transport conditions). (*laboratory/clinical*) 4.4
12. Store blood components in correct storage conditions if not immediately required for transfusion. (*laboratory/clinical*) 4.4.2
13. Check: (*clinical*) 4.6
    - identity of patient
    - identity of blood product
    - patient's blood request documentation.
14. Check required pre-medications. (*clinical*) 4.7
15. Record baseline vital signs (blood pressure, respiratory rate, temperature and pulse). (*clinical*) 4.7.1
16. Administer blood component. (*clinical*) 4.7.2
17. Document in the patient's notes: (*clinical*) 4.7.4
    - type and volume of each component transfused
    - unique donation number of each unit transfused
    - blood group of each unit transfused
    - time at which the transfusion of each unit started and ended
    - identity of the person administering the blood.
18. Monitor the patient before, during and after transfusion. (*clinical*) 4.7.3
19. Identify and respond immediately to any adverse effect. (*clinical*) 4.7.4
20. Record any transfusion reactions in the patient's notes and report according to hospital policy and procedure. (*clinical/laboratory*) 4.7.4

4.2 Ordering blood components

4.2.1 Obtaining an informed transfusion consent

Once transfusion is deemed necessary, it is important that the treating physician explains the proposed transfusion to the patient (or guardian), as part of informed consent. The consent discussion should be recorded in the patient's notes or on a specific informed consent form that the patient signs once explanations have been given.

The transfusion consent discussion includes:

- information about the anticipated benefits of the transfusion and the reason it is required;
- the potential non-infectious and infectious hazards of transfusion;
- the potential risks of not receiving the transfusion;
- outlining available alternatives appropriate to the medical condition;
- the opportunity for the patient to ask questions;
- documentation that consent was obtained and the indication for transfusion;
- written documentation for the patient indicating the component(s) transfused.

A transfusion consent might be waived during an emergency. The consent form may also serve to document refusal of transfusion. Patients of the Jehovah's Witness faith and some other faith- based or cultural groups may choose not to receive any or all blood components. In some cases, plasma fractions and autologous or non-cellular blood components may be acceptable, and these options should be discussed.

In many countries the law defines it as an assault to transfuse a patient who has refused, even if refusal is life-threatening. The Jehovah's Witnesses may have a liaison worker trained to assist patients, relatives and hospital staff in these difficult instances.

As patients may have no recollection of the consent discussion, a written record that the patient has been given the information and that questions have been answered is valuable in a medico- legal setting. It is important to be familiar with local rules.

4.2.2 Defining the urgency of transfusion

When there are clinical and laboratory indications that transfusion is required, the procedure for ordering will depend on the urgency of the requirement as defined below:

- emergency need for immediate use (within 10–15 minutes, if blood products are not maintained in the emergency room or intensive care units themselves);
- urgent need (within 1 hour);

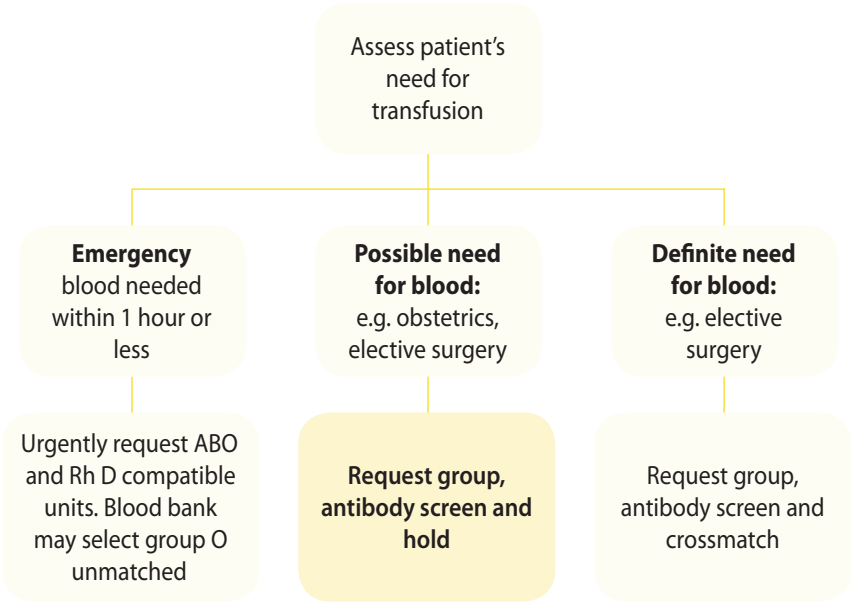
- routine but definite need for blood (within 3–4 hours);
- routine, possible need for blood.

Urgent blood requirements may be termed "emergency" or "stat" with release of group specific or group O unmatched red cells as soon as possible. It is important to ensure agreement regarding the specific language used by clinical and blood bank staff to avoid misinterpretation of urgency. Categories of urgency with specific language denoting expected time to blood delivery may be defined.

Routine blood requirements are ordered as a crossmatch and lead to patient and donor blood group testing, patient antibody screening and a method for compatibility testing.

A *possible* need for blood may be ordered as a group and screen. This request leads to a patient blood group and antibody screen with no donor or compatibility testing until or unless units of red cells are requested (Fig. 4.1).

Figure 4.1. Blood ordering policy



4.2.3 Ordering blood in an emergency

In the accident and emergency/casualty department, operating room or labour ward, it is often necessary to order blood urgently. There may be several massively bleeding patients who need blood quickly. In these situations, mistakes in identifying patients and labelling blood samples can easily occur. It is essential that procedures for ordering blood in an emergency are clear and simple and that everyone knows and follows them (Box 4.2).

Box 4.2. Ordering blood in an emergency

1. Insert intravenous (IV) cannula, collect a blood sample for compatibility testing.
2. For each patient, label the blood sample tube and the blood request form with the patient's name, date of birth and unique hospital number at the bedside. If the patient is unknown, use an emergency reference number according to hospital SOP.
3. Communicate the transfusion request by telephone and transport samples to the blood bank; ensure that the blood bank is informed of the patient's location and any transfers to other clinical areas.
4. Use consistent patient identifiers on all subsequent requests for the same patient.
5. Identify a single staff member to order blood and communicate with the blood bank. This is especially important if several injured patients are being treated at the same time.
6. Communicate the urgency of the transfusion request.
7. Ensure that both physicians and the blood bank know:
   - who is transporting testing samples and blood components to and from the blood bank; and
   - where the patient will be.

Notes

1. The blood bank will send group O un-crossmatched blood if there is no time for the completion of pre-transfusion testing.
2. Un-crossmatched emergency blood (O RhD-positive or O RhD-negative) may be available from an emergency fridge after hours and/or routinely in certain locations in the hospital.
3. Completed documentation concerning the units used, including the unit number, should be returned to the blood bank as soon as possible after the units are transfused.

4.2.4 Ordering blood for elective surgery

Sufficient time between the blood order and the time of surgery allows for completion of compatibility testing and helps ensure availability of compatible blood. Requests for blood for elective surgery should be guided by a local blood ordering schedule.

Many elective operations rarely require blood transfusion. Therefore, it is unnecessary for a compatibility test (crossmatch) to be performed for every surgical procedure.

Time and money can be saved by avoiding unnecessary crossmatching while still ensuring blood is readily available for all patients who need it. Identifying those surgical patients who should have a "group and screen" (see section 4.3.4), and those who require a crossmatch can be determined through development of a maximal surgical blood ordering schedule (MSBOS).

The MSBOS is a table of expected blood use for each elective surgical procedure. It lists the number of units of blood routinely crossmatched for each surgery type. It should reflect the expected blood use for common procedures and depends on the complexity of surgery and the expected blood loss. The MSBOS should also inform the use of a group and screen for patients undergoing procedures for which transfusion is rarely required.

An MSBOS should always be developed locally by the hospital transfusion committee together with clinicians responsible for prescribing blood and the blood bank. It may be prepared in accordance with national guidance or adapted from a model MSBOS for local use. See Chapter 8 for details on the process of developing an MSBOS.

The MSBOS is a guide to optimize blood use and compatibility testing and should never overrule actual patient need as determined by clinical assessment. In facilities where inexperienced staff manage preoperative blood ordering, standardized ordering practices may be particularly beneficial.

The MSBOS should be regularly reviewed and adjusted to ensure that it remains effective.

4.2.5 Patient identification

Prior to blood sampling for pretransfusion testing each patient should be clearly identified using a unique identity wristband or other attached marker with:

- a unique hospital reference number;
- full name; and
- date of birth.

Without clear identification and a policy for identifying the patient, group-specific blood cannot be safely administered. The patient's unique identifiers should be used on the blood sample tube, blood request form and all testing documentation.

When a patient cannot be reliably identified at the time of admission, the hospital reference number should always be used to identify the patient until full and correct details are available and communicated to the hospital blood bank. For subsequent testing and transfusion, the unique hospital ID number should be formally associated with the patient's name and date of birth.

4.2.6 The blood request form

When blood is required for a transfusion, the prescribing clinician must complete a standard blood request. All the details requested must be filled in accurately and legibly.

An example of a blood request form is given in Fig. 4.2. This sometimes includes a compatibility test record, which should be completed in the laboratory before the blood is issued.

The essential information for the blood sample and request form includes:

- unique patient identifiers (see section 4.2.5);
- the quantity and type of blood components required; and
- the time and place at which they are needed.

Blood bank staff are correct to refuse a sample for testing when either the blood request form or the patient blood sample are inadequately identified, or the details do not match, as these samples frequently contain the wrong patient's blood in the tube (known as a WBIT error).

Figure 4.2. Example of a blood request form

HOSPITAL: _____ Date of request: _____

PATIENT DETAILS

Family name: _____ Date of birth: _____ Gender: _____

Given name: _____ Ward: _____

Hospital reference no.: _____ Blood group (if known): ABO ☐

Address: _____ Rh D ☐

_____

HISTORY

Diagnosis: _____ Antibodies: Yes/No _____

Reason for transfusion: _____ Previous transfusions: Yes/No _____

Haemoglobin: _____ Any reactions: Yes/No _____

Relevant medical history: _____ Previous pregnancies: Yes/No _____

REQUEST

☐ Group, screen and hold patient's serum

☐ Provide product

Date required: _____

Time required: _____

Deliver to: _____

Whole blood ☐ units

Red cells ☐ units

Plasma ☐ units

Platelet concentrate ☐ units

NAME OF DOCTOR (print): _____ **SIGNATURE:** _____

IMPORTANT: *This blood request form will not be accepted if it is not signed or any section is left blank* .

LABORATORY USE ONLY

Patient ABO ☐

Rh D ☐

	Donor typing		Compatibility testing						
Donation pack no.	ABO	Rh	Antibody screen	AHG XM	RT Saline XM	Date of match	Time of match	Date of issue	Time of issue

Signature of tester: _____

4.2.7 Blood samples for blood group and compatibility testing

Box 4.3 outlines the steps involved in taking a blood sample for compatibility testing.

All staff responsible for taking blood samples should be specifically trained for this task. National rules or standards should be followed if available. Where these are not available, procedures and training materials may be adapted from international publications.

The blood bank should not accept requests for blood unless all the patient's details on the blood sample match those on the blood request form. When details do not match, a new sample and request form are required and use of unmatched group O red cells may be considered if there is a need for urgent transfusion before testing is complete.

Box 4.3. Procedure for taking blood samples for compatibility testing

1. If the patient is able to answer, ask him or her to identify themselves by given name, family name, and date of birth. If the patient is unable to answer, ask a relative or staff member to verify the patient's identity.

2. Check the patient's name against:
   - patient's identity wristband or label;
   - patient's medical notes; and
   - completed blood request form.

3. Take the blood sample into the appropriate sample tube.

4. Label the sample tube clearly and accurately at the patient's bedside immediately after the blood sample is taken. Never label samples away from the patient. The label should include:
   - given name and family name
   - date of birth
   - hospital reference number
   - location
   - date
   - signature/documentation of person taking the sample.

   Never sign for a sample collected by a colleague.

   Ensure that the patient's name is spelled correctly.

   Do not label tubes before obtaining the specimen because of the risk of putting the intended patient's blood into the wrong tube.

5. A medical record entry indicating the time and date and tests collected may be required.

6. Transport the blood sample and request form to the blood bank.

4.3 Blood groups and pretransfusion testing

The International Society of Blood Transfusion (ISBT) Working Party Committee on Red Cell Immunogenetics and Blood Group Terminology recognizes and defines blood group systems.(*5*)

ABO, Rh, Kell, Kidd, Duffy, MNS, P, Lewis and Lutheran are the nine major blood group systems. For several of these blood groups, antibodies to their associated antigens are clinically significant because they can cause acute haemolytic transfusion reactions, delayed haemolytic transfusion reactions and/or haemolytic disease of the fetus and newborn. (*6,7,8,9,10*)

The main goals of pre-transfusion testing are to:

- ensure compatibility of transfused red cells with antibodies in patient plasma; and
- avoid stimulating the production of new red cell antibodies in the recipient, particularly anti-RhD.

Pretransfusion test procedures include patient testing for:

- ABO group
- RhD type
- antibody screen
- antibody identification, if screen positive.

Pretransfusion test procedures confirm donor:

- ABO group
- RhD type
- antigen type (phenotype) for antigens corresponding to patient antibodies, if present.

The next pretransfusion step involves compatibility testing.

In addition to the blood group testing, the blood bank is responsible for:

- ensuring that only units of blood that have been tested and found negative for transfusion- transmissible infections are tested for compatibility;
- ensuring clear and correct labelling of donor red cell units with ABO and RhD typing;
- checking that a blood request form has been fully completed and that identifiers match those on the patient's blood sample;

- selecting blood components: potential alternatives should be discussed with the ordering physician as required;
- performing compatibility testing (crossmatch) and ensuring that red blood cell (RBC) units with a safe ABO and RhD type are supplied for the patient;
- labelling compatible RBC units specifically for the patient and issuing them as required: the blood bank may reserve these units for a limited time according to local policies;
- appropriate identification of un-crossmatched group O red cells issued in an emergency.

4.3.1 ABO antigens and antibodies

ABO blood groups are the most important in red cell transfusion. Red cells are classified as: O, A, B and AB. Individuals who lack A or B antigens have antibodies in plasma corresponding to the antigen missing from red cells or other tissues (see Table 4.1). Red cell antigen typing for ABO is sometimes referred to as the "forward" group while detection of corresponding antibodies in plasma (or serum) is the "reverse" group (Table 4.1).

ABO antigen and antibody testing are important for patient and donor testing. Anti-A and anti-B antibodies occur "naturally" without prior sensitization to the corresponding antigen through transfusion. Therefore, these antibodies are present in almost all individuals.

Table 4.1. Expected forward and reverse reactions for ABO blood groups

	Forward (antigen testing)		Reverse (antibody testing)	
Blood group	**Anti-A antisera**	**Anti-B antisera**	**Group A red cells**	**Group B red cells**
	Patient/donor red cells		**Patient/donor plasma**	
A	+	–	–	+
B	–	+	+	–
O	–	–	+	+
AB	+	+	–	–

+ agglutination / – no agglutination.

4.3.2 ABO incompatibility: the risk for haemolytic reactions

Safe blood transfusion depends on avoiding incompatibility between the donor's red cells and the patient's antibodies. Severe acute haemolytic transfusion reactions are nearly always caused by transfusing red cells that are ABO incompatible with the patient. These reactions can be fatal. They most often result from errors made in identifying the patient when blood samples are being taken for pretransfusion testing or when red cells are transfused.

Anti-A or anti-B recipient antibodies can cause destruction (haemolysis) of incompatible transfused red cells as soon as they enter the circulation. Since group O red cells lack A and B antigens, they may be given to individuals of any ABO blood group and should be used if un- crossmatched transfusion is required.

In some circumstances, such as plasma and whole blood transfusion, it is also important that the donor antibodies are compatible with the patient's red cells or that they are present at a low titre.

It is not always essential, however, to give blood of the identical ABO group. Compatible blood groups can be selected (see Table 4.2).

Because of the importance of ABO compatibility for safe transfusion, ABO testing on both patient and donor samples should ideally be confirmed on more than one sample to ensure the test results match. A current sample may be compared to a historical typing result or the group may be confirmed on a second sample collected at a different time than the first. Similarly, donor ABO testing should be performed at the time of donor blood collection and labelling, and again at the transfusion facility.

Careful records of ABO blood groups of donors and recipients should be maintained and routinely reviewed at the time of blood group testing as part of ABO confirmation.

Table 4.2. Red cell, platelet and plasma compatibility in the ABO system

Blood group of recipient	A/B antigen on recipient red blood cells	A/B antibodies in recipient plasma	Compatible plasma from donor group	Compatible red cells from donor group	May receive platelets from group
A	A	Anti-B	A, AB	A, O	A, AB, B, O
B	B	Anti-A	B, AB	B, O	B, AB, A, O
AB	A, B	None	AB	A, B, AB, O	AB, A, B, O
O	None	Anti-A, anti-B	A, B, AB, O	O	O, AB, A, B

Source: adapted from Gupta A, Bigham M. Blood components. In: Clarke G, Chargé S, editors. *Clinical guide to transfusion* [Online]. Ottawa: Canadian Blood Services; 2021 (https://professionaleducation.blood.ca/en/transfusion/clinical-guide/blood-components, accessed 1 February 2021).

4.3.3 RhD antigens and antibodies and other blood group antigens

Red cells have many non-ABO antigens. In contrast to the ABO system, antibodies in these blood group systems are "acquired antibodies". Individuals rarely make antibodies against these antigens unless they have been exposed to them by previous transfusion or during pregnancy and childbirth.

The most important and most antigenic of the non-ABO antigens is the RhD antigen. Anti-D antibody develops after an antigen-negative individual is sensitized by RhD-positive red cells. For example, an RhD-negative woman may develop anti-D following pregnancy with an RhD-positive baby or following transfusion of RhD-positive red cells. Even a single transfusion of RhD-positive red cells to a RhD-negative person may provoke anti-D alloimmunization.

Anti-D antibodies are "clinically significant antibodies". This indicates that they can cause:

- haemolytic transfusion reaction by rapid destruction of RhD-positive red cells in a sensitized recipient with anti-D antibodies;
- haemolytic disease of the newborn in a subsequent pregnancy of a RhD-negative woman with a previous RhD sensitization.

Because RhD exposure will frequently result in alloimmunization of an RhD-negative individual, efforts should be made to transfuse such individuals with RhD-negative blood to prevent the formation of anti-D. This is especially important in women with childbearing potential.

There are many other antigens on the human red cell. Examples include:

- Rhesus: C, c, E, e
- Kell: K, k
- Duffy: Fy^a, Fy^b
- Kidd: Jk^a, Jk^b

Like anti-D, antibodies in these blood group systems are mainly acquired antibodies following exposure to the corresponding antigen through transfusion or during pregnancy and childbirth. These antibodies may be clinically significant.

In the presence of clinically significant antibody/antibodies in the recipient plasma, red cells selected for transfusion should be negative for the corresponding antigen and/or crossmatch compatible.

Prophylactic phenotype matching of red cells for these antigens (in the absence of antibodies in the recipient plasma) is not routine practice. That said, there are groups of patients who benefit from "antigen matched" red cells, such as those who are chronically transfused.

Prophylactic antigen matching is particularly important in patients with sickle cell disease or thalassaemia. If possible, Rh (CcDEe) and Kell matched red cells should be provided to these patients. This strategy can prevent the formation of antibodies against these red cell antigens, and the associated complications.

4.3.4 Group and screen

The "group and screen" procedure is also known as a type and screen.

The patient's ABO and RhD type are determined and an antibody screening test is performed. If the screen is negative, the plasma (or serum) is stored (refrigerated or frozen) in the laboratory for several days. The validity of the group and screen is typically 72 hours (3 days) for patients who have been transfused or are pregnant, and up to 45 days for non-transfused, non-pregnant patients being evaluated for elective surgery.

If the patient has a valid group and screen, the blood bank will usually need only 15–30 minutes to have crossmatched blood ready for issue for that patient.

If the initial sample has a positive antibody screen, the antibody is identified and donor blood that is negative for the antigen is found through antigen typing and then a crossmatch. These units can then be kept on hand for the patient for a predefined period.

This approach optimizes the blood bank's RBC inventory by avoiding holding multiple crossmatched units of red cells for patients when they are unlikely to need them, while ensuring that red cells can be provided quickly if required.

4.3.5 Serological compatibility testing

A serological crossmatch refers to compatibility testing of patient and donor samples by mixing patient plasma and donor red cells, with evaluation for agglutination and haemolysis. If no agglutination or haemolysis is present, the donor and recipient are compatible.

A full serological crossmatch involves several steps starting with assessment for agglutination or haemolysis immediately after mixing and centrifugation of cells and serum. This step is called the **immediate spin (IS) crossmatch**.

The next step involves incubation of cells and serum at 37 °C followed by washing, centrifugation and review for agglutination. This phase will detect uncommon immunoglobulin M (IgM) antibodies that directly cross-link the cells and are reactive at 37 °C. After washing, anti-human globulin (AHG) is added and the cells are again incubated, centrifuged and the tubes reviewed for agglutination. This is termed the **AHG crossmatch.** This phase of reactivity detects immunoglobulin G (IgG) antibodies from patient plasma that are bound to the donor red cells.

This full serological crossmatch procedure will detect IgG antibodies and IgM anti-A and anti-B and is the most sensitive compatibility test. It may be enhanced through addition of potentiators such as polyethylene glycol (PEG) or low ionic-strength saline (LISS) which shorten the incubation time and increase the sensitivity for antibody detection.

The crossmatch may be abbreviated at the IS step in a patient with a negative antibody screen and no history of clinically significant red cell allo-antibodies. Here, the IS crossmatch ensures donor and recipient ABO compatibility. The IS crossmatch can be completed in approximately 5 minutes and is useful when transfusion is urgent.

Following red cell transfusion, a recipient may occasionally develop an antibody to donor red cell antigens over several days to weeks.

In a recipient previously exposed to red cells with prior antibody development, repeat red cell transfusion can result in an anamnestic antibody response with a rapid rise in antibody levels over a few days.

To detect new antibodies, pretransfusion antibody screening and compatibility testing within 3 days (72 hours) before planned transfusion is widely recommended. With ongoing transfusion, repeat testing at 3-day intervals is usually required. Permanent records of blood groups and detectable antibodies are required.

Records must be reviewed with each transfusion request to ensure ABO and Rh are consistent with historical records, and that previously detected antibodies are taken into account.

Neonatal transfusion represents a special testing circumstance, since most neonates do not have anti-A or anti-B in their plasma. When performing blood group testing on a neonate, it is permissible to test the forward blood group only. Crossmatch of neonatal samples may involve testing maternal plasma with ABO-compatible donor red cells, as antibodies in neonates are those passively acquired from the mother. Repeat compatibility testing is not generally required after an initial crossmatch for the first 4 months of life, as neonates are not expected to make new antibodies. Local policies may vary.

4.3.6 Other systems for ensuring red cell compatibility

In some countries, a "bedside" test is used to determine the ABO group of the patient and of the blood units supplied. This is performed using a grouping card pretreated with blood typing reagents, which is supplied with detailed instructions.

Another method is called a **computer crossmatch** and depends on a validated system to confirm testing results on patient samples and donor red cells. This system requires that donor units have two ABO tests and that patient samples have two ABO tests and a negative antibody screen and no historical record of antibodies. The computer confirms ABO compatibility based on the test results for patients with a negative antibody screen and a negative antibody history.

4.3.7 Compatibility problems

If antibody screening or a positive crossmatch indicate an antibody, further tests are needed. Once the antibody has been identified, red cell units negative for the corresponding antigen may be provided.

Compatible donor red cells for patients with red cell antibodies are necessary to avoid a haemolytic transfusion reaction. Depending on the antibody/antibodies, the search for antigen-negative red cells, and compatibility testing, can cause considerable delay.

When urgent transfusion is required, and compatible red cells are not immediately available the risk of delay in transfusion must be weighed against the risk of a haemolytic transfusion reaction. Non-ABO antibodies are most likely to cause a delayed reaction, which may pose less risk to the patient than a delay in transfusion.

When a patient has a pan-reactive auto-antibody, it is sometimes necessary to transfuse red cell units that are not compatible. Again, the risk of withholding transfusion in this situation must be weighed against the risk of a haemolytic reaction. Ideally, in this situation, donor red cells that are as closely matched to the recipient's red cell phenotype as possible should be transfused. For example, C/c E/e and Kell tested red cells that match the recipient's red cell phenotype could be provided to the recipient if possible.

4.4 Collecting blood components prior to transfusion

One cause of transfusion reactions is the transfusion of a unit of red cells that was intended for a different patient. This may be due to mistakes made when collecting blood from the blood bank. Therefore, it is essential that an SOP for the collection of blood from the blood bank is in place. Staff should be appropriately trained, and the procedure followed.

An example is given in Box 4.4.

Box 4.4. Procedure for collecting blood from the blood bank

1. Bring written documentation with patient identifiers.

2. Ensure that the details on the attached compatibility label exactly match the details on the patient documentation:
   - patient's family name and given name
   - patient's hospital reference number
   - patient's ward, operating room or clinic
   - patient's ABO and RhD group
   - donor unit ABO and RhD group.

3. Enter the required information in the blood collection register. Include:
   - time of issue
   - ABO group issued (may be ABO-compatible or ABO-identical).

4.4.1 Storing and transporting blood components

Consult the circular of information for blood and blood components provided by the blood supplier for details of storage temperature and duration of storage.

4.4.2 Storage and transport requirements

The proper storage of blood components depends on:

- regularly monitored storage equipment including blood bank refrigerators, freezers and platelet agitators, and satellite blood refrigerators;

- controlled temperature during transportation of blood and blood components.

Two rules govern the storage and transportation of blood components:

- **4-hour rule: Transfusion should be completed within 4 hours of initiation.** Transfusion must be initiated within 30 minutes of removal of blood or blood components from controlled-temperature storage.

- **30-minute rule: Components left out of controlled-temperature storage for more than 30 minutes without initiating transfusion should be discarded.**

Note that in some countries this rule is evolving and additional information is available in published blood administration guidelines.

- Equipment used for blood storage should be regularly maintained and connected to emergency power which is checked at defined intervals to ensure an immediate switch to emergency power if needed.

- Storage equipment should have alarms with audible signals. Alarm activation points should be set at temperatures that allow time for corrective action to be taken before blood components reach unacceptable temperatures. Equipment should be monitored at least twice per day and records must be kept.

- Thermometers used in storage equipment should be checked against certified calibrated thermometers at least annually and the checks documented.

- Procedures outlining alternative storage arrangements when equipment for storing components is malfunctioning should be developed.

- Once components have left the designated storage equipment, the transfusion should begin within 30 minutes of removal. If the transfusion is delayed, storage in a temperature- monitored satellite blood refrigerator or validated transport box is acceptable.

- Typically, transport boxes are validated for specific numbers and types of components for specified intervals.

- Clinical staff are responsible for ensuring that blood components issued by the blood bank are kept at the correct temperature until transfused.

- All clinical staff who retrieve blood components should be trained to comply with procedures for blood refrigeration.
  - When stored in a refrigerator with reagents or blood samples, components should be segregated to avoid possible contamination.
  - The door should be opened only when necessary to remove or replace blood.
  - Arrange the blood to allow air circulation. Store blood containers upright (e.g. in baskets) or laid flat on shelves.
  - The time of removal of blood from controlled storage should be documented.

4.5 Visual inspection

Blood components must be inspected for signs of deterioration and the visual inspection documented.(*11*)

Discoloration or signs of leakage may be a warning that blood is bacterially contaminated and could cause transfusion-transmitted sepsis with serious or fatal consequences for the recipient. Other visual signs may indicate donor or manufacturing problems leading to compromise of components.

When blood components fail visual inspection, the hospital's procedure for action and reporting should be followed. The unit should be quarantined to prevent use, and should have clearly labelled tags affixed as well as being physically separated from the routine inventory.

4.5.1 When to perform visual inspection

Inspection for signs of deterioration should be performed:

- before shipping to another facility;

- upon receipt from the supplier or another facility;

- during component manufacturing;

- at the time of compatibility testing;
- before issue from the blood bank;
- on arrival in the ward or operating theatre;
- upon return to inventory; and
- when a transfusion reaction is reported.

4.5.2 How to perform visual inspection of the blood components (Fig. 4.3)

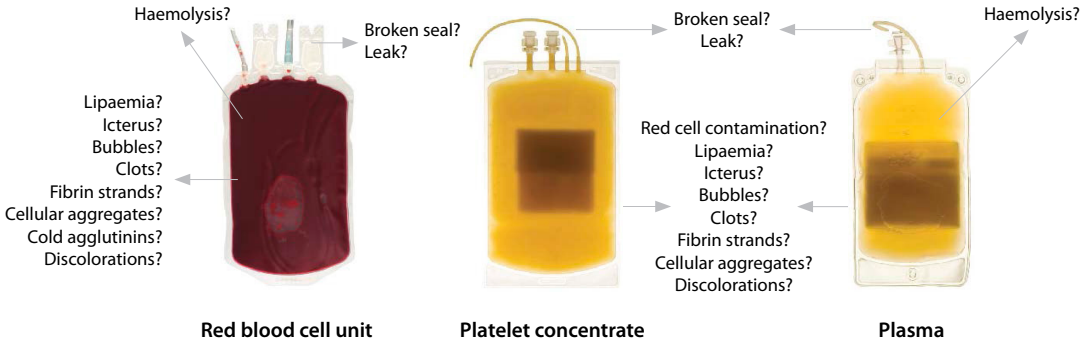
- Inspection of the blood product should take place in a well-lit area.
- Segments should not be used to assess a red cell component as they may not reflect the content of the unit.
- Mix red cells and allow them to settle until the colour of the plasma layer is visible.
- Note that normal cryoprecipitate appears as a thick, opaque, whitish concentrated precipitate at the bottom of the bag. Upon thawing it appears as an even, thick whitish liquid.
- Evaluate for haemolysis (light pink to dark red) in the supernatant of red cells and in platelets or plasma.
- Check red cells for dark purple to black discoloration indicating possible bacterial contamination.
- Inspect for large or unusual air bubbles, clots, fibrin strands, grey discoloration and opacity in any component, which may also indicate bacterial contamination.
- Note any clots or fibrin strands (small to large dark red or purple masses and/or white masses or thread-like strands that do not disperse with manipulation).
- Assess for lipaemia (opaque or milky white colour).
- Assess for icterus (bright yellow to brown appearance).
- Note cellular aggregates (white or opaque masses that do not disperse with manipulation).
- Look for cold agglutinins (large RBC masses that do not disperse with manipulation).
- Check for any signs of damage or leakage of the container.

4.5.3 Actions in response to affected components

If there are signs of haemolysis; discoloration or features that lead to a suspicion of bacterial contamination; damage or leakage in the unit; large clots; fibrin strands; cellular aggregates or cold agglutinins, the unit should not be transfused. The blood bank must be informed, and the unit discarded or quarantined for further evaluation.

Blood components with lipaemia or icterus are generally acceptable for transfusion unless the features interfere with testing.

Figure 4.3. Signs of deterioration in red cells, platelets and plasma



Source: Reproduced with permission from Visual Assessment Guide. Ottawa: Canadian Blood Services; 2009. (https://profedu.blood.ca/en/transfusion/best-practices/visual-assessment-guide.)

4.6 Pretransfusion steps

Before obtaining a blood component for transfusion, the patient record should be checked for the transfusion order and consent records. The blood component should be obtained and transported from the hospital blood bank or satellite blood refrigerator according to local procedures.

Prior to transfusion, it is vital to confirm the patient's identification and to perform component verification in the presence of the recipient. This is especially important in an emergency setting, where emergency identifiers should be checked.

The identity check confirming that the blood component is the correct one for the identified patient is the crucial final opportunity to detect an identification error and prevent a potentially incompatible transfusion.

4.6.1 Transfusion instructions and requesting the blood components

- The transfusion request and blood administration instructions are prescribed by a physician or authorized practitioner.
- Recent laboratory values and patient condition determine the necessity for the transfusion and guide the appropriate dose and rate of infusion.
- The blood tests listed in Table 4.3 may be used to monitor the need for and/or effectiveness of the transfusion.

Table 4.3. Tests used to monitor the need for and/or effectiveness of the transfusion

Blood component/product	Laboratory blood test
Red blood cells	Haemoglobin
Platelet	Platelet count
Frozen plasma	International Normalized Ratio (INR)
Cryoprecipitate	Fibrinogen

- Instructions for transfusion must include:
  - patient's first and last name and a unique identifier
  - location
  - diagnosis/indication
  - type of blood components required
  - number of units required or volume (for paediatric patients)
  - patient's weight (for paediatric patients)
  - urgency of the transfusion
  - any special requirements (for example, irradiation or washed components)
  - rate of infusion
  - pre-medications or diuretics if required
  - prescriber's name.

4.6.2 Equipment required for blood administration

Cannulae for infusing blood products:

- should be flexible plastic for preserving venous integrity;
- must be sterile, disposable and never reused; and
- of the recommended IV access size (Table 4.4).

Table 4.4. Sizing of cannulae for infusing blood products

Blood component	IV access size
Red blood cells – routine transfusion in adults	20–22 G (gauge)
Red blood cells – rapid transfusion in adults	16–18 G
Other blood components	Any size
Children	22–25 G
All components – adults and children	Central venous access device (CVAD)
Note: Rapid transfusion under pressure through a small IV cannula can cause haemolysis.	

- Leukoreduced red cells and platelets, frozen plasma and cryoprecipitate should be infused through a standard blood administration set containing an integral 170–260-micron filter to remove fibrin strands or clots.

- Flush the blood tubing, completely wetting the filter. For small paediatric patients, the blood tubing may be primed with the blood component instead of normal saline to avoid volume overload.

- Transfuse platelets through a fresh administration set. Red cells may follow platelets through the same blood administration set, but should not precede platelets.

- Frequency of changing the blood administration set and number of products that can be transfused through an infusion set depends on the type of infusion set used. The manufacturer's recommendations should be followed. Twelve hours is usually considered the maximum time of use because of the risk of bacterial proliferation.

- Paediatric transfusion sets should be used for paediatric patients. When blood components are being administered by syringe, the blood must be drawn into the syringe by an aseptic technique through an approved blood filter.

- When transfusing through a central venous access device with multiple lumens, medications and/or solutions can be infused through other lumens without damaging the blood components if the device is approved for this purpose.

- Pumps/rapid infusion devices:
  - are used in patients with major haemorrhage: infusion rates from 6 to 30 L/hour are possible;
  - often incorporate a blood warmer;
  - require a large-gauge venous access catheter.

- Blood warming is indicated for rapid transfusions. Cold blood can cause venous spasm.

- Blood warmers are most commonly used for:
  - rapid transfusion rates (adults: >50 ml/min, children: >15 ml/kg per hour);
  - exchange transfusion in infants and neonates;
  - trauma situations where core-rewarming measures are indicated;
  - patient rewarming during cardiopulmonary bypass procedures;
  - transfusion for patients with clinically significant cold agglutinins.

- Blood should only be warmed in a specifically designed, maintained and approved blood warmer set at 37 °C. Blood warmers should have a visible thermometer and an audible warning alarm for temperatures exceeding 42 °C. The operating temperatures should be documented on the patient infusion record.

- Red cells must not be warmed above the set point temperature. Overheating may cause haemolysis.

- Blood should never be warmed by placing it under the patient, near a radiator, heater or a stove, or by placing it in a bowl of hot water as this could lead to the haemolysis of the red cells and liberation of potassium ions (K^+) which could be life-threatening. Standard microwave ovens should not be used as they cause focal overheating and red cell haemolysis.

- Blood warmer, administration and pump sets must incorporate an approved blood filter (170–200 microns).

4.6.3 Collecting the blood component

Before picking up the blood component from the blood bank, ensure that the patient is ready for the transfusion:

- Connect the primed IV tubing to the patient's IV site to ensure patency.
- Properly identify the patient being transfused.
- Administer any premedication that may be ordered.
- Arrange for component pickup from the blood bank using appropriate documentation.

4.6.4 Component and patient verification

Checking blood immediately prior to the transfusion is critical as this is the last opportunity to identify any errors in identification of the recipient.

When issuing the blood from the blood bank, the blood bank should provide identification documentation and a compatibility label with the issued blood units, including all the information shown in Fig. 4.4. The compatibility information should be attached to each component.

Figure 4.4. Example of a compatibility label

Patient's given name	Patient's surname/family name
Patient's date of birth	Patient's hospital number (identity number)
Patient's location	Patient's ABO and RhD blood group
Donation number of blood unit	Type of component
Expiry date	Donor unit blood group
Special requirements	
Interpretation of compatibility test: ❑ Compatible ❑ Least incompatible ❑ Uncrossmatched, issued for emergency transfusion	
Technologist:	Date:

Upon arrival of the issued blood component at the clinical area, the information on the accompanying document should be checked against the transfusion order and the compatibility label of the unit. This includes verifying:

- that the unique component identifiers on the component label match those on the accompanying compatibility label;
- that the unique patient identifiers on the component match those of the intended recipient;
- the ABO and RhD compatibility of the component and the recipient; and

- that the blood component has passed the visual assessment.

The final identity check should be made at the patient's bedside immediately **before** beginning the transfusion. It should be performed by two clinical team members, at least one of whom should be a registered nurse or physician (Box 4.5).

If any discrepancies are detected during the checking process, **do not proceed**. Contact the blood bank.

One of the two staff involved in the checking process **must** hang the blood immediately after checking and commence the transfusion. If there is a delay, the checking process **must** be repeated.

Blood transfusion must be started as soon as possible after the blood has been received from the blood bank and transfusion completed within 4 hours of initiation.

Box 4.5. Blood component check and confirmation of patient's identification at the patient's bedside

1. Obtain the following to perform the patient identity check:
   - the blood unit;
   - the compatibility label; and
   - the transfusion order.

2. Blood component checks:
   - Check the transfusion order for component type and volume required.
   - Verify consent.
   - Visually inspect the component.
   - Check donation number on the bag and compare it to the compatibility label.
   - Check the ABO and RhD blood group on the unit label and compare to the patient blood group on the compatibility label.
   - Check the expiration date on the blood component label.
   - Check any special requirements in the transfusion order and confirm on the unit label and/or compatibility label (e.g. irradiation).

3. Confirmation of patient identification:
   - Check the patient's identity wristband is securely attached.
   - Ask the patient or a staff member to identify the recipient.
   - Follow the hospital guidelines for identification of patients with unconfirmed identity.
   - Ensure that the stated full name and date of birth are identical to those on the wrist band, blood component compatibility label and the transfusion order.
   - Ensure that the hospital number on the compatibility label is identical to the blood order, medical record and identity wrist band.

4. Do not proceed if any discrepancies are found or if there are any concerns regarding the integrity of the component. Contact the blood bank.

5. The compatibility label must remain attached to the blood unit throughout the transfusion.

4.7 Administration of blood components (*12,13,14,15*)

4.7.1 Initiating the transfusion

In non-urgent situations, transfusions should take place during the daytime hours if possible, as more staff are usually available to assist if an adverse event occurs than are available at night.

No medicines or infusion solutions other than normal saline (0.9% sodium chloride, NaCl) should be added to any blood component.

- Additives such as calcium can cause citrated blood to clot.
- Dextrose solution (5%) can lyse red cells.

If an intravenous fluid other than normal saline or a colloid solution must be given at the same time as blood components, it should be given through a separate IV line to avoid any risk.

Patients must be appropriately monitored to detect transfusion reactions as quickly as possible.

The following are general steps for preparing and initiating a blood transfusion:

- Explain the transfusion procedure to the patient.
- Instruct the patient or caregiver regarding signs or symptoms of transfusion reaction.
- Ensure pre-medications are given if ordered.
- Obtain baseline vital signs including:
  - temperature;
  - blood pressure;
  - pulse;
  - respiration rate;
  - oxygen saturation (if available);
  - auscultation for patients at risk for volume overload.
- Confirm that the blood component matches the transfusion order.
- Confirm the blood component expiry date and time.
- Complete the component and patient verification process at the bedside in the presence of the patient (Box 4.5).
- Obtain the required equipment (see section 4.6.2).
- Prime the administration line and filter.
- Initiate the transfusion. Start with a slow rate unless transfusion is extremely urgent.

- When transfusion is complete, disconnect the blood tubing and follow local SOPs for retention of blood bags and tubing (for example keep in a fridge for 24 hours). Dispose of the used blood tubing and blood bags in the biohazard container after the required storage interval.

4.7.2 Dosage, time limit, rate of administration and expected outcome

Transfusion should be commenced and completed within a specified time.

- Time limits have been determined where temperatures in hospital buildings are between 22 °C and 25 °C. If the ambient temperature is very high, shorter "out-of-refrigerator" times should be used.

- If a unit is not completed within the allowed time limit, discontinue its use and dispose of the remainder according to hospital policies.

Appropriate transfusion rates vary significantly between patients according to their individual clinical circumstances. (*16,17,18*) Some patients are at a greater risk for circulatory overload and require slower transfusion. For very slow infusion rates that exceed the allowable time limit, and where sterile facilities for dividing units are available, consider dividing the component to allow transfusion of smaller volumes within the allowable time. Alternatively, once the maximum allowable time is reached, if further transfusion is still required, an additional unit should be requested.

For neonates and children, the exact volume and time for transfusion should be prescribed.(*19,20*) Dose or transfusion volume for paediatric patients should be calculated and prescribed in millilitres with a specified transfusion rate (see Table 4.5).

Table 4.5. Dosage, time limit, rate of administration and expected outcome of transfused components

		Adults	Paediatric patients
RED BLOOD CELLS	**Dose**	• Based on the haemoglobin (Hb) level • Transfuse one unit at a time then reassess	• 10–15 ml/kg or use transfusion formula: **[desired Hb (g/L)–actual Hb (g/L)] × weight (kg) × 0.5** • Transfuse one dose at a time then reassess • Transfusion volume should generally be calculated to take the post-transfusion Hb to no more than 20 g/L above the transfusion threshold, usually a maximum of one unit
	Time to start	Within 30 minutes of their removal from controlled temperature storage	
	Rate of administration and infusion time	• Start slowly (50 ml/hour) for the first 15 minutes • Rate may be increased if transfusion is well-tolerated with no adverse reaction • One unit is usually transfused over 2 hours • Consider slower rates for patients at risk of circulatory overload • During major haemorrhage, very rapid transfusion (each unit over 5–10 min) may be required	• Start slowly (1 ml/kg per hour) for the first 15 minutes • Usual administration rate : 5 ml/kg per hour • Maximum administration rate: 150 ml/hour
	Maximum infusion time	4 hours from the time of their removal from controlled- temperature storage	
	Expected increment/ dose	• Each dose is expected to raise the Hb level by about 1 g/dL	

		Adults	Paediatric patients
PLATELET CONCENTRATES	**Dose**	• 4–5 units random donor platelets (or one pool) • 1 apheresis unit	• Neonates and children < 40 kg: 1 whole blood platelet unit per 10 kg • Children ≥ 40 kg: a single apheresis unit or equivalent
	Time to start	Immediately upon arrival in the clinical area	
	Rate of administration and infusion time	• Start slowly (50 ml/hour) for the first 15 minutes • Recommended transfusion time per dose is >60 minutes, preferably slower to avoid administering large cytokine bolus quickly	• 10–20 ml/kg per hour
	Maximum infusion time	4 hours from time of their removal from controlled-temperature storage	
	Expected increment/ dose	• Each dose should raise the platelet count by at least $15–25 \times 10^9$/L and up to 40×10^9/L. • If increments in platelet count are not adequate, investigation for platelet refractoriness should be commenced.	
FROZEN PLASMA	**Dose**	Based on the coagulation status of the patient as measured by laboratory tests, and/or clinical indication e.g. plasma exchange.	
	Time to start	As soon as possible after thawing to avoid loss of labile clotting factors	
	Rate of administration and infusion time	• Start slowly (50 ml/hour) for the first 15 minutes • Infusion rate is typically 10–20 ml/kg per hour, although more rapid transfusion may be appropriate when treating coagulopathy in major haemorrhage • Recommended infusion time is 60–120 minutes/unit	• 10–20 ml/kg per hour • Start at no more than 5 ml/minute
	Maximum infusion time	4 hours from time of their removal from controlled temperature storage	
	Expected increment	Not applicable	
CRYOPRECIPITATE	**Dose**	• 5–10 units of whole blood- derived cryoprecipitate or 5 units of apheresis cryoprecipitate	• 5–10 ml/kg to maximum of 10 units
	Time to start	As soon as possible after thawing	
	Rate of administration	• Infusion rate is typically 10–20 ml/kg per hour (30– 60 min per five-unit pool)	• 10–20 ml/kg per hour (i.e over 30– 60 minutes) • Start at no more than 5 ml/minute
	Maximum infusion time	4 hours from time of their removal from controlled temperature storage	
	Expected increment	Each dose will increase the fibrinogen by 0.5 g/dl	

4.7.3 Monitoring the transfused patient

Ensuring patient safety is the most important aspect of caring for a patient during transfusion. Baseline observations and monitoring during and after the transfusion will help to detect any signs and symptoms of a transfusion reaction. Early detection ensures that action can be taken quickly and efficiently. The steps are outlined in Box 4.6.

Box 4.6. Monitoring the transfused patient

1. For each component transfused, monitor the patient:
   - pre-transfusion (within 30 minutes)
   - after the first 15 minutes
   - at prescribed intervals according to hospital policy and depending on clinical condition and specific transfusion orders
   - on completion of the transfusion
   - during any transfusion reaction.

   Repeat with each subsequent unit.

2. Repeat vital signs more often for patients:
   - at greater risk for circulatory overload (elderly patients, paediatric patients, patients with cardiovascular disease)
   - who have experienced previous transfusion reactions
   - who are clinically unstable.

3. At each stage, document in the medical record:
   - general appearance
   - temperature
   - pulse rate
   - blood pressure
   - respiratory rate (O_2 saturation if available)
   - chest auscultation for patients at risk for volume overload
   - fluid balance (if indicated).

4. Monitor the patient closely for the first 15 minutes of the transfusion to detect early signs and symptoms of transfusion reaction.

5. Continue to monitor the patient after the end of the transfusion to identify any signs and symptoms of delayed transfusion reactions.

6. Provide discharge instructions concerning possible signs and symptoms to the recipient or to a responsible caregiver if direct medical observation or monitoring will not be available post-transfusion.

If a transfusion reaction is suspected, immediately stop the transfusion and maintain vascular access. The blood administration IV tubing should be disconnected. Return the component and tubing to the blood bank together with a report of the reaction.

4.7.4 Documenting the transfusion

The following information should be recorded in the patient's notes

1. **Pretransfusion documentation** (see section 4.2)

2. **During transfusion:**
   - pretransfusion checks of patient's identity, blood unit and compatibility label;
   - record of vital signs made before, during and after transfusion;
   - the transfusion details,
     - date of transfusion
     - type and volume of each component transfused
     - unique donation number of each unit transfused
     - blood group of each unit transfused
     - time at which the transfusion started and ended
     - any equipment used (for example, pumps and blood-warming devices)

  - any transfusion-related adverse event
  - any follow-up testing done,
- name and signature of the staff initiating the transfusion.

3. **Post-transfusion**
   - Record the management and outcome of any transfusion reactions or other adverse events.
   - Record whether the transfusion achieved the desired outcome (for example, an improvement in symptoms).

4.8 Component manipulations

Many post-collection manipulations of donor blood may be undertaken to provide optimal transfusions to specific patient groups.

4.8.1 Leukoreduction

Leukoreduction is the removal of donor white blood cells (WBC) from the blood component, aiming for residual < 5 × 10^6 WBC/unit. This may be accomplished in several ways:

- Apheresis donations may be optimized to exclude WBC from the collected donor blood.
- Whole blood donations, red cells and platelets may be filtered to remove WBC using specific leukoreduction filters.

These methods provide pre-storage leukoreduction removing donor WBC prior to storage of components.

Bedside leukoreduction includes a leukoreduction filter in the IV set used to transfuse the red cells or platelets to the patient. This method can be used if facilities are not available for pre-storage leukoreduction. In this setting the leukoreduction occurs after the blood has been stored for some time post-donation and WBC fragments or cytokines released from WBC into the stored blood component may be transfused.

Effective pre-storage leukoreduction limits febrile transfusion reactions and human leukocyte antigen (HLA) alloimmunization in recipients. Pre-storage leukoreduction also decreases the potential for transmission of bloodborne pathogens that are leukocyte-associated. This includes cytomegalovirus (CMV) and human T-lymphotropic viruses (HTLV). Leukoreduction may contribute to decreased risk of transmission of prions.

Plasma components do not require leukoreduction as leukocytes are present in limited numbers following plasma separation and do not typically survive freezing and thawing.

In the absence of universal leukoreduction, leukoreduced components could be reserved for patients with frequent febrile transfusion reactions, those who may be harmed by HLA alloimmunization (such as future organ or stem cell transplant recipients, or those who require frequent platelet transfusion) and those most at risk from transmission of CMV by transfusion (see section 4.8.4).

4.8.2 Irradiation (*21,22,23,24*)

Irradiation refers to the use of gamma or X-ray treatment of cellular blood components to inactivate lymphocytes present in the blood donation. This is important as a means of preventing transfusion- associated graft-versus-host-disease (TA-GVHD). TA-GVHD is a rare, serious complication occurring in transfusion recipients where the donor is a first- or second-degree relative, recipients of HLA-matched platelets and very occasionally among transfusion recipients with profound cell- mediated immunodeficiency.

Prevention depends on successful inactivation of viable lymphocytes in the donated blood. This process is not replaceable by having the component leukoreduced. Leukoreduction does not remove enough leukocytes to substitute for irradiation in preventing TA-GVHD in at-risk recipients. It is likely to be beneficial in reducing risk, however, and might be considered as a helpful measure if irradiation is not available. In addition, a comprehensive review(*23*) has shown that TA-GVHD has never been reported with red cell units transfused more than 14 days following collection. This suggests that longer storage time may favourably impact the risk of TA-GVHD. Where irradiated and leukoreduced units for an at-risk recipient are not available, pre-storage leukoreduced red cells > 14 days post collection may provide a measure of safety although such a unit should still be considered to have a high risk of causing TA-GVHD and is not ideal for transfusion.

Ideally, irradiation of the red cell occurs immediately prior to transfusion, without prolonged post- irradiation storage. Irradiation damages RBC membranes as well as the targeted leukocytes. Consequently, irradiated red cell components have increased supernatant haemolysis, potassium and other changes. Irradiated red cell components have a decreased shelf-life and there is a limit on the age of a unit of red cells that is eligible for irradiation. As the shelf-life of platelets is short, no further reduction in shelf-life is required post-irradiation.

Frozen plasma components (such as fresh frozen plasma and cryoprecipitate) do not require irradiation. However, plasma that is never frozen may contain viable leukocytes and should be irradiated prior to transfusion to at-risk recipients.

The dose of radiation is at least 15 cGy delivered to all portions of the component. Commercially available stickers provide confirmation of irradiation through a colour change with radiation exposure.

Examples of guidelines for irradiation of blood products and on the patients for whom irradiation is indicated can be found on several websites (see references).

4.8.3 Washed red cells and platelets

Washing of red cells and platelets refers to the sequential mixing of the blood component with saline, followed by centrifugation and supernatant removal, repeated one or more times. This process gradually decreases the plasma and plasma proteins present in the supernatant of the cellular blood components. This technique usually applies to red cells but can be utilized for platelets.

Methods for washing include manual addition and removal of saline, or automated cell washing. The latter allows for a closed system without risk of bacterial contamination and with limited reduction in component shelf-life. Because of the open system required for washing of blood components with the manual methods, the shelf-life of the washed product is often decreased to 24 hours post-wash. With automated closed system washing, a 7–14-day post-wash expiry of manipulated components may be allowable depending on local standards and policies.

Washing blood components is most commonly indicated for patients with a history of severe allergic or anaphylactic reactions. Occasionally these reactions reflect IgA deficiency with anti- IgA antibodies or an-haptoglobinaemia with anti-haptoglobin antibodies. In either case, or in the more common idiosyncratic allergic/anaphylactic events, washing serves to remove plasma proteins (including IgA and haptoglobin) from an RBC component and may prevent such reactions.

Some advocate the use of washed red cells for prevention of mild allergic reactions but there is little evidence supporting this practice. With no evidence of benefit and potentially increased risk of component contamination, washing to prevent minor allergic reactions is not generally recommended.

In patients with the rare transfusion-associated complication called post-transfusion purpura, washed red cells may also be provided.

4.8.4 CMV testing

A large number of healthy individuals are cytomegalovirus (CMV) seropositive. Most are asymptomatic. These individuals carry CMV within their leukocytes in a latent form and, if they are blood donors, they may pass CMV to a transfusion recipient. Serological testing of blood donors for anti-CMV antibodies is one way of preventing transfusion-associated CMV transmission. The other is effective pre-storage leukoreduction. Since CMV is cell-associated, effective leukoreduction removes CMV-containing leukocytes and markedly reduces the risk of CMV transmission to transfusion recipients.

Both CMV antibody testing and pre-storage leukoreduction are acknowledged as effective means of dramatically reducing the risk of transfusion-transmitted CMV. Whether the combination of antibody testing and leukoreduction confers additional benefit remains controversial.

Many blood suppliers have ceased CMV testing where leukoreduced blood components are routinely available. Some jurisdictions continue to use CMV antibody testing as a means of identifying donors whose blood components should not be used in patients most at risk of transfusion-transmitted CMV.

Patient populations deemed at highest risk from CMV infection include the fetus receiving intrauterine transfusion and recipients of allogeneic bone marrow or stem cell transplantation who are CMV seronegative and who have received a donation from a CMV-seroposivite bone marrow or stem cell donor. CMV seronegative pregnant women may also be considered high risk owing to the significant adverse effects of prenatal maternal CMV infection on the fetus.

References

1. Directorate of General Health Services (BANBACT), Mohakhali, Technical assistance by WHO. Standard operating procedures for Blood Transfusion http://www.who.int/bloodsafety/transfusion_services/sop-bts_bangladesh.pdf?ua=1; 2013. (accessed 04 December 2018).
2. Robinson, A. Harris, S. Atkinson, C. et al. The administration of blood components: a British Society for Haematology Guideline. Transfusion Medicine, 2018, 28, 3–21 (with audit templates) https://b-s-h.org.uk/guidelines/guidelines/administration-of-blood-components/ (accessed 05 March 2019).
3. World Health Organization New Delhi. Model Standard Operating Procedures for Blood Transfusion Service. http://apps.searo.who.int/PDS_DOCS/B0235.pdf?ua=1; 2002. (accessed 04 December 2018).
4. WHO Expert Committee on Biological Standardization. WHO Technical Report Series 1004 Annex 3: Guidelines on management of blood and blood components as essential medicines. http://www.who.int/bloodproducts/brn/ManBloodEM_GL_WHO_TRS_1004_web_Annex_3.pdf?ua=1; 2017. (accessed 04 December 2018).
5. "Blood Group Allele Tables." Red Cell Immunogenetics and Blood Group Terminology, International Society of Blood Transfusion, https://www.isbtweb.org/working-parties/red- cell-immunogenetics-and-blood-group-terminology. Accessed 27 June 2021.
6. Milkins C, Berryman J, Cantwell C, Elliott C, Haggas R, Jones J, M. Rowley,M. Williams & N.Win Guidelines for pre-transfusion compatibility procedures in blood transfusion laboratories British Committee for Standards in Haematology 2013;23:3-9. https://b-s- h.org.uk/guidelines/guidelines/pre-transfusion-compatibility-procedures-in-blood- transfusion-laboratories/
7. Davis BA, Allard S, Qureshi A, Porter JB, Pancham S, Win N, Cho G, Ryan K. Guidelines on red cell transfusion in sickle cell disease. Part I: principles and laboratory aspects. British Committee for Standards in Haematology 2017;176:179-191. https://b-s- h.org.uk/guidelines/guidelines/red-cell-transfusion-in-sickle-cell-disease-part-I/
8. Transfusion Science Standing Committee Australian & New Zealand Society of Blood Transfusion. Guidelines for transfusion and immunohaematology laboratory practice; Revised 1st Edition January 2020. Available at: https://anzsbt.org.au/wp- content/uploads/2021/01/FINAL-Guideline_- for_Transfusion_and_Immunohaematology_Laboratory_Practice_Published_20210125.pdf.
9. AABB. Standards for Blood Banks and Transfusion Services. 30th ed: 2016.
10. Joint United Kingdom Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee. In: Norfolk D, editor. Handbook of Transfusion Medicine. https://www.transfusionguidelines.org/transfusion-handbook; 2014. (accessed 04 December 2018).
11. Canadian Blood Services. Visual Assessment Guide https://professionaleducation.blood.ca/sites/msi/files/VAG_en.pdf; 2009. (accessed 04 December 2018).
12. Lima A. Bloody Easy-Blood Administration. http://nurses.transfusionontario.org/; 2015. (accessed 04 December 2018).
13. New Zealand Blood Service. Transfusion Medicine Handbook. https://www.nzblood.co.nz/assets/Transfusion-Medicine/PDFs/Transfusion-Medicine- Handbook-2016.pdf; 2016. (accessed 04 December 2018).
14. Callum JL, Pinkerton PH, Lima A, Lin Y, Karkouti K, Lieberman L, Pendergrast JM, Robitaille N, Tinmouth AT, Webert KE. Bloody Easy 4. 2016. http://transfusionontario.org/en/documents/?cat=bloody_easy (accessed 04 December 2018).
15. Blood Book: Australian Blood Administration Handbook 2020. https://transfusion.com.au/bloodbook
16. Handin RI, Lux SE, Stossel TP. Blood: Principles and Practice of Hematology: Lippincott Williams & Wilkins; 2003.
17. McCullough J. Transfusion Medicine. Oxford: John Wiley & Sons; 2011.
18. Canadian Blood Services. Clinical Guide to Transfusion. Ed. Clarke G, Charge S. https://professionaleducation.blood.ca/en/transfusion/clinical-guide-transfusion;2017. (accessed 04 December 2018).
19. New HV, Berryman J, Bolton-Maggs PH, Cantwell C, Chalmers EA, Davies T, et al. Guidelines on transfusion for fetuses, neonates and older children. British journal of Haematology 2016;175(5):784-828. https://b-s-h.org.uk/guidelines/guidelines/transfusion-for-fetuses-neonates-and-older- children
20. National Blood Authority. Patient Blood Management Guidelines: Module 6 Neonatal and Pediatrics; Quick Reference Guide, https://www.blood.gov.au/pbm- 2017. Accessed 04 Dec 2018
21. Prokopchuk Gauk O, Solh Z. Clinical Guide to Transfusion, Chapter 15 CMV Seronegative, Irradiated and Washed Blood Components. Canadian Blood Services; 2017. https://profedu.blood.ca/en/transfusion/clinical-guide/cmv-seronegative-irradiated-and- washed-blood-components (accessed 04 December 2018).
22. Prokopchuk Gauk O, Morrison D. Recommendations for use of irradiated blood components in Canada. National Advisory Committee on Blood and Blood Products. http://www.nacblood.ca/resources/guidelines/downloads/Recommendations_Irradiated_Bloo d_Components.pdf (accessed 04 December 2018).
23. Kopolovic I, Ostro J, Tsubota H, Lin Y, Cserti-Gazdewich CM, Messner HA, Keir AK, DenHollander N, Dzik WS, Callum J. A systematic review of transfusion-associated graft- versus-host disease. Blood 2015 126:406-414. https://doi.org/10.1182/blood-2015-01-62087
24. British Society for Haematology. Use of irradiated blood components, https://b-s-h.org.uk/guidelines/guidelines/use-of-irradiated-blood-components/; 2010. (accessed 04 December 2018).

Suggested reading

Immunohaematology laboratory practice

Transfusion Science Standing Committee Australian & New Zealand Society of Blood Transfusion. Guidelines for transfusion and immunohaematology laboratory practice; Revised 1st Edition January 2020. https://anzsbt.org.au/wp-content/uploads/2021/01/FINAL-Guideline_- for_Transfusion_and_Immunohaematology_Laboratory_Practice_Published_20210125.pdf

Pre-transfusion testing

Milkins C, Berryman J, Cantwell C, Elliott C, Haggas R, Jones J, M. Rowley,M. Williams & N.Win Guidelines for pre-transfusion compatibility procedures in blood transfusion laboratories British Committee for Standards in Haematology 2013;23:3-9. https://b-s-h.org.uk/guidelines/guidelines/pre-transfusion-compatibility-procedures-in-blood- transfusion-laboratories/

Blood administration

Robinson, A. Harris, S. Atkinson, C. et al. The administration of blood components: a British Society for Haematology Guideline. Transfusion Medicine, 2018, 28, 3–21 (with audit templates) https://b-s-h.org.uk/guidelines/guidelines/administration-of-blood-components/

CHAPTER 5

GENERAL MEDICINE AND HAEMATOLOGY

Key points

1. This chapter covers selected medical disorders in which anaemia or cytopenias are important.

2. Blood transfusions should only be given if clinically indicated and not solely because an arbitrary threshold of haemoglobin or platelet concentration has been reached.

3. Transfusions should not be initiated if the patient is stable, physiologically adapted and the cytopenias are likely to improve with non-transfusion measures.

5.1 Introduction

This chapter covers many complex medical disorders whose management often requires blood transfusions. In patients with severe thalassaemia and sickle cell disorders, red cell transfusions together with medical management are essential for increasing survival. Bone marrow failure syndromes often require repeated administration of blood components, together with specialized interventions. For the bleeding disorders, recent advances in medical therapy can reduce the reliance on transfusions. Anaemia due to haematinic deficiencies and malaria, significant causes of morbidity in many parts of the world, can usually be managed without red cell transfusions. While newer drugs have transformed human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDs) into a chronic disease, blood transfusion remains an important cause of HIV transmission.

While the salient features of selected medical disorders are discussed in this chapter, these are not meant to replace guidelines or textbooks. The physiology of body fluids, anaemia and aspects of blood components and apheresis have been extensively reviewed in other chapters. These topics should be revisited as needed in addition to studying the sections in this chapter.

Learning outcomes

After reading this chapter, the reader will be able to understand the principles of diagnosis and management of major inherited and acquired haematological and general medical conditions which may require management including transfusion support.

5.2 Deficiency of haematinics

The commonest haematinic deficiencies encountered globally are of iron, vitamin B12 and folic acid. Examples of the various causes of these deficiencies are given in Table 5.1.

Table 5.1. Major causes of hematinic deficiencies

Hematinic	Iron	Vitamin B12	Folic acid
Dietary insufficiency	Vegetarian diet	Vegetarian diet	Poor diet
Increased requirement	Growth, pregnancy, menstrual loss	NA	Growth, pregnancy, chronic haemolytic anaemias, exfoliative skin diseases, some medications
Reduced absorption	Malabsorption syndromes	Pernicious anaemia (absent intrinsic factor), impaired absorption in terminal ileum, fish tapeworm, bariatric surgery	Malabsorption syndromes
Blood loss	Menstrual loss, uterine pathology Gastrointestinal bleeding	NA	NA

NA, not applicable.

Iron deficiency

Worldwide, half the cases of anaemia are due to iron deficiency, which causes microcytic, hypochromic anaemia, with low ferritin unless co-existing inflammation is present, in which case the ferritin may be within the normal range. In severe iron deficiency, koilonychia and cheilosis may be seen *(1)*.

Treatment of iron deficiency

The following aspects are important in treating iron deficiency:

- Treat the underlying cause.
- Hookworm infestation is a major cause of iron deficiency in many regions due to ongoing, low-grade gastrointestinal (GI) blood loss.
- In adult males and menopausal women, iron deficiency anaemia should lead to investigations of GI blood loss, especially malignancy.
- Other causes of microcytic hypochromic anaemia should be considered (for example, haemoglobinopathies (thalassaemias), inflammation and, rarely, sideroblastic anaemia).
- Oral and intravenous (IV) iron replacement should be administered as appropriate and tolerated by the patient.

Vitamin B12 and folate deficiency

Both vitamin B12 and folate deficiencies can cause megaloblastic anaemia characterized by macrocytosis and hypersegmented neutrophils. Patients with severe vitamin B12 deficiency can show associated neurological deficits.

Vitamin B12 has the following characteristics:

- It is present in non-vegetarian foods.
- The daily requirement is 2.5 µg.
- The body stores between 2 and 5 mg (adequate for 1–2 years).
- It is absorbed through the terminal ileum and requires gastric intrinsic factor.
- A very small amount (<1%) is passively absorbed throughout the GI mucosa.

Folic acid has the following characteristics:

- It is present in plant- and animal-derived foods and is destroyed by prolonged boiling.
- The daily requirement is 100–200 µg.
- The body stores 5–20 mg (adequate for 3 to 4 months only).

- Deficiency develops rapidly if there is fast cell turnover as in chronic haemolytic anaemia.
- It is absorbed through the upper small intestine.

Treatment of vitamin B12 and folate deficiency

Treatment should take into account the following:

- If the patient has symptomatic anaemia, neurological deficits (vitamin B12 deficiency), or when treating pregnant women or neonates, urgent replacement is recommended.
- Treatment may need to be indefinite.
- Do not give folic acid alone if there is concomitant vitamin B12 deficiency, as it might precipitate a neurological crisis due to vitamin B12 being diverted to haemopoiesis.
- Intramuscular (IM) or deep subcutaneous vitamin B12 and oral preparations are available as cyanocobalamin and hydroxycobalamin.
- Parenteral vitamin B12 is recommended initially (to overcome potential poor absorption).
- The typical adult parenteral vitamin B12 dose is 1000 µg once or twice a week until deficiency (and anaemia) is corrected, then once every 1 to 3 months for maintenance *(2, 3)*.
- Oral vitamin B12 can also be used in patients with malabsorption, at a dose of 1000– 2000 µg daily, as this allows passive absorption without the need for intrinsic factor or absorption at terminal ileum.
- Oral folic acid, 400 µg daily, is adequate for treating folate deficiency. For megaloblastic anaemia 5 mg a day (up to 15 mg in severe malabsorption) is recommended *(2, 3)*.

5.3 Haemolytic anaemias including glucose-6-phosphate dehydrogenase (G6PD) deficiency

Haemolytic anaemia (HA) is suspected when anaemia not related to blood loss, haematinic deficiency or bone marrow failure is seen in a patient with clinical and laboratory features of haemolysis and compensatory erythropoiesis.

In a classical presentation of HA, there is anaemia, jaundice, splenomegaly, reticulocytosis, unconjugated hyperbilirubinaemia, increased lactate dehydrogenase (LDH) and low haptoglobin. Most HAs are extravascular and splenomegaly is a feature of reticuloendothelial expansion. Aspects of clinical and laboratory features are shown in Table 5.2. HA is not a single disease, and each cause has protean manifestations.

Hereditary haemolytic anaemias

Hereditary haemolytic anaemias are classified as:

- membrane defects, for example, hereditary spherocytosis

- haemoglobin defects, for example, sickle cell disease and thalassaemia (discussed in section 5.6)
- enzyme deficiencies, for example, G6PD deficiency.

Acquired haemolytic anaemias

Acquired haemolytic anaemias can be classified as:

- immune-mediated, for example, autoimmune haemolytic anaemia (AIHA); or
- non-immune.

G6PD deficiency

- G6PD deficiency is an X-linked inherited disorder affecting red blood cells (RBCs) in which haemolysis is typically precipitated by an acquired factor.
- G6PD generates NADH and protects RBCs from oxidative injury.
- It is prevalent in regions where malaria was/is endemic.
- Variants of G6PD deficiency are seen.
- Clinical manifestations range from asymptomatic, episodic acute haemolysis to chronic haemolysis.
- Acute haemolysis is precipitated by certain foods (fava beans), drugs (primaquine) or infection.
- Haemolysis is both extravascular and intravascular.
- Peripheral blood smear shows microspherocytes, "bite" cells. Special stains show Heinz bodies.

Management principles

- In acute, severe HA, the rate of decline of haemoglobin and the patient's clinical status determines the management.
- A rapid fall in haemoglobin can be fatal and requires immediate intervention, including red cell transfusions and IV fluids. Consultation with blood bank and haematology experts is recommended.
- For acquired HA, if immune haemolysis is suspected, a direct antiglobulin test (DAT) (Coombs' test) should be performed. A positive result suggests immune-mediated haemolysis, like AIHA. Note that there is a high rate of positivity of DAT caused by antibodies that are unlikely to cause haemolysis.
- In chronic compensated HA, avoid transfusions when possible.
- Other tests should be directed by findings from patient history, examination and peripheral blood film (Table 5.2).

Specific treatment

- *G6PD deficiency*: remove offending agent (drugs, food), transfuse red cells if required for symptomatic anaemia. Transfused blood will not be haemolysed. Provide a list of drugs and foods to be avoided.
- *AIHA*: steroids, splenectomy, rituximab, immune suppression, treat underlying disease. Blood typing and crossmatching may be a challenge *(4)*.
- *Infection-related*: treat infection such as sepsis and malaria.
- *Acute intravascular haemolysis*: transfuse red cells if symptomatic, hydrate to reduce renal damage.
- *Supportive*: prescribe folic acid, avoid iron replacement (unless the patient is also iron deficient).

Table 5.2. Special features of haemolytic anaemia

Clinical feature	**Implications and conclusions**
Pallor, jaundice, splenomegaly	Triad suggestive of haemolytic anaemia, features nonspecific
History of blood transfusion in past 2– 4 weeks	May suggest acute or delayed haemolytic transfusion reaction
Recent fever, infection, medication	Haemolysis related to infection or drugs (immune-related, G6PD)
Laboratory finding	
Macrocytosis, reticulocytosis, polychromasia	Suggests compensatory erythropoiesis (these features also present after acute blood loss, or in response to haematinics)
Increased bilirubin (unconjugated) and LDH	Levels depend on severity of haemolysis
Haptoglobin reduced to absent	Low or unmeasurable levels in intravascular haemolysis
Haemoglobinaemia, haemoglobinuria, haemosiderinuria	Suggests intravascular haemolysis, can lead to renal failure. Causes: haemolytic transfusion reactions, G6PD deficiency, burns, severe sepsis, severe AIHA, falciparum malaria, traumatic (bongo drummers, march haemoglobinuria)
Spherocytes in blood film	Classically in AIHA and hereditary spherocytosis
Schistocytes in blood film	Traumatic haemolysis, thrombotic microangiopathy
Intracellular organisms	Malaria or other parasites
Sickle cells	Sickle cell disease
Hypochromic microcytic cells	Thalassaemias, iron deficiency
Bite cells and blister cells	Suggestive of oxidative haemolysis due to G6PD deficiency or oxidative medications
Target cells	Seen in thalassaemia and haemoglobinopathies

LDH, lactate dehydrogenase; G6PD, glucose-6-phosphate dehydrogenase; AIHA, autoimmune haemolytic anaemia.

5.4 Malaria

Etiology

Malaria is caused by one of five species of plasmodium: *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale* and *P. knowlesi*. Transmission is mainly by the bite of an infected female *Anopheles* mosquito, but in rare cases, it may occur after transfusion of infected blood or transplacentally. In 2016, there were an estimated 216 million cases of malaria worldwide, with 90% in Africa, followed by South-East Asia.

Pathogenesis

The plasmodium life cycle takes place in two hosts:

- human: asexual cycle, termed schizogony.
- mosquito: sexual cycle in female *Anopheles* mosquitoes.

Clinical features

The incubation period of malaria varies from 9 to 40 days, depending on the species. The classical features are fever with chills and rigours, occurring in paroxysms. Severe malaria requires urgent intervention.

Diagnosis

Microscopic demonstration of the malarial parasite remains the gold standard. Thin and thick blood smears, stained with Giemsa, are required. A thick film is more sensitive than thin film, but not adequate to detect species or degree of parasitaemia. Microscopic diagnosis requires a trained operator.

Rapid diagnostic tests (RDTs), using finger-prick blood to detect antigens specific to the species of plasmodium have high sensitivity, but need quality control. These are particularly useful in areas where microscopy is not available. The RDTs are:

- histidine rich protein (HRP2): for *P. falciparum*;
- LDH: can be specific for *P. vivax* and *P. falciparum* or pan-malarial;
- aldolase: pan-malarial aldolase.

Management

The most important antimalarial drugs are listed in Table 5.3. The choice of antimalarial therapy is determined by the prevalent plasmodium species as well as the drug resistance patterns and is best summarized by the regional malaria control programme. For severe malaria, parenteral therapy is recommended. Various artemisinin-based combination therapies (ACT) are available. WHO-recommended fixed-dose combinations are preferred. For chloroquine-sensitive plasmodium species (for example, *P. vivax*), chloroquine can be used *(5)*.

Table 5.3. Drugs for the treatment of clinical malaria

Most effective agents for drug-sensitive plasmodium species	Artemisinin derivatives (artesunate, artemether, dihydroartemisinin), chloroquine, amodiaquine, mefloquine, quinine, lumefantrine
Synergistic lower efficacy drugs	Doxycycline, sulfonamides, pyrimethamine
Artemisinin-based combination therapies (ACT)	artesunate + amodiaquine; artemether + lumefantrine; artesunate + mefloquine; artesunate + sulfadoxine-pyrimethamine; dihydroartemisinin + piperaquine
Gametocidal and for exo-erythrocytic stages (radical cure)	Primaquine (can cause haemolysis in G6PD deficiency)

G6PD, glucose-6-phosphate dehydrogenase.

Blood transfusion

The decision to transfuse blood is based on the degree and rapidity of anaemia development, the physiological state of compensation and availability of safe blood. As a general guideline, transfusion should be considered if the haemoglobin level falls to below 7 g/dl in adults and to below 5 g/dl in children based on their symptoms and signs.

5.5 HIV/AIDS

HIV infection and AIDS is caused by viruses belonging to the family of human retroviruses and the subfamily of lentiviruses, mainly HIV-1 and occasionally HIV-2.

Transmission

The highest risk of acquiring HIV per exposure is after transfusion of blood contaminated with the virus. Other modes of transmission are sexual, needle-stick and transplacental. However, blood transfusion is a rare cause of HIV transmission in many countries as the risk of transmission has been greatly reduced by the implementation of appropriate procedure for donor selection and the blood screening.

Stages and clinical course of HIV infection.

After viral transmission to an individual, there are classically three clinical stages.

1. Acute HIV infection: the patient may be entirely asymptomatic, or develop a viral "infectious mononucleosis" type of illness with fever, myalgias, sore throat, adenopathy and skin rash. The HIV viral load is high.

2. Chronic HIV infection without AIDS.

3. AIDS: characterized by a CD4 count <200 cells/mm^3 or any AIDS-defining condition.

AIDS-defining illnesses can be classified according to infecting organism, pathology or organ involvement with different clinical manifestations. A high index of suspicion is required to diagnose underlying HIV/AIDS. A simplified categorization is given in Table 5.4.

Table 5.4. AIDS-defining conditions

AIDS-defining illnesses, classified in broad groups	
Bacterial infections (multiple, recurrent)	• Salmonella septicaemia • Pneumonia
Fungal infections	• Candidiasis • Coccidiodomycosis • Cryptococcosis • Histoplasmosis • *Pneumocystis jirovecii* pneumonia
Viral	• Cytomegalovirus (CMV) disease (other than liver, spleen, lymph nodes), retinitis • Herpes simplex: chronic ulcers or bronchitis, oesophagitis, pneumonitis
Mycobacterium	• *Mycobacterium tuberculosis* • *Mycobacterium avium* complex or *kansasii* or other species: disseminated or extrapulmonary
Parasitic	• Toxoplasmosis of the brain • Cryptosporidiosis, chronic intestinal
Central nervous system	• Progressive multifocal leukoencephalopathy (PML) • Encephalopathy attributed to HIV
AIDS-defining illnesses, classified in broad groups	
Malignancy	• Cervical cancer, invasive • Kaposi's sarcoma • Lymphoma: Burkitt's • Lymphoma: immunoblastic • Lymphoma: primary brain
Wasting syndrome of brain	

Source: Adapted from Centers for Disease Control and Prevention *(6)*.

Management

Individuals infected with HIV are treated with combination antiretroviral therapy (ART). This treatment has led to a major reduction in morbidity, mortality and spread of disease by reducing viral loads. An ART regime generally consists of three agents, a dual nucleoside combination plus a third agent from another class to prevent and treat any resistant strains (Table 5.5).

Due to provision of low-cost generic drugs, funding and political support, the availability of ART in low- and middle-income countries has increased tremendously. Different strategies and drug combinations are being used in various countries and the regional recommendations should be followed.

Table 5.5. Drugs used in the treatment of HIV/AIDS

Class of drugs	Specific medications
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)	Lamivudine, zidovudine, tenofovir, abacavir, emtricitabine
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Nevirapine, efavirenz, etravirine, rilpivirine
Protease inhibitors	Ritonavir, darunavir, atazanavir
Entry inhibitors	Maraviroc, enfuvirtide
Integrase inhibitors	Raltegravir, elvitegravir, dolutegravir

Anaemia and blood transfusion in HIV/AIDS patients

There are multiple causes of anaemia in people living with HIV/AIDS, including chronic inflammation, infections, medications and deficiencies *(7)*. Management is symptomatic with treatment of the cause. Transfusions are indicated as per the recommendations given in earlier sections.

5.6 Bone marrow failure

Bone marrow (BM) failure results in an inability to produce adequate blood cells, which manifests as anaemia, leukopenia and thrombocytopenia – alone or in combination as pancytopenia. Examples of the various causes are shown in Table 5.6.

Table 5.6. Examples of causes of bone marrow (BM) failure

Mechanism	Main causes
Hypocellular BM	
Aplastic anaemia	• Idiopathic in 70–80% of cases • Post-hepatitis (likely autoimmune): 10–15% of cases • Some medications for example, chloramphenicol • Inherited: Fanconi's anaemia and many other causes now increasingly recognized using molecular diagnostics
Hypoplastic with abnormal cells	• Hypoplastic myelodysplastic syndrome (MDS) • Hypoplastic acute leukaemia
Cellular BM	
Infiltration	Acute leukaemia, lymphoma, myeloma, metastasis
Megaloblastic	Vitamin B12 or folate deficiency
Normal hypercellular	Hypersplenism
Systemic disease	Kala-azar, tuberculosis

Clinical manifestations

The clinical manifestations are caused by the cytopenias as well as the underlying disorders.

- *Anaemia*: in BM failure, the fall in the haemoglobin level is generally slow (at 1 g/dl per week) unless there is bleeding or haemolysis.

- *Thrombocytopenia*: bleeding is mainly in the skin (petechiae, ecchymosis) and mucosa (gums, epistaxis, GI bleeding, menorrhagia). Spontaneous serious bleeding occurs if platelets levels are <10 000/µl (intracranial, retinal, GI), while bleeding after trauma or surgery may occur with milder thrombocytopenia.

- *Neutropenia*: sudden onset of severe infections (bacterial or fungal) can occur when absolute neutrophil count is <500/µl.

Underlying disease-related features vary according to the underlying cause, which includes a wide range of inherited and acquired disorders.

Investigations

The most important investigations are complete blood counts (CBC), peripheral blood film and BM examination. Further investigations depend on the likely cause, and may include flow cytometry, cytogenetics and microbiological testing.

Management

The management of BM failure syndromes is complex and based on the underlying cause. An outline is given in Table 5.7. Aplastic anaemia is relatively more common in low- and middle-income countries and treatment requires sophisticated resources *(8)*.

The indications for transfusion of blood components are covered in other sections. Due care should be taken to minimize risks of alloimmunization and transfusion-related infections. Use of granulocyte colony-stimulating factor (G-CSF) and tranexamic acid are covered in other chapter.

Table 5.7. Principles of management of BM failure syndromes

Cause	Treatment
Supportive care	
Anaemia	Transfuse red cells if anaemia is symptomatic and severe
Thrombocytopenia	• Platelet transfusions if bleeding, or prophylactically • Tranexamic acid
Neutropenia	Use G-CSF selectively in life-threatening infection. Granulocyte transfusion can be considered in very severely infected patients if resources are available
Infection and fever	Use antibiotics and antifungal agents early, empirically. See guidelines on "febrile neutropenia"
Exposure to toxins	Stop exposure to potentially myelotoxic drugs or chemicals

Cause	Treatment
Specific treatment	
Aplastic anaemia	Based on resources and etiology: • Allogeneic bone marrow transplantation (BMT) if a donor is available and age of patient is <40–50 years • Anti-thymocyte globulin and cyclosporin if no donor is available or age of patient is >40–50 years • Anabolic steroids, eltrombopag
Megaloblastic anaemia	Vitamin B12, folic acid
Infective causes	Treat the infection
Malignancy-related	Specialized oncology therapy

G-CSF, granulocyte-colony stimulating factor.

5.7 Genetic disorders of haemoglobin

Genetic disorders of haemoglobin are the most important inherited monogenic disorders and beta- thalassaemia and sickle cell disease are the most frequent of these. These haemoglobinopathies are seen predominantly in malaria-endemic areas, as the carrier state provided a survival advantage against the severe types of malaria.

Sickle cell disease (SCD) is a qualitative globin defect. This is due to an abnormal beta-globin allele carrying the sickle mutation, which leads to sickle cell trait or SCD. There are three states:

- Homozygous state (HbSS): this is the most severe.
- Compound heterozygous states (HbSC, HbS/beta thal): these tend to be less severe than HbSS.
- Carrier state: HbAS: this is not usually clinically significant.

In sub-Saharan Africa, more than 300 000 newborns have HbSS, while the trait is present in 10–20% of the population in central Africa.

Thalassaemias are quantitative globin defects. Mutations in the alpha- or beta-globin genes lead to reduced or absent alpha or beta chain production, termed as thalassaemia. The most severe form is beta- thalassaemia in which the beta-globin chain is reduced or absent.

Sickle cell disease

Sickle haemoglobin is less soluble than adult or fetal haemoglobin and deoxygenated sickle haemoglobin (HbS) undergoes polymerization, binding to the RBC membrane, which increases its rigidity. The affected RBC morphologically resembles a sickle. Intravascular sickling causes vaso-occlusion of microcirculation, release of cytokines, leukocyte interactions with tissue ischaemia and damage.

The diagnosis of SCD is made after birth as the fetal haemoglobin declines. Investigations include microscopy (sickle cells), haemoglobin electrophoresis, high performance liquid chromatography (HPLC) and/or DNA testing. For low-resource countries, point-of-care (POC) testing can be used for screening. In a recent trial a POC test kit, using test

strips embedded with monoclonal antibodies against haemoglobin A, S and C, could detect them by visual inspection in about 10 minutes at a low cost (<US$ 2 per test) *(9)*. Other technologies that simplify detection of SCD are being developed and tested.

The main complications seen in sickle cell anaemia can be acute or chronic. They include:

- Vaso-occlusive crises: pain crisis, acute chest syndrome, stroke, priapism, renal infarction and splenic infarction.
- Infections (due to splenic dysfunction) and sepsis: pneumococcal, haemophilus influenza and meningococcal infection.
- Acute crises characterized by a sudden fall in the haemoglobin level, which can be life- threatening:
  - aplastic crisis: mainly due to parvovirus B19 infection, with a sudden drop in reticulocytes, resolving in 2–4 weeks;
  - splenic sequestration: sudden pooling of blood in the spleen;
  - haemolytic crisis: exacerbation of haemolysis.
- Chronic organ damage: neurological decline, pulmonary arterial hypertension, renal impairment, sickle nephropathy, pigment gall stones, jaundice, folic acid deficiency and iron overload.

Management

The principles of management are outlined below:

- Infection prevention: immunization (pneumococcal haemophilus and meningococcal), penicillin prophylaxis
- Pain control: analgesia, hydration, oxygen, hydroxyurea
- Acute crisis: exchange RBC transfusion whenever possible, otherwise RBC transfusions
- Acute organ dysfunction: hydration, consider exchange transfusion
- Chronic organ damage: hydroxyurea, regular transfusions
- Folic acid deficiency: regular folic acid
- Iron overload: iron chelators.

Hydroxyurea is a useful drug which induces production of fetal haemoglobin (HbF) and has shown clinical efficacy in reducing acute vaso-occlusive events, chronic organ damage, infection, malaria, transfusion and death *(10)*. Treatment with hydroxyurea should be initiated in childhood, with a recommended starting dose of 15–20 mg/kg per day and subsequently increased to the maximum tolerated dose.

Transfusions in sickle cell disease

Blood transfusions are indicated in specific situations for sickle cell anaemia for the following reasons:

1. To increase tissue oxygenation by increasing HbA in acute anaemic crises.

2. To decrease the percentage of sickle haemoglobin to <30% to reduce viscosity, sickling and subsequent vaso-occlusion.

3. To suppress endogenous erythropoiesis.

When there is an urgent need to reduce the percentage of HbS, exchange RBC transfusion can be done by trained personnel, if facilities exist.

Beta-thalassaemia

Homozygous beta-thalassaemia results in reduced production of beta chains, leading to accumulation of unpaired alpha-chains, which precipitate and cause ineffective erythropoiesis and haemolysis of red cells. Combinations of the beta-thalassaemia allele with haemoglobin variants (HbS or HbE) result in varying clinical phenotypes.

Beta-thalassaemia is diagnosed by microscopy (microcytic hypochromic RBCs), haemoglobin electrophoresis, HPLC and/or genetic testing. It is important to take a sample before any blood transfusion.

Although beta-thalassaemia is traditionally classified as thalassaemia major, intermedia and minor, a more practical classification is:

- transfusion-dependent thalassaemia (TDT): requiring regular blood transfusion, before the age of 2 years; or
- non-transfusion-dependent thalassaemia: requiring occasional transfusions at times of growth, surgery, pregnancy and stress.

Heterozygous beta-thalassaemia (minor or carrier state) is typically asymptomatic, with only mild hypochromic microcytic anaemia.

Clinical features of beta-thalassaemia (TDT)

- Anaemia: presents by 6–12 months of age, severe haemoglobin deficiency (3–4g/dl).
- Jaundice: haemolysis, gallstones, viral hepatitis (transfusion-related).
- Hepatosplenomegaly: extramedullary haemopoiesis, haemolysis.
- Skeletal deformities: facial changes, deformities in bones.
- Iron overload: skin pigmentation, cardiac, liver and endocrine damage.
- Endocrinopathies: hypogonadism, hypothyroidism, diabetes mellitus (due to iron overload).

The principles of management are given in Table 5.8. With regular blood transfusion and iron chelation, patients who adhere to their treatment have a near normal lifespan *(11)*.

Table 5.8. Management of transfusion-dependent thalassaemia

Measure	Rationale and precautions
Blood transfusion	Keep pretransfusion haemoglobin levels between 9 and 10 g/dl
Iron chelation	Start soon after regular transfusions begin. Available agents: • Deferoxamine: parenteral, subcutaneous, requires pump • Deferiprone: oral, three times a day • Deferasirox: oral once a day
Splenectomy	Beneficial in reducing transfusion requirements in selected cases
Allogeneic bone marrow transplant	Potentially curative; best results if performed in the first decade of life

5.8 Congenital bleeding and clotting disorders

Features suggestive of bleeding disorders (hereditary or acquired) are:

- spontaneous bleeding
- excessive bleeding after trauma, dental extraction, or during menstruation or childbirth
- delayed bleeding after surgery or trauma
- bleeding from multiple sites.

Disorders of bleeding are classified into three main types:

1. Platelet disorders: these include skin bleeding (petechiae, bruising) or from the mucosa (epistaxis, menorrhagia).
2. Coagulation disorders: these include joint bleeding, muscle bleeding, and bleeding during or after trauma or surgery.
3. Vascular disorders: these resemble platelet bleeding disorders.

Investigations

Specific tests for bleeding disorders are platelet counts, prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time (TT) and, rarely, skin bleeding time. Specific coagulation factor assays are required to diagnose factor deficiencies and platelet aggregation testing is needed to diagnose platelet disorders. Genetic tests for detecting mutations related to congenital coagulopathies can be done in reference laboratories.

Features suggestive of congenital bleeding disorders are:

- family history
- early age of onset

- typical presentation (joint bleeds in patients with haemophilia).

The most severe congenital bleeding disorders are haemophilia A and B, which are due to deficiency of Factor VIII and Factor IX, respectively *(12)*.

- Haemophilias are X-linked recessive disorders (affecting male children of maternal carriers); one third are due to spontaneous mutation.
- Haemophilia A is more common and accounts for 80–85% of all haemophilias.
- Severity depends on level of factor and can be classified as mild, moderate or severe.
- Diagnosis: prolonged aPTT, low Factor VIII or Factor IX level, genetic diagnosis.
- Treatment: factor concentrate replacement can be:
  - episodic (on demand); or
  - prophylactic home-/outpatient-based (to prevent damage).
- Musculoskeletal management is comprehensive and team-based.
- For appropriate care those affected should carry identification with their diagnosis and information on its severity.
- Establish a network of haemophilia treatment centres, based on local resources and in partnership with international centres of excellence.

Von Willebrand disease (VWD) is the most common inherited bleeding disorder and is caused by a decrease in the level or activity of Von Willebrand factor (VWF). It has the following characteristics:

- mostly autosomal dominant
- clinically presents as platelet disorder (platelet plug formation is impaired)
- diagnosis is by low VWF antigen and activity and low Factor VIII.

Treatment is as described below.

Management principles for common congenital bleeding disorders

1. Avoid antiplatelet drugs: for example, aspirin, non-steroidal anti-inflammatory drugs (NSAIDs).
2. Avoid intramuscular injections.
3. Antifibrinolytic drugs are useful in mild, mainly mucosal bleeding.
4. Desmopressin (DDAVP) releases Factor VIII and VWF from storage pools, raising levels 3- to 5-fold in patients with mild haemophilia A and most types of VWD. It is also useful in the treatment of platelet dysfunction.

5. Factor VIII concentrates, either fractionated plasma-derived (containing other clotting factors) or recombinant can be given.

6. Factor IX concentrates, either fractionated plasma-derived or recombinant can be given.

7. VWF, either fractionated plasma-derived (in factor VIII concentrates) or recombinant can be given.

8. Cryoprecipitate contains fibrinogen, Factor VIII, Factor XIII and VWF but should only be used when fractionated or recombinant specific factor replacement therapy is not available.

9. Fresh frozen plasma (FFP) should only be used when fractionated or recombinant specific factor replacement therapy is not available.

10. Blood transfusion should be used only for replacement of red cells.

The optimum management of haemophilia and VWD requires raising deficient factors to appropriate levels, which is not effectively achievable with FFP, cryoprecipitate or fresh blood. In resource-poor regions, where these are the only products available, they may be used in emergency life- and limb-saving situations. However, they are associated with poorer outcomes and a risk of transfusion-transmitted infections.

5.9 Acquired bleeding and clotting disorders

Features suggestive of bleeding disorders have been described in section 5.7. In contrast to haemophilia where joint bleeding is common, acquired coagulation disorders are characterized by large ecchymoses, deep tissue haematomas and internal bleeding. The major causes of acquired coagulation disorders and their management are outlined below. Important investigations are: platelet counts, PT, aPTT, TT and fibrinogen. Coagulation factor assays, fibrin degradation products (FDP) and platelet function tests may be required in special cases.

Blood components may be required for treatment of severe anaemia (red cell transfusions) or to prevent bleeding (platelet concentrates or clotting factors).

Coagulation disorders

1. *Disseminated intravascular coagulopathy* is characterized by:

   - bleeding from multiple sites and venepuncture sites;

   - usually being caused by an underlying etiology, such as:
     - trauma, burns
     - sepsis
     - obstetric complications
     - snake-bite
     - cancer.

- prolonged PT, aPTT, TT, low platelets, low fibrinogen, increased FDPs, thrombotic microangiopathy and intravascular haemolysis;

- Treatment *(13)*:
  - Treat underlying cause, which determines outcome.
  - Replace deficient clotting factors (plasma transfusion) and platelets when indicted.
  - Avoid heparin.

2. *Vitamin K deficiency* (malabsorption, malnutrition), or vitamin K antagonist anticoagulants (warfarin):

   - PT and international normalized ratio (INR) prolonged (low levels of factors II, VII, IX and X).

   - Treatment:
     - In the case of vitamin K deficiency or if anticoagulation is not required, administer vitamin K, 10 mg orally or intravenously, for 3 days.
     - If anticoagulation is essential, administer:
       - prothrombin complex concentrate (PCC) or FFP
       - low-dose vitamin K <1 mg
       - optimize dose of anticoagulant.

3. *Coagulopathy of liver disease*:

   - Initially PT is prolonged, later aPTT and TT are prolonged and there is a deficiency of most clotting factors.

   - If bleeding is significant, replace clotting factors with FFP or cryoprecipitate.

4. *Heparin overdose*:

   - aPTT and TT are typically prolonged.

   - Stop heparin and use antidote.

5. *Overdose of low-molecular-weight heparin or non-vitamin K antagonist oral anticoagulants (NOAC)*:

   - Routine coagulation tests may be normal.

   - Access to reversal agents varies per country or region.

   - These agents generally have a short half-life: withhold medication; if needed use PCC if available, and supportive care.

   - Other conditions are beyond the scope of this chapter. Seek specialist advice on their diagnosis and management.

Platelet disorders

1. *Immune thrombocytopenia (ITP)*

   - ITP reduces platelet counts (due to increased destruction). Coagulation test (for example, PT, aPTT) results should be normal. BM examination may be normal or it can show an increased number of megakaryocytes (performing a BM biopsy is not routinely required in typical ITP).

   - Treatment:
     - Avoid platelet transfusions unless bleeding is life-threatening (as platelets will be destroyed).
     - Administer steroids or intravenous immunoglobulin (IVIG) as initial therapy if treatment is required. Subsequent therapeutic options include, splenectomy, rituximab, immunosuppressive agents.
     - Administer antifibrinolytics such as TXA.
     - Avoid antiplatelet drugs: for example, aspirin, NSAIDs.

2. *Congenital causes of thrombocytopenia*, due to reduced production:

   - low platelet count, may have other features associated with underlying cause;

   - BM: depends on underlying cause (for example, amegakaryocytic thrombocytopenia);

   - management: refer to section 5.5 (Bone marrow failure).

3. *Platelet dysfunction*

   - mostly due to medications like aspirin;

   - normal platelet counts, abnormal platelet function tests (not required if cause is obvious);

   - stop the drug if possible – bleeding is self-limiting;

   - give platelet transfusion for significant bleeding.

5.10 Management of burn patients

Burns cause injury to the skin and other tissues due to heat. They are classified according to the depth of injury:

1. superficial: epidermal;

2. partial-thickness: includes portions of dermis;

3. full thickness: all layers of dermis and often subcutaneous tissue injured;

4. extension to deep tissues (fourth-degree): underlying soft tissue.

Various methods are available to assess total body surface area (TBSA).

- Rule of nines (valid for adults): head is 9% TBSA, each arm 9%, each leg 18%, anterior and posterior trunk are each 18%, and perineum is 1%.
- Palm method: the palm of the patient's hand including fingers is 1% TBSA.

The extent (surface area) of burns determines whether a patient should be transferred to a specialized unit. The patient should be transferred to a burns unit if burns affect >10% of body surface area in children or elderly people, or >20% in adults. Transfer to a burns unit is also necessary if >5% of the body surface area is affected by full thickness burns and also if burns involve the face, eyes or genitalia, as well as for patients with inhalation burns.

Patients need urgent resuscitation with maintenance of airways, breathing and circulation. Fluid replacement is required in adults if burns affect >15% of the body surface area (10% in children), to ensure organ perfusion with the aim of urine output between >0.5 and 1.0 ml/kg per hour or 30–50 ml per hour in adults. The following are also required:

- disability control
- pain control
- management of hyper-catabolism
- infection prevention
- wound care.

In regions where there are no dedicated burns centres, the survival chances of patients with >50% burns are very low. If there are multiple patients with burns injuries, triage may be required to save the greatest number.

Blood transfusion in burns patients

In patients with severe burns, or when more than 10% of the body surface area is involved, it is common for anaemia to develop due to acute thermal injury, as well as blood loss following skin grafting and surgery.

Formerly, it was common practice to transfuse blood to keep haemoglobin levels >10 g/dl. More recent studies suggest that the transfusion trigger should be reduced and liberal blood transfusion (i.e., transfusion of RBCs at higher haemoglobin thresholds) may be detrimental *(14)*.

- Anaemia is well tolerated so long as intravascular volume is maintained.
- There is no universal haemoglobin threshold value for blood transfusion in burns patients. It should be based on the patient's clinical condition, physiological state, blood volume and need for surgical intervention.
- Supplementation with folic acid and vitamin B12 should be considered.
- Iron supplementation should be avoided, as iron therapy can increase the risk of infections and production of free radicals.

References

1. Camaschella C. Iron-deficiency anemia. N Engl J Med. 2015;372:1832–43.
2. Devalia V, Hamilton MS, Molloy AM. Guidelines for the diagnosis and treatment of cobalamin and folate disorders. Br J Haematol. 2014;166:496–513.
3. Hoffbrand V. Megaloblastic anemias. In: Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J, editors. Harrison's principles of internal medicine. New York (NY): McGraw-Hill; 2015.
4. Go RS, Winters JL, Kay NE. How I treat autoimmune hemolytic anemia. Blood. 2017;129:2971– 79.
5. White NJ, Pukrittayakamee S, Hien TT, Faiz MA, Mokuolu OA, Dondorp AM. Malaria. Lancet. 2014;383:723–35.
6. Selik RM, Mokotoff ED, Branson B, et al. Revised surveillance case definition for HIV infection — United States, 2014. MMWR 2014;63(RR03):1-10. (https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6303a1.htm, accessed 24 January 2021).
7. Fekene TE, Juhar LH, Mengesha CH, Worku DK. Prevalence of cytopenias in both HAART and HAART naive HIV infected adult patients in Ethiopia: a cross sectional study. BMC Hematol. 2018;18:8. doi: 10.1186/s12878-018-0102-7.
8. Young NS. Aplastic anemia. N Engl J Med. 2018;379:1643–56.
9. Steele C, Sinski A, Asibey J, Hardy-Dessources M-D, Elana G, Brennan C et al. Point-of-care screening for sickle cell disease in low-resource settings: A multi-center evaluation of HemoTypeSC, a novel rapid test. Am J Hematol. 2019;94:39–45.
10. Tshilolo L, Tomlinson G, Williams TN, Santos B, Olupot-Olupot P, Lane A et al. Hydroxyurea for children with sickle cell anemia in sub-Saharan Africa. N Engl J Med. 2019;380:121–131.
11. Cappellini MD, Porter JB, Viprakasit V, Taher AT. A paradigm shift on beta-thalassaemia treatment: How will we manage this old disease with new therapies? Blood Rev. 2018;32:300– 11.
12. Srivastava A, Brewer AK, Mauser-Bunschoten EP, Key NS, Kitchen S, Llinas A et al. Guidelines for the management of hemophilia. Haemophilia. 2013;19:e1–47.
13. Squizzato A, Hunt BJ, Kinasewitz GT Wada H, Ten Cate H, Thachil J, et al. Supportive management strategies for disseminated intravascular coagulation. An international consensus. Thromb Haemost. 2016;115:896–904.
14. Curinga G, Jain A, Feldman M, Prosciak M, Phillips B, Milner S. Red blood cell transfusion following burn. Burns. 2011;37:742–52.

Suggested reading

Ware RE, de Montalembert M, Tshilolo L, Abboud MR. Sickle cell disease. Lancet. 2017;390:311–23.

Dunkley S, Lam JCM, John MJ, Wong RSM, Tran H, Yang R et al. Principles of haemophilia care: The Asia-Pacific perspective. Haemophilia. 2018;24:366–75.

Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: Recommendations for a public health approach. Geneva: World Health Organization; 2013 (https://www.who.int/hiv/pub/guidelines/arv2013/download/en/, accessed 24 January 2021).

Guidelines for the treatment of malaria, third edition. Geneva: World Health Organization; 2015 (https://www.who.int/malaria/publications/atoz/9789241549127/en/, accessed 24 January 2021).

Farmakis D, Angastiniotis M, Eleftheriou A. A short guide to the management of transfusion dependent thalassaemia. Nicosia: Thalassemia International Federation; 2017 (https://issuu.com/internationalthalassaemiafederation/docs/short_guide-low_res, accessed 24 January 2021).

CHAPTER 6

OBSTETRICS: DIAGNOSIS AND MANAGEMENT OF ANAEMIA IN THE OBSTETRIC PATIENT

Key points

1. Anaemia in pregnancy is defined as a haemoglobin concentration of less than 11 g/dl in the first and third trimesters, and 10.5 g/dl in the second trimester.

2. The diagnosis and effective treatment of chronic anaemia in pregnancy is an important way of reducing the need for future transfusions. The decision to transfuse blood should not be based on haemoglobin levels alone, but also on the patient's clinical need.

3. Blood loss during normal vaginal delivery or caesarean section does not normally necessitate transfusion provided that the maternal haemoglobin level is above 10.0–11.0 g/dl before delivery. The haemoglobin concentration should return to normal by 2 weeks postpartum. If this does not happen, further investigation is required.

4. Obstetric bleeding may be unpredictable and massive. Every obstetric unit should have a current protocol for major obstetric haemorrhage and all staff should be trained to follow it.

5. If disseminated intravascular coagulation is suspected, do not delay treatment while waiting for the results of coagulation tests.

6. The administration of anti-RhD immunoglobulin to all RhD-negative mothers within 72 hours of delivery is the most common approach to the prevention of Rhesus disease of the newborn.

6.1 Introduction

Chronic anaemia and acute blood loss in pregnancy are major causes of maternal morbidity and mortality worldwide. Anaemia in pregnancy also increases the likelihood of intrauterine growth retardation, premature birth and fetal loss. Anaemia in pregnancy and its effects on maternal and perinatal morbidity and mortality can be avoided by effective prevention and treatment. It is therefore essential to identify anaemia and take early corrective measures. This will minimize the risks to mother and child and reduce the need for transfusion if obstetric haemorrhage occurs.

The goal of this chapter is to provide information on the natural changes of pregnancy that impact haematological parameters and guidance on pre-emptive measures that can be taken to improve the outcome for both mothers and their newborn children.

Learning outcomes

After studying this chapter, the reader should be able to:

1. Describe the haematological changes in pregnancy.
2. Make an informed assessment of the obstetric patient and be able to diagnose chronic anaemia.
3. Promote preventive measures to reduce chronic anaemia in the obstetric patient.
4. Provide appropriate treatment for the obstetric patient with chronic anaemia.
5. Provide appropriate treatment for the obstetric patient with acute blood loss.
6. Identify the fetus at risk of haemolytic disease and take measures to prevent haemolytic disease of the fetus and newborn (HDFN).

6.2 Physiological and haematological changes during pregnancy

During pregnancy, several haematological changes occur. These are described in the following sections.

Plasma volume

There is a 40–50% increase in plasma volume, which reaches its maximum by week 32 of gestation. This is accompanied by a similar increase in cardiac output. These changes:

- increase blood supply to the uterus;
- increase the excretory capacity of the kidneys;
- help dissipate heat produced as a result of the elevated metabolic rate during pregnancy;

- protect the fetus against impaired placental perfusion as a result of aortal-caval compression by the gravid uterus.

Red blood cells

The mother's red cell mass increases by 18–25% during pregnancy. This occurs more slowly than the increase in plasma volume and is of smaller magnitude. As a consequence, pregnancy is naturally associated with a physiological anaemia (also referred to as dilutional anaemia). It is important to note that an elevated haemoglobin concentration during pregnancy may be a sign of pre-eclampsia in which plasma volume is reduced.

Iron metabolism

The mother's iron requirement is increased during the last two trimesters of pregnancy because of the demands of the fetus and the increase in maternal red cell mass. Up to 80% of the increased requirement occurs in the last trimester. The total iron requirement over the whole pregnancy is approximately 1300 mg (Fig. 6.1), which is made up of:

- 300 mg for the fetus
- 50 mg for the placenta
- 450 mg for the increase in the maternal red cell mass
- 250 mg for the mother's "basal" iron losses
- 250 mg for blood loss during a normal vaginal delivery (500 ml).

Although intestinal iron absorption increases during pregnancy, dietary iron intake may not be able to meet the increased iron requirement. Thus the body's iron stores may be drawn upon to compensate. If these stores are inadequate, the mother will become anaemic if iron supplements are not given.

Coagulation and fibrinolytic systems

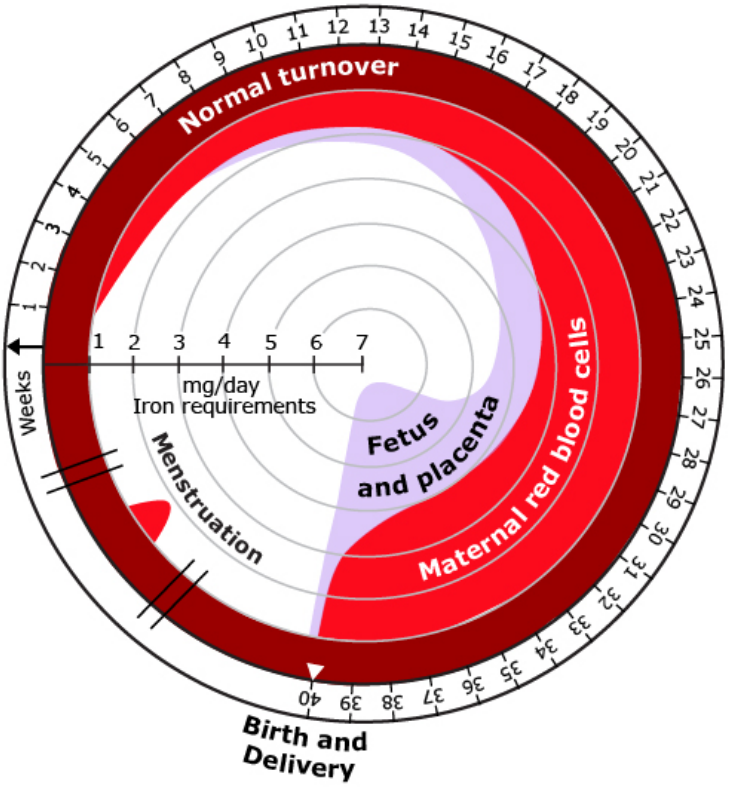
For more information, see section 1.2 in Chapter 1: General physiology.

During pregnancy, a physiological hypercoagulable state develops. There is an increase in both platelet activation and the levels of coagulation factors, particularly fibrinogen, Factor VIII and Factor IX. In addition, the fibrinolytic system is suppressed. The effect is to protect the mother from haemorrhage during labour and delivery. However, these changes also result in an increased susceptibility to thromboembolism.

ACTIVITY 6.2

Identify any gaps in your knowledge and understanding of the physiological and haematological changes in pregnancy that might affect your assessment and management of obstetric patients.

Figure 6.1. Iron requirements during pregnancy



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6.3 Chronic anaemia in pregnancy

Anaemia in pregnancy, as defined by the World Health Organization (WHO), is a haemoglobin concentration of less than 11 g/dl in the first and third trimesters. In the second trimester, a fall of 0.5 g/dl due to increased plasma volume is allowed for and a cut-off value of 10.5 g/dl is used, as shown in Table 6.1.

Table 6.1. Defining anaemia in pregnancy

Stage of pregnancy		Anaemic if less than (g/dl)
First trimester	0–12 weeks	11.0
Second trimester	13–28 weeks	10.5
Third trimester	29 weeks–term	11.0

6.3.1 Causes of anaemia

The two most common causes of anaemia in pregnant women are physiological anaemia, due to the expansion of plasma volume as described in section 6.1, and iron deficiency. However, it is important to consider other etiologies of anaemia during the evaluation of a pregnant woman who presents with anaemia.

Iron deficiency

Several factors may contribute to iron deficiency in pregnant women. The most common cause, particularly in resource-limited settings, is insufficient dietary intake of foods rich in iron or limited access to foods that enhance iron absorption (see Table 6.2).

Table 6.2. Food sources and iron

Iron-rich foods	Liver
	Beef
	Turkey
	Shrimp
	Beans
	Lentils
	Enriched cereals
Iron absorption-enhancing foods	Citrus fruits (oranges, grapefruit)
	Strawberries
	Broccoli
	Peppers
Iron absorption-diminishing foods	Dairy products
	Soya products
	Coffee/tea
	Spinach

Additional contributors to iron deficiency include parasitic infections (for example, hookworm and schistosomiasis), which can rapidly lead to iron deficiency anaemia in individuals whose dietary intake of iron is low and whose body iron stores are already depleted. Depletion may be due to blood loss during prior pregnancies and/or menstruation, or short birth intervals, since it may take up to 2 years to replenish pre-pregnancy iron stores.

Folate deficiency

Folate requirements during pregnancy increase by up to eightfold above the non-pregnant state, especially in the last trimester and during lactation. Body stores of folate are limited and dietary folate may be insufficient. Consequently, anaemia (either macrocytic or normocytic) may develop. Because folate deficiency may occur in addition to iron deficiency anaemia it is important to consider the possibility of folate deficiency in a pregnant woman who shows a poor response to iron supplementation.

Vitamin B12 deficiency

Deficiency of vitamin B12 is due to malabsorption or to dietary deficiency. Fortunately, dietary deficiency is rare, but should be suspected in the following circumstances:

- patients who decline to eat any animal protein (vegans);
- patients from populations whose diet contains little or no animal protein; and

- patients at risk for malabsorption secondary to bariatric surgery involving the ileum.
- HIV infection

If a patient has anaemia with leukopenia, thrombocytopenia, lymphadenopathy and/or oral candidiasis, consider the possibility of HIV infection.

Malaria

Haemolysis due to malaria is an important cause of severe anaemia in pregnancy. If malaria is suspected in a pregnant woman, early diagnosis and treatment is essential to minimize the risk of maternal morbidity and mortality and the need for transfusion. For women diagnosed with uncomplicated *Plasmodium falciparum* infection in the first trimester of pregnancy, the WHO guidelines recommend 7 days of treatment with quinine and clindamycin.[1] Artemisinin-based combination therapy is recommended for women diagnosed in the second or third trimester of pregnancy. Women diagnosed with uncomplicated *P. vivax, P. ovali, P. malariae* or *P. knowlesi* infection should be treated with chloroquine (or quinine in chloroquine-resistant areas) during the first trimester of pregnancy and with artemisinin-based combination therapy if diagnosed in the second or third trimester.

Sickle cell disease

Anaemia in sickle cell disease is usually severe and may be exacerbated by acute sequestration of sickled cells in the spleen or, more commonly, by the aplastic crisis that occurs when bone marrow red cell production slows down during acute infections. Folate deficiency is common in sickle cell disease because of high red cell turnover. Because the body does not excrete iron and recycles the iron from the red cells, iron deficiency in women is no more common than in the general population.

6.3.2 Assessment of chronic anaemia in pregnancy

When anaemia is detected, it is important to determine the cause and assess its severity, including any evidence of clinical decompensation (see Table 6.3).

Table 6.3. Clinical assessment of anaemia in pregnancy

Clinical history	
Nonspecific symptoms of anaemia	Tiredness/loss of energy
	Light-headedness
	Shortness of breath
	Headache
	Ankle swelling
	Worsening of any pre-existing symptoms, e.g. angina
History and symptoms relating to the underlying disorder	Nutritional deficiency: poor dietary history
	Short birth intervals
	Previous history of anaemia
Bleeding during current pregnancy	

[1] For the latest updates to WHO recommendations, consult the website (https://app.magicapp.org/#/guideline/4807).

Physical examination	
Signs of anaemia and clinical decompensation	Pale mucus membranes (palms, nailbeds)
	Rapid breathing
	Tachycardia
	Raised jugular venous pressure
	Heart murmurs
	Ankle oedema
	Postural hypotension
	Altered mental state
Signs of an underlying disorder	
Evidence of blood loss	

Assessment should be based on:

- patient's clinical history;
- physical examination; and
- laboratory investigations to determine the specific cause of anaemia: for example, serum ferritin, folate, or vitamin B12 deficiency.

6.3.3 Prevention and management of chronic anaemia in pregnancy

The prevalence of anaemia during pregnancy can be reduced by:

- prevention and management of nutritional anaemia; and
- adequate antenatal care.

The following measures are particularly important in preventing nutritional anaemia in pregnant women.

- education about nutrition, food preparation and breastfeeding, with particular emphasis on the effects on the fetus and newborn;
- the provision of adequate maternal and child health care; and
- access to family planning information, education and services.

Nutritional supplementation

Iron

Dietary sources of iron: Iron deficiency is mainly due to inadequate nutrition and resource limitations precluding access to iron-rich foods. It is important to be aware of the two types of dietary iron (haem and non-haem) since their bioavailability differs:

- Haem iron is well-absorbed and is present in foods of animal origin, such as meat, poultry and fish.
- Non-haem iron is poorly absorbed and is present in foods of plant origin, such aswhole grain cereals, tubers and vegetables.

The absorption of non-haem iron requires the presence of vitamin C or meat, poultry or fish in the diet.

Iron supplementation: In pregnant women found to have iron deficiency anaemia, iron repletion with either oral supplementation beyond that available in prenatal vitamin supplements or intravenous administration is recommended (see Table 6.4). Oral iron supplementation at a dose range of 60–200 mg of elemental iron/day is most appropriate for most women who are diagnosed with iron deficiency during the first trimester of pregnancy. It is safe, inexpensive and readily available. To improve adherence, some recommend an alternate-day dosing regimen, which enhances iron absorption and reduces the gastrointestinal discomfort often associated with daily dosing.

Table 6.4. Iron supplements

Preparation	Dose
Ferrous fumarate	106 mg elemental iron per 325 mg tablet
Ferrous sulfate	65 mg elemental iron per 325 mg tablet
Ferrous gluconate	34 mg elemental iron per 300 mg tablet
Iron dextran	50 mg elemental iron per ml, IM or IV
Ferric gluconate	12.5 mg iron per ml, IV only
Iron sucrose	20 mg iron per ml, IV only

IV, intravenous; IM, intramuscular.
Note that other preparations may be available in different locations.

Intravenous iron therapy is reserved for women who cannot tolerate oral iron supplementation or who are identified later in pregnancy (second or third trimester) as being iron deficient. Note that intravenous iron therapy is generally not administered during the first trimester due to lack of safety data for first trimester administration.

It is important to monitor haematological parameters to assess response to iron repletion. In general, if women adhere to the dose regimen for the iron supplements, and no other factors that could impair absorption are identified (for example, underlying malabsorption syndromes), one should expect to see an increase in haemoglobin levels within 2–3 weeks following initiation of repletion therapy.

Folate

Dietary sources of folate: A diet rich in legumes, green leafy vegetables and fortified grains provides sufficient folate for the non-pregnant woman. However, in resource-limited areas, or in countries where fortification has not been mandated, a risk for folate deficiency exists. Thus, folate supplementation in women planning for pregnancy (preconception supplementation) and during pregnancy is recommended.

Folate supplementation: The currently recommended dose for folate supplementation is 400 micrograms/day beginning before conception, or as soon as pregnancy is confirmed, up to 3 months postpartum. Most prenatal vitamin supplements contain 1 milligram folate, more than sufficient to meet the increased demands of pregnancy.

For women with multi-gestation pregnancies, haemolytic disorders or personal or family history of neural tube defects, higher supplementation doses are recommended (5 milligrams).

Vitamin B12

Vitamin B12 supplementation: Pregnant women have a slightly increased daily requirement for vitamin B12, which can be readily met through diet and prenatal vitamin supplements. If there is laboratory evidence for deficiency, oral or parenteral supplementation can be used (1000 micrograms orally, every day, or 1000 micrograms intramuscularly, every 4 weeks).

ACTIVITY 6.3

Look back at section 6.3. What factors can cause anaemia during pregnancy?

Review the records of the last 25 obstetric patients at your hospital. Note the haemoglobin levels recorded during pregnancy.

- How many of the pregnant women had their haemoglobin level or haematocrit measured during the last trimester?
- How many were anaemic?
- How many were prescribed iron?

Do your findings indicate appropriate care of women during pregnancy? If not, talk to senior colleagues about any steps that could be taken to improve their care.

ACTIVITY 6.3.1

Are any guidelines available in your hospital on the assessment and management of chronic anaemia in pregnancy? Are they accurate and comprehensive? Are they used systematically by all health workers involved in antenatal care?

If there are no guidelines or you think they could be improved, prepare some draft guidelines and discuss them with senior colleagues.

6.4 Major obstetric haemorrhage

Obstetric haemorrhage, defined as excessive bleeding antepartum, intrapartum or postpartum, remains a leading cause of maternal morbidity and mortality worldwide. It may result from excessive bleeding from the placental site, from trauma or both. Uterine atony, or failure of the uterus to contract after delivery is the most common cause of postpartum haemorrhage. There are known risk factors associated with postpartum haemorrhage such as previous postpartum haemorrhage, fetal macrosomia, abnormal placentation and multiple gestation. More than half of women who experience postpartum haemorrhage have no identifiable risk factors. Prompt recognition and management of obstetric haemorrhage reduces the number of maternal deaths.

Major obstetric haemorrhage may or may not present with clear signs of hypovolemic shock as described below. Healthy individuals can successfully compensate for as much as 20 to 25% blood loss before overt signs of hypovolemia are clinically evident. Due to the physiological effects induced by pregnancy, however, women may demonstrate very few signs of hypovolemia even in the face of substantial blood loss. When risk factors for haemorrhage are present or haemorrhage is suspected, thorough assessment of clinical status is essential to detect clinical decompensation.

6.4.1 Signs of hypovolemia in major obstetric haemorrhage

- palpitations
- dizziness
- diaphoresis
- tachypnoea
- increased thirst
- hypotension
- tachycardia
- increased capillary refill time
- reduced urine output
- decreased level (or loss) of consciousness.

6.4.2 Causes of major obstetric haemorrhage

Massive haemorrhage may occur at any time during pregnancy, at time of delivery or most commonly, postpartum. Table 6.5 lists clinical conditions that may result in obstetric haemorrhage.

Table 6.5. Clinical conditions associated with obstetric haemorrhage

Fetal loss in pregnancy which may result in:	Incomplete abortion
	Septic abortion
Ruptured ectopic pregnancy:	Tubal
	Abdominal
Antepartum haemorrhage, which may be caused by:	Placenta previa
	Placental abruption
	Ruptured uterus
	Vasa previa
	Incidental haemorrhage from genital tract
Traumatic lesions including:	Episiotomy
	Laceration of perineum or vagina
	Laceration of cervix
	Ruptured uterus

Primary postpartum haemorrhage, which may be caused by:	Uterine atony
	Retained products of conception
	Traumatic lesions
	Abnormally adherent placenta (accreta)
	Clotting defects
	Acute uterine inversion
Secondary postpartum haemorrhage, which may be caused by:	Puerperal sepsis
	Retained products of conception
	Tissue damage following labour
	Breakdown of uterine wound after caesarean section
Disseminated intravascular coagulation induced by:	Intrauterine death
	Amniotic fluid embolism
	Sepsis
	Pre-eclampsia
	Placental abruption
	Retained products of conception
	Induced abortion
	Excessive bleeding
	Acute fatty liver

6.4.3 Management of major obstetric haemorrhage

The gravid uterus at term has a blood flow > 500 ml per minute through its circulation. Swift compression of the dilated uterine spiral arterioles by the uterine muscles is necessary to prevent excessive blood loss. If the myometrium fails to contract appropriately, rapid blood loss will continue even after the third stage of labour. Should first- and second-line uterotonics such as oxytocin and misoprostol, respectively, fail to control postpartum bleeding, blood product transfusion along with invasive procedures such as intrauterine balloon tamponade, uterine artery ligation and hysterectomy may be needed as life-saving measures. An antifibrinolytic agent such as tranexamic acid is an additional pharmacological agent that may be used in these cases.

The patient's life may depend on a rapid response from the obstetric team. Every obstetric unit should have a clearly defined protocol for managing obstetric haemorrhage and all staff should be trained to follow it. Protocols for massive transfusion and emergency-released blood products should be in place in all maternity units. Box 6.1 provides guidelines for the management of major obstetric haemorrhage.

Box 6.1. Guidelines for management of obstetric haemorrhage

Resuscitate

1. Administer high concentrations of oxygen.
2. Position the patient head down, tilt/raise the legs.
3. Establish intravenous access (if not already present) with two large-bore cannulae (14G or 16G).
4. Infuse crystalloid replacement fluids or colloids as rapidly as possible.
5. Notify the blood bank/activate massive transfusion protocol.
   - 5.1 Give Group O, RhD-negative emergency-released red blood cells until ABO type is known.
   - 5.2 Once antibody screen is completed, give fully crossmatched red cells when available.
   - 5.3 Give AB plasma if ABO type is not known to blood bank.
6. Use a pressure infusion device and warming device, if possible.
7. Call extra staff to assist as necessary.

Monitor/investigate

1. Ensure blood bank has a current sample for crossmatching additional blood products.
2. Order complete blood count and coagulation tests. Continue to monitor.
3. Continuously monitor pulse, blood pressure, capillary refill time and respiratory rate.
4. Insert urinary catheter and measure hourly output.

Stop the bleeding

1. Identify the cause of bleeding.
2. Examine the cervix and vagina for lacerations.
3. If there are retained products of conception and uncontrolled bleeding, treat as disseminated intravascular coagulation (DIC).
4. If uterus is hypotonic/atonic:
   - 4.1 Ensure bladder is empty.
   - 4.2 Give intravenous oxytocin, 20 units.
   - 4.3 Give intravenous ergometrine, 0.5 mg.
   - 4.4 Administer oxytocin infusion (40 units in 500 ml).
   - 4.5 Administer bi-manual compression of the uterus.
   - 4.6 If bleeding continues, administer deep intramuscular or intramyometrial prostaglandin directly into the uterus.
   - 4.7 If bleeding continues consider use of 1 gram (100 mg/ml) intravenous tranexamic acid at a rate of 1 ml/min (given over 10 minutes), as long as it is given within 3 hours of birth.
     - 4.7.1 A second dose of 1 gram tranexamic acid may be given if bleeding continues after 30 minutes, or if bleeding restarts within 24 hours of completing the first dose.
5. Consider surgery/hysterectomy earlier rather than later.

Intraoperative blood salvage

Intraoperative blood salvage may reduce the amount of allogeneic blood products transfused to the woman having a major obstetric haemorrhage.

6.4.4 Disseminated intravascular coagulation

Disseminated intravascular coagulation (DIC) is a cause of massive obstetric haemorrhage. It may be triggered by placental abruption, intrauterine fetal death, eclampsia, amniotic fluid embolism and many other causes. The clinical picture ranges from major haemorrhage with or without thrombotic complications, to a clinically stable state that might only be detected by laboratory testing (Box 6.2 and Table 6.6).

Box 6.2. Management of disseminated intravascular coagulation

1. Treat the cause.
   - Deliver fetus and placenta.
   - Evacuate uterus, as indicated for retained or necrotic tissue.
2. Give uterine stimulants to promote contraction: e.g. oxytocin, ergometrine and/or prostaglandin.
3. Establish intravenous access and begin fluid resuscitation. In many cases of acute blood loss, the development of DIC can be prevented if blood volume is restored with a balanced salt solution: e.g. lactated Ringer's solution.
4. Use blood products to help control haemorrhage.
5. If the patient is massively haemorrhaging, transfuse blood products according to the Massive Transfusion Protocol. If blood loss is less severe, transfuse products according to laboratory values and clinical signs and symptoms.
   - If haemoglobin is < 7 g/dl and the patient is bleeding, transfuse red blood cells.
   - If the prothrombin time and activated partial thromboplastin time is > 1.5 times control, transfuse fresh frozen plasma at 10–15 ml/kg.
   - If platelet count is $< 50 \times 10^9$/L and the patient is bleeding, transfuse one platelet dose (1 apheresis platelet or whole blood-derived equivalent).
   - If fibrinogen is low (< 200 mg/dl) and the woman is bleeding, replace with cryoprecipitate. Give at least 10 packs, prepared from single donor units.
   - If cryoprecipitate is not available, give fresh frozen plasma (10–15 ml/kg): 1 unit for every 2 units of red blood cells or lyophilized human fibrinogen concentrate if available.

ACTIVITY 6.4

Are any guidelines available in your hospital on the management of major obstetric haemorrhage? Are they accurate and comprehensive? Are they used systematically by all staff involved in obstetric care? Are the necessary drugs readily available and easy to access? Does your obstetric unit perform protocol drills? Does your obstetric unit conduct post-event briefs?

If there are no guidelines or you think they could be improved, find out whether any have been produced elsewhere and try to obtain a copy. If none are available, prepare some draft guidelines and discuss them with your colleagues involved in caring for obstetric patients.

Once the guidelines have been agreed upon, organize a teaching session for all obstetric staff.

Monitor whether the guidelines are being used correctly and arrange any further training that may be required.

Table 6.6. Laboratory tests to evaluate for disseminated intravascular coagulation (DIC)

Laboratory tests
Platelet count
Prothrombin time (PT or international normalized ratio (INR))
Activated partial thromboplastin time (aPTT)
Thrombin time (TT): particularly helpful in establishing the presence or absence of DIC
Fibrinogen: normal concentrations at term should be 4.0–6.0 g/L
Fibrin degradation products (FDPs)
If laboratory tests are available, they will show:
Reduced coagulation factors (so all coagulation tests are prolonged)
Low fibrinogen and fibrin degradation products
Low platelet count: $< 50 \times 10^9$/L
Fragmented red blood cells on peripheral smear
If these tests are not available, the following simple test for DIC can be used.
1. Take 2–3 ml of venous blood into a clean plain glass test-tube (10 × 75 mm).
2. Hold the tube in your closed fist to keep it warm (i.e. at body temperature).
3. After 4 minutes, tip the tube slowly to see if a clot is forming. Then tip it again every minute until the blood clots and the tube can be turned upside down.
4. The clot will normally form within between 4 and 11 minutes, but in blood from a woman with DIC, the blood will remain fluid well beyond 15 to 20 minutes.

If DIC is suspected, do not delay treatment while waiting for the results of coagulation tests.

DIC is always secondary to an underlying process. Treatment should be directed towards the precipitating cause. Replacement of blood products is indicated when there is bleeding with acute DIC. The goal is to control the bleeding.

6.5 Haemolytic disease of the fetus and newborn (HDFN)

Fetal red blood cells can enter the maternal circulation throughout gestation. Under normal circumstances, however, feto-maternal bleeding occurs mainly at separation of the placenta during delivery. If the mother lacks blood group antigens from the father that are carried on the fetal red cells, she may produce immunoglobulin (Ig)G antibodies against these antigens. During subsequent pregnancies, these antibodies may cross the placenta and destroy fetal red cells.

Maternal antibodies to fetal red cells may also arise as a result of a previous blood transfusion. These will only affect the fetus if its cells carry the offending red cell antigen.

HDFN due to ABO incompatibility between mother and infant does not affect the fetus in utero but is an important cause of neonatal jaundice.

HDFN due to RhD incompatibility is an important cause of severe fetal anaemia in countries where a significant proportion of the population is RhD-negative. RhD-negative mothers develop antibodies to a RhD-positive fetus, especially when the mother and infant are of the same or compatible ABO blood type. The fetal red cells are haemolysed, causing severe anaemia. The fetus may die in utero or be born with severe oedema, anaemia and jaundice.

Severe neurological damage after birth can be caused by a rapidly rising bilirubin concentration unless this is corrected by exchange transfusion. A skilled specialist team is needed to provide effective antenatal and neonatal care both to the pregnant woman and the newborn.

HDFN due to other blood group antibodies can also occur, in particular anti-c (also within the Rh blood group system) and anti-Kell. These two antibodies, together with anti-D are the only ones likely to cause significant anaemia in utero and to require fetal transfusion, with some very rare exceptions.

6.5.1 Red cell blood group typing and screening for red cell alloantibodies

The ABO and RhD group of all pregnant women should be determined when they first present for prenatal care, and the mother's serum should also be screened for any IgG antibodies to red cells which can cause HDFN or could cause problems in obtaining compatible blood in the event of obstetric haemorrhage.

If antibodies are detected at a prenatal visit, the antibody titre should be monitored to assess for an interval increase that may be indicative of HDFN related to maternal antibody-fetal antigen incompatibility.

If no red cell alloantibodies are detected at the first prenatal visit, the pregnant woman should be re-evaluated by red cell antibody screening at 28–30 weeks gestation.

6.5.2 Management of the alloimmunized pregnant woman

Serial antibody titres

Prenatal history is important in determining optimal management of the alloimmunized pregnant woman. For patients with a previously affected fetus/newborn, serial titres are not recommended.

Rather, fetal well-being should be monitored through noninvasive ultrasound/Doppler technology to determine middle cerebral artery (MCA) velocity, and if required, fetal blood sampling (see below). For patients without a prior history, serial antibody titres every 4 weeks during the second and third trimesters may be helpful to determine risk for affected pregnancies. In general, an antibody titre of 0 to 1:8 predicts low risk for HDFN (except for anti-K where risk for HDFN does not correlate with antibody titre). Critical titres are considered as greater than 1:8 and necessitate monitoring by MCA Doppler or possibly fetal blood sampling.

Paternal red cell antigen typing

Red cell antigen typing of red cells from the father of the baby may help to determine the risk of the fetus' red cells being positive for the antigen to which the maternal antibody is directed. For example, in a case where the mother's antibody screen is positive for anti-K and the father of the baby is K-positive/k-positive (the antithetical allele), the baby has a 50% chance of being positive for the K-antigen. For some red cell antigens, in particular, the RhD antigen, red cell genotyping (where available) may be required to predict risk for fetal red cell antigen status.

Noninvasive monitoring by Doppler middle cerebral artery (MCA) blood flow velocity

Noninvasive monitoring of MCA blood flow velocity has been shown to be highly correlated with previously standard invasive modalities used to assess for HDFN (e.g. amniotic fluid bilirubin analysis). Serial assessment is important to improve the sensitivity and specificity of methods for assessing this risk. In affected pregnancies, as the fetus becomes progressively more anaemic, the MCA blood flow velocity increases. Once a critical threshold is met, fetal blood sampling is recommended to determine haemoglobin and initiate transfusion, if indicated.

Fetal blood sampling (FBS)

If the equipment is available, fetal blood sampling can, in cases of doubt, identify the blood group and the haemoglobin concentration directly. Transfusion via the umbilical cord (intrauterine transfusion) can then be given to correct anaemia.

6.5.3 Prevention of HDFN

Red blood cell selection for females of childbearing potential

To reduce the risk for alloimmunization in females of childbearing potential, several countries endorse the use of antigen-negative red cells for transfusion. Universally, RhD-negative units are selected for transfusion to RhD-negative females (and, in some cases, RhD-untyped females).

Additionally, some European countries endorse the use of K-negative red cells for all females of childbearing potential; and others extend this further to include Rh-c and E, in addition to K- negative units.

RhD immune globulin (RhIg)

The prevention of Rhesus disease of the newborn is based on the use of RhIg in RhD-negative women. RhIg prevents the sensitization and production of antibodies by an RhD-negative mother following exposure to RhD-positive red cells that may have entered the maternal circulation.

Approaches to prevention of Rhesus disease include:

- postpartum administration of RhIg to those RhD-negative women who give birth to an RhD-positive newborn;
- selective administration of RhIg antenatally to cover procedures or accidents in which risk for maternal–fetal blood exchange is high; and
- antenatal prophylaxis.

Postpartum prophylaxis

Postpartum prophylaxis is the most common approach to the prevention of Rhesus disease.

RhIg is administered at a dose of 300 micrograms (1500 IU) intramuscularly to an RhD-negative mother within 72 hours of delivery if the newborn is RhD-positive. A 300 microgram dose of RhIg provides protection for up to 30 ml of fetal whole blood (15 ml of fetal red cells). If a Kleihauer-Betke or other test is performed to assess the volume of fetal blood in the maternal circulation and shows more than 10 ml of fetal red cells in the maternal circulation, additional RhIg must be given at a dose to cover the amount of fetal blood detected. RhIg dosing calculators can be found on the Internet to assist with determination of dose.

Selective prophylaxis

If a potentially sensitizing event (see Box 6.3) occurs during the antenatal period, administration of RhIg is universally recommended. Recommendations on dosing vary according to country of origin and gestational age. Readers are encouraged to review local guidelines for RhIg dosing.

Box 6.3. Selective RhIg prophylaxis in the antenatal period

- Procedures during pregnancy
  - Amniocentesis
  - Cordocentesis
  - Chorionic villus sampling
- Threatened abortion/antepartum haemorrhage
- Abdominal trauma
- External cephalic version
- Intrauterine fetal death
- Therapeutic termination of pregnancy
- Ectopic pregnancy

Antenatal prophylaxis

The introduction of RhIg administration to RhD-negative women following delivery of an RhD- positive baby dramatically reduced the rate of RhD-alloimmunization. The rate was further lowered following introduction of antenatal RhIg administration in the third trimester of pregnancy. Thus, some countries have developed guideline recommendations for antenatal RhIg administration to RhD-negative pregnant females at weeks 28–32 gestation, provided the patient's red cell antibody screen is negative for anti-D.

There are two options for an intramuscular dosage schedule, both of which appear equally effective:

- RhIg administration, no less than 100 micrograms (500 IU), at 28 and 34 weeks.
- RhIg administration, 300 micrograms (1500 IU), at 28 weeks.

Decisions regarding which of the two dosage schedules to adopt should be considered in light of local and national guidelines, patient preference and likelihood of adherence to the treatment (if the first option is selected).

ACTIVITY 6.5

What is the local protocol for monitoring pregnant women with anti-D antibodies or other antibodies? Is it used appropriately and consistently?

Is RhIg readily available in your obstetric unit or clinic? Do you have guidelines in place for antepartum management of the RhD-negative patient and use of RhIg?

If you feel that the procedures are inadequate or ineffective, speak with your senior colleagues to determine how management might be improved.

Suggested reading

Achebe M, Grafter-Gvili A. How I treat anemia in pregnancy: iron, cobalamin, and folate. Blood. 2017;129:940–49.

American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 95. 2008.

Delaney M, Matthews DC. Hemolytic disease of the fetus and newborn: managing the mother, fetus and newborn. Hematology Am Soc Hematol Educ Program. 2015:146–51.

Lockhart E. Postpartum hemorrhage: a continuing challenge. Hematology Am Soc Hematol Educ Program. 2015:132–7.

Vogel JP, Oladapo OT, Dowswell T, Gülmezoglu AM. Updated WHO recommendation on intravenous tranexamic acid for the treatment of post-partum haemorrhage. Lancet Glob Health. 2018;6:e18–e19.

WHO Guidelines for the treatment of malaria, third edition. Geneva: World Health Organization; 2015 (https://www.who.int/malaria/publications/atoz/9789241549127/en/, accessed 25 January 2021).

WHO Recommendations on antenatal care for a positive pregnancy experience. Geneva: World Health Organization; 2016 (https://www.who.int/reproductivehealth/publications/maternal_perinatal_health/anc- positive-pregnancy-experience/en/, accessed 25 January 2021).

WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomized, double-blind, placebo-controlled trial. Lancet. 2017;389:2105–16.

CHAPTER 7

PAEDIATRICS AND NEONATOLOGY

Key points

1. Evidence suggests that restrictive rather than liberal haemoglobin thresholds for red blood cell (RBC) transfusions are efficacious and safe in both neonates and children.

2. Outside the setting of massive or exchange transfusion, the indications for plasma are very limited.

3. Restrictive use of platelet transfusions is also recommended.

7.1 Introduction

This chapter addresses the indications and practical considerations of transfusion of red cells, platelets, plasma and cryoprecipitate in neonates, older infants, children and adolescents. The general aspects of safe preparation and administration of blood are covered elsewhere. This information will therefore not be repeated here, except to highlight areas where special attention and/or special procedures are required when administering transfusions to paediatric patients. Neither will the full range of treatments required for the disorders discussed be covered; it is assumed that clinicians will always strive to provide specific treatment for the underlying disorder leading to the need for transfusion.

Learning outcomes

After reading this chapter, the reader should be able to:

1. List the causes of neonatal anaemia
2. Know when to transfuse and manage hyperbilirubinaemia by exchange transfusions
3. Understand principles of red cell transfusion in patients with sickle cell disease and thalassaemia
4. Manage red blood cell transfusions in sickle-cell disease and thalassaemia patients
5. Understand the practical aspects of red blood cell (or whole blood) transfusion
6. Know when to transfuse platelets, and understand the practical aspects
7. Know when plasma transfusions are indicated, and understand the practical aspects

7.2 Anaemia and red blood cell/whole blood transfusions

Since whole blood (WB) is the only RBC-containing product available in many low-income countries (LIC) and low/middle-income countries (LMIC), we will use the generic term RBC transfusion to refer to a transfusion of an RBC concentrate or a WB unit. For most patients (other than those with sickle-cell disease or thalassaemia), the only appropriate indication for an RBC transfusion is to correct an inadequate (or to avoid an imminent inadequate) oxygen-carrying capacity caused by an inadequate RBC mass that cannot be corrected, in a timely manner, by safer treatments. In this case, the goal of transfusion is to relieve the indication for transfusion and not necessarily to achieve a normal haemoglobin concentration.

Neonatal period (up to 4 months of age)

The mean haemoglobin concentrations at birth of babies born at term, 32 weeks gestation and 28 weeks gestation are 16.5 g/dl, 15 g/dl and 13.5 g/dl respectively. In a term neonate, anaemia at birth is defined as a haemoglobin concentration below 13.5 g/dl; the lower limits of normal for preterm infants are somewhat lower and vary according to gestational age at birth.

Anaemia at birth

Anaemia present at birth may be the result of haemolysis, blood loss or bone marrow failure.

Haemolysis is most often due to haemolytic disease of the newborn (HDN), a chronic, in-utero immune process due to fetal–maternal blood group incompatibility. RhD incompatibility is the most frequent cause of clinically significant HDN whereas other blood group incompatibilities (for example, Kell) are only occasionally the cause. Although ABO fetal–maternal blood group incompatibility is common, this does not usually result in anaemia at birth. Rarely, congenital haemolytic or aregenerative anaemias may cause anaemia at birth.

Blood loss can be antenatal or intrapartum. Antenatal blood loss is most often chronic and is due to transplacental fetal–maternal transfusion or twin–twin transfusion. Intrapartum blood loss is usually acute and may be external (for example, placenta previa, ruptured umbilicus or vasa previa), internal (for example, subperiosteal, subgaleal, intracranial or adrenal haemorrhage, traumatic fracture, extensive bruising or extravasation), or transplacental when umbilical cord obstruction prevents adequate venous return, resulting in fetal–placental transfusion. The haemoglobin level immediately after acute blood loss at delivery is normal but falls within a few hours after fluid equilibration restores blood volume.

Bone marrow failure is uncommon. It may be caused by antenatal infection (for example, rubella or parvovirus B19) or rare genetic diseases (for example, Diamond-Blackfan anaemia).

Postnatal anaemia

All infants show a decline in haemoglobin concentration, known as physiologic anaemia, in the first 8–10 weeks of life when erythropoietin production is transiently low. Haemoglobin concentration in term infants may fall to 9.5-10 g/dl; in preterm infants, these levels may fall to as low as 6–8 g/dl.

Delayed umbilical cord clamping should be performed in both term and preterm neonates who do not require immediate resuscitation. Delayed umbilical cord clamping increases the Hb level at delivery thereby increasing the infant's iron reserves which in turn decreases the nadir of physiologic anaemia and delays or prevents iron deficiency later in infancy. Delays of 1 and 3 minutes deliver about 20 ml/kg and 30 ml/kg of blood, respectively, to the newborn. Umbilical cord milking should be considered if the neonate's gestational age is at least 28 weeks and the clinical condition precludes delayed cord clamping (e.g. need for immediate resuscitation).

In addition to physiologic anaemia, anaemia after birth reflects the level of haemoglobin at birth, the amount of blood drawn for laboratory tests (iatrogenic anaemia), and haemolysis or postpartum haemorrhage, if present. Prevention of iatrogenic anaemia includes limiting blood sampling and using small blood collection containers and micromethods for laboratory studies.

The routine use of erythropoietin to decrease transfusions in preterm infants is not currently recommended.

Indications for RBC transfusions in neonates

Recommended guidelines for RBC transfusions to neonates vary, although, recent guidelines generally suggest quite restrictive haemoglobin thresholds. Suggested guidelines are shown in Table 7.1 (*1*, *2*).

Table 7.1. Suggested indications for neonatal transfusions[a]

Acute blood loss	≥ 10% TBV and signs of decreased oxygen delivery
	≥ 20% TBV
Chronic anaemia[c]	Moderate–significant mechanical ventilation and Hb ≤ 10 g/dl[b]
	Minimal mechanical ventilation and Hb ≤ 8 g/dl[b]
	Supplemental oxygen without mechanical ventilation and Hb ≤ 7 g/dl
	No supplemental oxygen, no signs of anaemia and Hb ≤ 7 g/dl and reticulocytes ≤ 100×10^9/L

TBV – total blood volume; term neonates = 85 ml/kg; preterm neonates = 100 ml/kg.

[a] Table does not apply to neonates with ongoing haemolysis.

[b] Adapted from reference (*1*); some guidelines (*2*) suggest slightly higher thresholds particularly in preterm neonates born < 32 weeks gestation.

Hyperbilirubinaemia and exchange transfusion

Worldwide, severe hyperbilirubinaemia, i.e. total serum bilirubin > 428 µmol/L (25 mg/dl) places hundreds of thousands of newborns at high risk of death or incapacitating long-term disability (kernicterus) due to acute bilirubin encephalopathy (ABE). The underlying cause of severe hyperbilirubinaemia is most often haemolysis due either to HDN or G6PD deficiency. Non-haemolytic risk factors for severe hyperbilirubinaemia include prematurity, infection, dehydration and caloric deprivation, birth trauma, enclosed blood collections, and family or sibling history of severe neonatal jaundice. Often there are multiple causes.

Newborns with haemolytic disease are at risk of ABE and kernicterus at lower levels (≥ 342 µmol/L or 20 mg/dl) than healthy term infants who may tolerate serum bilirubin levels up to 428 µmol/L (25 mg/dl). Critically high total bilirubin levels for preterm newborns have not been firmly established. The risk of kernicterus is high for all infants with bilirubin levels ≥ 513 µmol/L (30 mg/dl) and is increased by prematurity, haemolysis, sepsis, acidosis, hypoxaemia and hypoalbuminaemia, or exposure to drugs that displace indirect bilirubin from albumin. The threshold for initiating phototherapy depends upon postnatal age, the rate of total bilirubin rise and individual risk factors, and is generally 103–120 µmol/L (6–7 mg/dl) below the critical threshold for exchange transfusion.

The purpose of neonatal exchange transfusion (ET) is to prevent or treat ABE by rapidly removing unconjugated bilirubin from the circulation and tissues. If immune haemolysis is present, ET will also remove sensitized RBCs and plasma antibodies. ET is urgent whenever there are clinical signs of ABE or when total serum bilirubin reaches critical levels above which the risk of ABE is known to be high.

Thresholds for initiating phototherapy and ET are detailed in the *American Academy of Pediatrics Clinical practice guideline* (*3*). Although unconjugated indirect bilirubin is the neurotoxic agent, it is important to note that these guidelines are based on total serum bilirubin (indirect (unconjugated) + direct (unconjugated) bilirubin). The thresholds reflect optimal conditions in high-income countries (HIC); in LIC and LMIC with limited resources, treatment thresholds may need to be lowered based on the anticipated rate of bilirubin rise, personnel and equipment available, and expected delays in setting up equipment or obtaining blood.

An isovolumetric double-volume ET can be performed using the push-pull method via the umbilical vein (see Box 7.1) or simultaneously using the umbilical artery for blood removal and the umbilical venous line for blood infusion (*4*). The umbilical venous catheter is inserted only far enough to get good blood return and should be removed after the ET unless a second exchange is anticipated soon afterwards. If so, fluid must be continuously infused through a well-secured umbilical catheter to prevent blood stasis and clotting.

Box 7.1. Neonatal exchange transfusion (ET) procedure using a single blood vessel[a]

1. Give nothing by mouth during and for at least 4 hours after ET. Empty the stomach if the infant was fed within 4 hours of the procedure.
2. Closely monitor vital signs including heart and respiratory rates, temperature and pulse oximetry before, during and after ET. Have resuscitation equipment ready.
3. Using sterile technique, insert umbilical venous line just far enough to get good blood return (in a term infant about 5 cm from the level of the abdominal wall). Secure the line with tape or surgical suture.
4. Prewarm blood only if an approved, quality-controlled warmer is available. Do not use a water bath.
5. Exchange 10–15 ml increments in full-term infants and smaller volumes in preterm infants. Each cycle should be performed slowly, over about 4 minutes.
6. Agitate the blood unit intermittently to prevent red cell sedimentation.
7. If there is electrocardiogram (ECG) evidence of hypocalcaemia (prolonged Q-T intervals) or, if no ECG is available, clear clinical signs (jitteriness or tremor, especially with stimulation) slowly give 1–2 ml of 10% calcium gluconate solution intravenously. Flush tubing with normal saline before and after calcium infusion. Monitor for bradycardia during calcium infusion.
8. To complete a two-volume ET, transfuse 160–180 ml/kg for a full-term infant and 200 ml/kg for a preterm infant.
9. Send the last aliquot of blood withdrawn to the laboratory for determination of haemoglobin or haematocrit, blood glucose, total bilirubin, potassium and calcium, and group and crossmatch.
10. Post-exchange, continuously infuse a glucose-containing intravenous fluid to prevent hypoglycaemia.

[a] See the text for choice of blood product to use and reference (*4*) for further details about exchange transfusion.

At least two people are needed to perform an ET: one to perform the exchange and the other to record each infusion/withdrawal of blood, track the volume of blood exchanged and continuously monitor vital signs. ET should be performed by trained personnel in a location where monitoring and resuscitation equipment is available. Intensive phototherapy should be started as soon as possible while preparations for ET are underway, continued during the exchange, if possible, and continued after completion of the exchange.

A double-volume ET replaces approximately 85% of the infant's blood volume and lowers the total bilirubin level by approximately one half of the pre-exchange level. Following ET, the total bilirubin level rises to approximately two thirds of the pre-exchange level. Additional ET may be necessary.

For ABO incompatibility the ideal blood product for ET is reconstituted WB prepared by removing the supernatant fluid from a group O RBC concentrate and adding an equal volume of group AB plasma or plasma of the same ABO group as the patient. Where this cannot be easily or properly prepared, group O WB may be used, preferably a unit with low-titre anti-A/B. For other indications, WB or reconstituted WB of the patient's ABO group should be used. In the case of blood group incompatibility (other than ABO), the WB or RBC concentrate should be antigen-negative for the implicated antibody.

Potential complications of ET are summarized in Box 7.2.

Box 7.2. Potential complications of exchange transfusion[a]

Cardiovascular

- Portal vein thrombosis, other thromboemboli
- Blood vessel injury
- Dysrhythmias
- Volume imbalance
- Cardiorespiratory arrest
- Electrolyte and metabolic imbalances
- Hyperkalaemia
- Hypernatraemia
- Hypocalcaemia
- Hypoglycaemia
- Acidosis

Haematological

- Anaemia/polycythemia
- Thrombocytopenia

Infectious

- Sepsis
- Transfusion-transmitted infections

Miscellaneous

- Air emboli
- Necrotizing enterocolitis

[a] See also reference (*4*).

Older infants and children/adolescents

The WHO definitions of anaemia in infants and children are shown in Table 7.2 (*5*). WHO does not use separate definitions for normal haemoglobin concentrations according to ethnicity although it is now accepted that the lower limits of normal for haemoglobin concentrations in black persons are approximately 5–10% lower in childhood and 10–15% lower in adulthood than those of Caucasians. These differences are important when considering the presence or absence of anaemia but are not significant when considering the need for transfusion.

Table 7.2. WHO haemoglobin levels to diagnose anaemia at sea level (g/L)

Population	Non-anaemia (g/L)	Anaemia		
		Mild (g/L)	Moderate (g/L)	Severe (g/L)
Children 6–59 months of age	≥ 110	100–109	70–99	< 70
Children 5–11 years of age	≥ 115	110–114	80–109	< 80
Children 12–14 years of age	≥ 120	110–119	80–109	< 80
Non-pregnant women (15 years of age and above)	≥ 120	110–119	80–109	< 80
Pregnant women	≥ 110	100–109	70–99	< 70
Men (15 years of age and above)	≥ 130	110–129	80–109	< 80

Adapted from reference (*5*).

A systematic analysis of the global prevalence and burden of anaemia (as determined by years lived with disability) from 1990 to 2010 published in 2014 (*6*), using definitions of anaemia and its severity similar to those published by WHO, reported the overall global prevalence of anaemia in 2010 to be 32.9% (mild 18.4%, moderate 13.5%, severe 1.1%). The prevalence and burden of anaemia are inversely related to country income levels, with the highest burden in the LIC of sub-Saharan Africa (SSA). In all regions of the world, the burden is highest in women and children under 5 years of age, and those under 5 years had the least favourable changes between 1990 and 2010. Globally, iron-deficiency anaemia (IDA) is the most common etiology, while other causes of anaemia vary widely by geography, age and sex. For children in LIC and LMIC, the commonest causes of anaemia, after IDA, are malaria, hookworm infection (categorized separately from IDA) and haemoglobinopathies.

Indications for RBC/WB transfusions in general paediatric patients

Evaluation of an anaemic patient

Ideally decisions on RBC transfusion should be based on objective measurements of inadequate systemic and/or regional oxygen delivery. Unfortunately, such measurements are not readily available, even in high-resource settings. Thus, the haemoglobin concentration is the single most important laboratory measurement in determining the need for transfusion. A haemoglobin level should be obtained prior to any RBC transfusion. Except in a patient with extreme pallor, even experienced clinicians are not always able to accurately estimate haemoglobin concentration from a physical examination. Studies in low-resource settings have shown that not obtaining, or possibly not following up on ordered haemoglobin testing, can lead to inappropriate administration of RBC transfusions (*7*). While inappropriate use of RBC transfusions is a concern, equally or even more concerning, are the number of severely anaemic children in LIC and LMIC who do not receive RBC transfusion in a timely manner. Several studies from SSA have shown that critically ill children who present to acute care units with haemoglobin concentrations less than 5 g/dl are at risk of increased mortality if not transfused within 8 hours of presentation (*7, 8*). The reasons for not administering transfusions to these children are multifactorial: the main reason, unfortunately, is the lack of available blood. However, there are also reports that suggest that the lack of transfusion may, in some cases, be due to the failure to recognize the presence of severe anaemia.

Although haemoglobin concentration is a critical factor in deciding whether to administer an RBC transfusion, it is rarely the only factor to consider. Otherwise healthy adults and children have an impressive capacity to increase oxygen delivery to tissues as haemoglobin levels decrease, particularly if the decrease occurs slowly. Children with chronic anaemia, such as IDA due to inadequate iron intake or hookworm infection, may tolerate haemoglobin concentrations below 4–5 g/dl without need for transfusion if iron supplementation plus other treatments, as appropriate, can be

assured. By contrast, in situations such as acute haemorrhage without volume replacement, a seemingly "moderate" degree of anaemia may require urgent transfusion.

In determining the need for RBC transfusion in a child with severe (and sometimes moderate) anaemia, the following clinical factors should be considered:

- general state of health: well, mildly–moderately ill or critically ill
- nutritional status
- haemodynamic stability
- likely timeframe for the development of the anaemia: acute, subacute or chronic
- likely etiology: is correction possible with treatment other than blood transfusion?
- comorbidities that could affect adaptation/tolerance to anaemia and/or response to other treatments
- symptoms and signs to suggest that the anaemia is compensated or uncompensated.

Other questions to ask are:

- If the child is bleeding or has a history of bleeding, is the bleeding controlled or ongoing? What is the extent of the blood loss?
- Is there a need for an invasive procedure under general anaesthesia and/or is the child at risk of significant blood loss?

Up until the late 1990s, guidelines for the administration of RBC transfusions (in all age groups) were based on expert opinion as almost no evidence-based data were available. In HIC, these guidelines generally recommended transfusion at haemoglobin thresholds that studies performed over the past two decades have shown to be inappropriately liberal (i.e. they recommended using haemoglobin thresholds for transfusion that are unnecessarily high) thus exposing patients to transfusion risks without any observable benefit. Although most of these studies were performed in adult patients, it is reasonable to assume that paediatric patients, beyond the neonatal period, should be able to tolerate haemoglobin levels at least as low as those found to be safe in adult patients and, indeed, the few studies carried out in children have confirmed this.

Unlike the liberal guidelines for RBC transfusions that were used until relatively recently in HIC, the WHO guidelines for transfusion in acutely ill children have been much more restrictive – haemoglobin < 4 g/dl or haemoglobin 4–6 g/dl and clinical signs of complicated or decompensated anaemia – although also not evidence-based (*9, 10*). This is probably because the WHO guidelines were targeted more towards clinicians in LIC and LMIC where the blood supply is much more limited and where the risks of transfusion (particularly from transfusion-transmitted viruses and possibly also from errors) are higher than in HIC. With the development of evidence-based guidelines in HIC that recommend more restrictive use of RBC transfusions, the two approaches are converging.

A group of investigators from three SSA countries (Malawi, South Africa and Zimbabwe) have proposed a paediatric transfusion protocol for use in under-resourced environments. This protocol is based on the WHO guidelines but offers

more specific guidance with respect to the definition of complicated anaemia and adds a third category for children with severe malnutrition (for whom transfusions should be used more sparingly) (*7*). The definitions of complicated anaemia are shown in Table 7.3 and a comparison of the previous WHO guidelines with the 2010 paediatric blood transfusion protocol is summarized in Table 7.4.

Table 7.3. Comparison of definitions of complicated or uncompensated severe anaemia in children[a]

WHO 2001[b]	Clinical features of hypoxia i.e. acidosis or impaired consciousness
	Hyperparasitaemia (malaria) > 20%
WHO 2013[c]	Clinically detectable dehydration
	Shock
	Impaired consciousness
	Heart failure
	Deep, laboured breathing
	Hyperparasitaemia (malaria) > 10%
Suggested modification of WHO definitions[d]	Any respiratory distress
	Cool peripheries + capillary filling time ≥ 3 seconds
	Impaired consciousness (Ballantyne score ≤ 4)
	Prostration (≥ 1 year, alert but unable to sit; < 1 year, unable to drink or breastfeed)

[a] In each definition, only one criterion is required.

[b] Adapted from reference (*9*).

[c] Adapted from reference (*10*).

[d] Adapted from reference (*7*).

Table 7.4. Comparison of suggested modifications for a paediatric blood transfusion protocol with the WHO transfusion guidelines[a]

	Protocol comparison	
	WHO transfusion guidelines (WHO, 2001)	**Modified protocol**
No severe malnutrition		
Transfuse all children if:	Hb < 4 g/dL	Hb < 4 g/dL
Transfuse "complicated anaemia" patient also, if:	Hb = 4–6 g/dl	Hb = 4–6 g/dl
Volume of transfusion	20 ml/kg whole blood (or equivalent RBC volume)	20 ml/kg whole blood (or equivalent RBC volume)
	Give first 5 ml/kg red cells more rapidly to relieve the acute signs of tissue hypoxia	
Duration of transfusion	Complete transfusion in 4 hours	If complicated anaemia: first half in 1 hour and second half over 2 hours
		If uncomplicated anaemia: transfuse over 4 hours

	Protocol comparison	
	WHO transfusion guidelines (WHO, 2001)	**Modified protocol**
Severe malnutrition		
Transfuse all children if:	Not mentioned as a separate category	Hb < 4 g/dl
Transfuse "complicated anaemia" patient also, if:		Hb = 4–6 g/dl not for routine transfusion
Volume of transfusion		Decision made on individual clinical basis: 10 ml/kg whole blood (or equivalent RBC volume)
Duration of transfusion		Transfuse over 4 hours

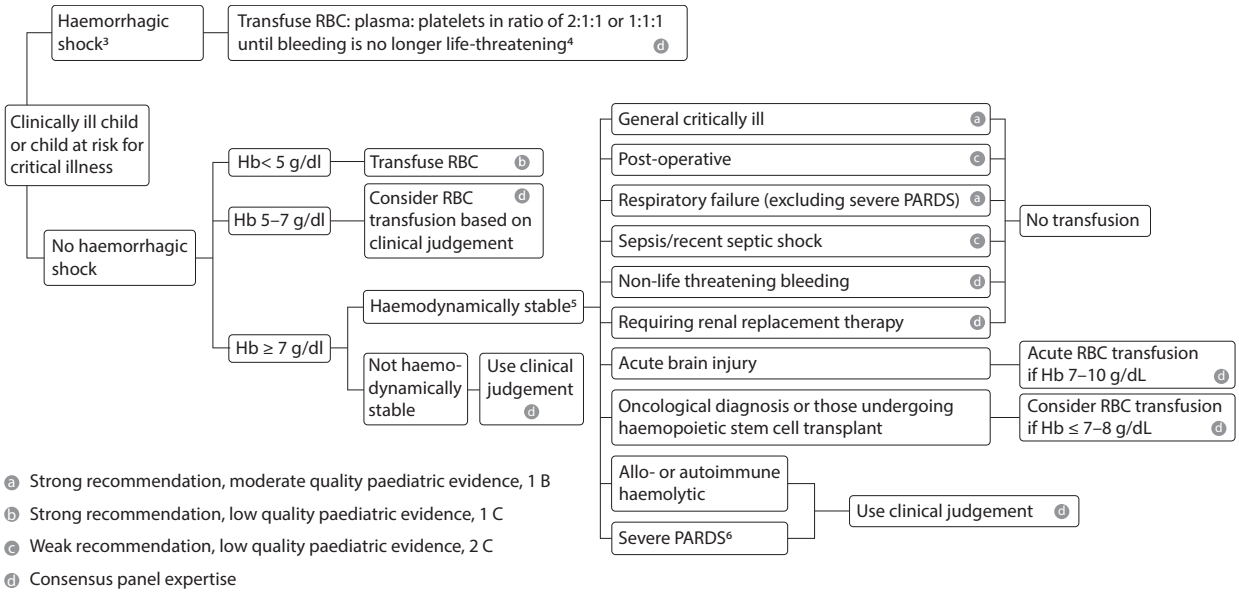
Hb, haemoglobin; RBC, red blood cell.

[a] Modified from reference (*7*). For definitions of complicated anaemia see Table 7.3. Severe malnutrition is defined as pitting oedema of both feet or severe visible wasting.

Note: These recommendations apply to acute or critically ill children; they may not necessarily apply to children with chronic anaemia or children with sickle-cell disease or thalassaemia (refer to text).

In 2018, a group of paediatric critical care physicians from Canada, Europe, South Africa and the United States published a series of guidelines for RBC transfusions in critically ill paediatric patients (*11*). Where possible these guidelines were evidence-based; where that was not possible, expert-based consensus statements were developed. The guidelines produced by this group are summarized in Fig. 7.1.

Figure 7.1. Transfusion and Anaemia Expertise Initiative (TAXI) recommendations for transfusion in critically ill children[1,2]



Hb: haemoglobin | PARDS: paediatric acute respiratory distress syndrome | RBC: red blood cell.

[1] Adapted from reference (*11*).
[2] Does not include children with sickle-cell anaemia (SCA), thalassaemia or cardiac disease; for children with SCA, see text and Tables 7.5 and 7.6; for children with thalassaemia see text and reference (*14*); for children with cardiac disease see reference (*11*).
[3] Severe bleeding in patients at risk of exsanguination.
[4] If available, may use whole blood instead.
[5] Haemodynamically stable = mean arterial pressure not more than 2 SD < normal for age and cardiovascular support not increased for at least 2 hours.

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RBC transfusions in patients with sickle-cell disease

Several studies and consensus documents have addressed the indications for RBC transfusion in patients with homozygous haemoglobin S (HbS) disease or HbS/β^0 thalassaemia (*12, 13*). For the sake of brevity, we refer to these two conditions together as sickle-cell anaemia (SCA). Indications for transfusion in other sickle-cell disease (SCD) conditions have not been studied and decisions on transfusion in patients with those conditions will not be specifically addressed. However, in general, for these conditions, the more the patient's phenotype resembles that of a SCA patient or the more severe the complication or potential complication, the more likely it is that the patient will benefit from an approach similar to that used for SCA patients.

RBC transfusions in patients with SCA may be given for acute or chronic complications and in either case may be simple transfusion(s) or ET(s), either manual or automated exchange.

The three reasons to administer an RBC transfusion in a patient with SCA are:

1. to increase tissue oxygenation;

2. to decrease viscosity by diluting the relative amount of HbS-containing RBCs;

3. to suppress endogenous erythropoiesis.

In acute situations, the main reason(s) for RBC transfusion is/are the first or the first and second. The main goal of chronic transfusion programmes is the third. For all situations, the goal with respect to post-transfusion haemoglobin should be to attain a total haemoglobin concentration of about 10–11 g/dl. It is important not to raise the haemoglobin above this level as this may lead to complications of hyperviscosity (including stroke). If the transfusion goal is to suppress endogenous erythropoiesis, then an additional goal is to decrease the HbS concentration below 30%.

Transfusions are not indicated for the treatment of uncomplicated painful crises and are also unlikely to be helpful in the acute treatment of priapism or isolated kidney injury, in the preoperative preparation for very low-risk surgical interventions not requiring general anaesthesia, or in patients with asymptomatic chronic anaemia due to chronic hypersplenism.

The indications and recommended transfusion type in acute situations are summarized in Table 7.5. Transfusion modalities (for either acute or chronic transfusions) are compared in Table 7.6 and the procedure for performing a manual ET is summarized in Box 7.3. In acute situations where a simple transfusion is recommended but the patient has a haemoglobin level ≥ 9 g/dl, a partial ET (often manual) should be performed. Alternatively, if an ET is recommended but cannot be carried out (either manually or by automated exchange) then a simple transfusion should be given provided that this can be done without raising the total haemoglobin concentration above 10-11 g/dl. If that is not possible, then every attempt should be made to transfer the patient to a centre where an ET can be performed. In situations where an ET is recommended but the patient's haemoglobin is very low, a simple transfusion should be given initially, and the patient re-evaluated for consideration of a subsequent ET.

Table 7.5. Indications for episodic (acute) red blood cell (RBC) transfusions in sickle-cell anaemia (SCA) patients (*12,13*)

Indication	Transfusion type
Aplastic crisis	Simple transfusion
Acute symptomatic blood loss or severe anaemia	Simple transfusion
Acute splenic sequestration	Simple transfusion[a]
Acute hepatic sequestration	Simple or exchange transfusion
Complicated painful crisis (i.e. drop of Hb ≥ 2 g/dl from baseline or Hb < 5 g/dl)	Simple transfusion
Mild to moderate ACS not responding to antimicrobials and other supportive treatment	Simple transfusion[b]
Severe ACS, i.e. an oxygen saturation < 90% despite supplemental oxygen	Exchange transfusion[c]
Prior to medium-risk surgery	Simple transfusion[b]
Prior to high-risk surgery	Exchange transfusion[c]
Multisystem organ failure	Simple or exchange transfusion
Acute intrahepatic cholestasis	Simple or exchange transfusion
Acute ischaemic stroke	Exchange transfusion[c]
Acute mesenteric "girdle" syndrome (acute sickling in the mesenteric vascular bed, liver and lungs)	Exchange transfusion[c]

Hb: haemoglobin | ACS: acute chest syndrome

[a] The RBC transfusion volume should be < 50% of the usual transfusion volume as RBCs sequestered in the spleen will return to the circulation.

[b] If the Hb ≥ 9g/dl, then a partial exchange transfusion should be performed.

[c] If an exchange transfusion cannot be performed then a simple transfusion should be given providing that this can be done without raising the total Hb concentration above 10–11g/dl. if the patient's Hb is very low then a simple transfusion should be given initially, and the patient re-evaluated for consideration of a subsequent exchange transfusion.

Table 7.6. Comparison of transfusion modalities in sickle-cell anaemia patients

	Simple transfusions	Manual exchange transfusions	Automated exchange transfusions
Convenience	Available in any transfusing facility	No special equipment required	Can only be performed in a major centre with specialized equipment and staff
	No special equipment and only basic training required	Additional training required	
Venous access	Ordinary single venous access	Requires two venous lines	Requires central venous access or two large-bore venous lines
Number of units required	1–2 units – enough to raise Hb level to 10 g/dl	More than for simple transfusion but less than for automated exchange	More than for manual exchange (8–12 units per exchange in an adult)
Iron accumulation	Inevitable over time with multiple transfusions	Occurs, but with less net gain than with simple transfusion	Does not usually occur

Box 7.3. Procedure for performing a manual exchange transfusion

Note: If haemoglobin (Hb) concentration is < 80 g/L, perform a simple transfusion before proceeding to a manual exchange transfusion.

Prior to beginning the procedure

1. Weigh the patient.
2. Ensure that the patient has two well-functioning large-bore venous accesses.
3. Calculate the patient's red cell mass that will be removed:
   - total blood volume removed × patient's haematocrit (expressed as a fraction).
4. Calculate the amount of blood to transfuse (*Note*: It is important to know the type of red blood cell (RBC) product available – refer to Table 7.7.)
   - red cell mass removed/haematocrit (expressed as a fraction) of blood unit.

Example of calculation for volume to transfuse: 30 kg child with haematocrit of 0.25, removing a total of 20 ml/kg, using whole blood with haematocrit of 0.40: (30 kg × 20 ml × 0.25)/0.40 = 375 ml. This will give a post-exchange haemoglobin (Hb) level that is approximately the same as the pre-exchange Hb. If a slightly higher post-exchange Hb is desired, then a slightly larger transfusion volume can be given.

First step: *Phlebotomy with simultaneous isovolaemic saline replacement*

- Phlebotomy: over 15–20 minutes, from one of the venous lines remove 10 ml/kg (up to a maximum of 500 ml total).
- Volume replacement: using the other IV access, simultaneously infuse the same volume of saline as the volume of blood being removed.

Second step: *RBC transfusion while performing a second phlebotomy*

- Phlebotomy: over 15–20 minutes, from one of the venous lines remove 10 ml/kg (up to a maximum of 500 ml total).
- Transfusion: using the other IV access, beginning at the same time as the phlebotomy, transfuse the calculated amount of blood over 30 minutes (or slightly longer if aiming to raise the post-exchange Hb level).

30 minutes post-procedure

- Do a complete blood count and obtain results rapidly.
- If the post-exchange Hb level is < 90 g/L, perform an additional transfusion if required.
- If the post-exchange Hb level is > 110 g/L, perform a phlebotomy if required.

In high-resource settings, chronic transfusion therapy, i.e. a programme of regular transfusions (approximately every 3–4 weeks), in order to maintain a HbS level below 30%, is recommended for primary stroke prevention in children 2–16 years old with confirmed abnormal (> 200 cm/sec) transcranial Doppler (TCD) velocities in any of the large cerebral arteries and for secondary stroke prevention in children who have had a previous stroke. Selected children (with no previous history of stroke) with abnormal TCDs but no severe vasculopathy may transition to hydroxyurea (HU) therapy after 1–2 years of transfusion therapy. Chronic transfusion therapy can be accomplished using simple transfusions or manual or automated exchange transfusions. Unfortunately, in many parts of the world, chronic transfusion therapy is either not available, not feasible, or is available but without the possibility of iron chelation therapy to prevent the inevitable and potentially fatal consequences of iron overload. In these settings it is reasonable to consider replacing transfusion therapy with, or transitioning from initial transfusion therapy to, HU at maximal tolerable doses.

Previously, patients with recurrent severe acute chest syndrome and/or recurrent disabling painful events were placed on chronic transfusion programmes. Most such patients can now be successfully managed with HU. The use of chronic transfusions in infants with severe or recurrent acute splenic sequestration is controversial. Many physicians will place such patients on a chronic transfusion programme until 2–4 years of age when a splenectomy will be performed.

Where possible, patients with SCD should receive RBC units that have been matched for the five most common Rhesus antigens (D, C, E, c, e) and the Kell antigen to decrease the risk of RBC alloimmunization (*14*). Some, although not all, experts also recommend that patients on chronic transfusion programmes should receive blood that is HbS negative (*14,15*). In addition to the transfusion complications described elsewhere, in SCA patients it is important to be aware that a delayed haemolytic transfusion reaction can present with a clinical picture of a painful episode occurring 1–2 weeks post-transfusion. In rare cases, SCD patients may experience hyperhaemolysis after an RBC transfusion. This is a potentially fatal reaction usually occurring within 7 days of transfusion in which there is haemolysis of both transfused RBCs and recipient RBCs leading to a lower haemoglobin level than before transfusion. It may or may not be associated with alloimmunization. In addition to supportive therapy, it is important to avoid further transfusion and treat the patient with high-dose IV corticosteroids and, if available, intravenous immunoglobulin, erythropoietin (if reticulocytopenic) and possibly eculizumab. Following the acute episode, patients not already on HU therapy should begin HU.

Thalassaemia patients

Thalassaemias are a heterogeneous group of genetic disorders characterized by a reduced production of globin chains of haemoglobin and ineffective erythropoiesis. Children with β-thalassaemia major require regular transfusions every 3–4 weeks if they are to survive. Maintaining a nadir haemoglobin concentration of 90–100 g/L before transfusion is usually sufficient to achieve adequate suppression of erythropoiesis and prevent disease-related complications. However, iron overload will develop over time and, if untreated, will lead to endocrine failure, liver disease and ultimately to cardiac failure, which is the major cause of death.

Some children have an intermediate form, called non-transfusion-dependent thalassaemia. They have residual β-chain synthesis but might require transfusions periodically and they will develop iron overload with time even if they are never transfused. Children with more severe β-thalassaemia intermedia may benefit from regular transfusions. This should be considered in children with growth failure, skeletal deformities or extramedullary erythropoietic masses.

With appropriate diagnosis of transfusion-related haemosiderosis by magnetic resonance imaging and timely chelation, affected children can now live well into adulthood. Several iron chelators are available. Deferoxamine (DFO) has been in use since the 1970s and is effective in reducing liver and cardiac iron overload. However, its infusion modality (prolonged daily subcutaneous infusion) is cumbersome and may affect adherence and quality of life. Deferiprone is a bidentate oral iron chelator introduced in the late 1990s. It improves both liver and cardiac overload in β-thalassaemia major patients. Deferasirox is a tridentate oral chelator introduced in the early 2000s and has been shown to be effective in treating both transfusion-dependent and non-transfusion-dependent thalassaemia. Both oral chelators can be used in combination with DFO (*16*).

7.3 Practical aspects of RBC/WB transfusion

RBC products

RBC-containing products include WB and RBC concentrates prepared either by removing approximately three quarters of the plasma/anticoagulant solution from the WB unit (traditionally known as “packed red cells”) or by removing

most of the plasma/anticoagulant solution from the WB unit and then resuspending the packed RBCs in an "additive" (nutrient) solution. Some characteristics of these products are summarized in Table 7.7. At the time of writing, there was no published study comparing WB with RBC concentrates for the treatment of anaemia in children. The choice of product is usually determined by what is available.

ABO group/Rh type

Except in emergency situations, WB and RBC units should be ABO group identical with the recipient, both for ease of ensuring ABO compatibility and for optimal inventory management. Acceptable substitutions for RBC concentrates are shown in Table 7.8. For WB, the same ABO blood group substitutions can be used but plasma compatibility should also be considered. This involves either performing a "minor compatibility" test (recipient RBCs with donor plasma) in addition to the usual "major compatibility" test (donor RBCs with recipient plasma) or using blood with low anti-A and anti-B titres when transfusing group O WB to recipients who are not themselves group O.

RhD-positive patients may receive RhD-positive or negative blood, although most RhD-negative blood should be reserved for RhD-negative patients, especially for females of childbearing age. RhD-negative patients should receive RhD-negative blood, but in extreme emergencies RhD-positive blood may be administered; a life-saving transfusion should not be withheld due to the lack of RhD-negative RBCs.

Table 7.7. Comparison of RBC-containing products

Product	Composition	Approximate haematocrit	Approximate volume[a] (ml)	RBCs per transfusion	
				Transfusion volume (ml/kg)	RBCs per transfusion (ml/kg)
Whole blood in CPD, CP2D or CPDA-1	RBCs Plasma[b] 200–250 ml Platelets[c]	0.40	500–550	20[e]	8
RBCs in CPD, CP2D or CPDA-1	RBCs Plasma[b] 50– 70 ml	0.75[d]	250	10	7.5
RBCs in additive solution	RBCs Minimal plasma[b] Additive solution 100 ml	0.60[d]	330	15	9

CPD, citrate-phosphate-dextrose; CP2D, citrate-phosphate-double dextrose; CPDA-1, citrate-phosphate-adenine anticoagulant-preservative; RBCs, red blood cells.

[a] In some South-East Asian countries 350 ml of whole blood (WB) is collected in 49 ml of anticoagulant-preservative solution, giving a total volume for a WB unit of approximately 400 ml. Volumes for RBC units will thus also be proportionately smaller, but the haematocrit levels should be similar.

[b] Plasma plus anticoagulant solution.

[c] Number equivalent to that in one platelet unit prepared from WB; platelets kept in cold storage may be efficacious for the treatment of bleeding (but not prophylaxis) for up to 14 days (*17*).

[d] Haematocrit varies with amount of plasma/anticoagulant removed. Values shown are those obtained with centrifugation; if "settling" by gravity without centrifugation is used, then the haematocrit levels will be considerably lower (e.g. 0.50–0.55) as well as the RBC content/ml.

[e] The usually recommended WB transfusion volume of 20 ml/kg should raise the Hb concentration (in a non-bleeding patient) by approximately 2.7 g/dl. The equivalent volume of RBC concentrates with haematocrits of 0.75, 0.60 and 0.55 are 10.7 ml/kg, 13.3 ml/kg and 14.5 ml/kg, respectively.

The white blood cell content varies according to production method and whether pre-storage leukoreduction is performed. Granulocytes are non-functional 12–24 hours after collection.

Table 7.8. Blood group substitutions in paediatric patients

Blood component	Recipient ABO group	Substitution blood group when isogroup component not available	Extreme emergency and/or when unable to confirm patient's blood group
RBC concentrate	O	none	Males: O pos Females: – first choice: O neg – second choice: O pos
	A	O	
	B	O	
	AB	first choice: A or B second choice: O	
Whole blood	O	None	Males: O pos Females: – first choice: O neg – second choice: O pos Ideally use O-low titres
	A	O with low-titre anti-A/B (O-low titres)	
	B		
	AB	first choice: A or B second choice: O-low titres	
Frozen plasma or fresh frozen plasma	O	first choice: A or B second choice: AB	first choice: AB second choice: A
	A	AB	
	B	AB	
	AB	none	
Platelets	O	first choice: A or B second choice: AB	first choice: AB second choice: A or B third choice: O (O-low titres) Do not pool units of different ABO groups
	A	AB	
	B	AB	
	AB	none	
Cryoprecipitate	O	Any	All ABO groups are acceptable. May pool units of different ABO groups (but then do not indicate an ABO group on the label)
	A		
	B		
	AB		

- Always try to use the same blood group as that of the patient.
- Group O neg red cell concentrates are compatible with all groups but should be used judiciously because of their short supply.
- Group AB plasma/platelets are compatible for all plasma/platelet transfusions but should be used judiciously because of their short supply.
- In patients weighing < 10 kg avoid non-isogroup plasma/platelet transfusions unless components can be volume-reduced or are known to have low anti-A/B titres.

Storage age/product manipulation

RBC units of any storage age can be safely used for small-volume transfusions (≤ 20 ml/kg) in neonates and children (*18,19*). For massive transfusion in neonatal or small paediatric patients blood stored for ≤ 7–10 days (or if only older units are available with the supernatant fluid removed) should be used, as the potassium content of older units may pose a risk of hyperkalaemia. Removal of additive solutions from RBC units stored in these solutions was previously considered prudent for massive transfusion in neonates but is no longer routinely performed (except for units >7–10 days old). Leukoreduction and irradiation of RBC units is discussed in Chapter 3.

Partial units

If an entire blood unit is not required for a neonatal or paediatric patient, ideally a partial unit should be used. Small "paediatric" units are sometimes prepared by the blood supplier (using a closed system to maintain unit integrity). Alternatively, the required volume can be removed from the full unit into a transfer pack at the transfusing facility. To prevent septic transfusion reactions resulting from possible introduction of bacteria at this step, this must either be done using a sterile connecting device that splices and re-channels tubing preserving sterility of the units (in which case the expiry date does not change) or the blood in both the transfer pack and the original bag must be transfused with 24 hours of entry into the unit (with storage at 2–6 °C until transfusion).

Aliquots for neonates may also be prepared in a syringe, using specialized neonatal syringe sets with built-in filters. Blood in the syringe must be transfused immediately; if prepared using a sterile connecting device the blood in the original unit retains its original expiry date, otherwise it expires 24 hours after entry into the unit.

Complete information about the unit (blood group, unit number, expiry date and time) must appear on a label on the transfer pack or syringe and, if prepared non-sterilely, the revised expiry date and time must be indicated on the original unit.

Transfusion volumes

Within a given jurisdiction the clinician needs to know which RBC products are available in order to determine optimal transfusion volumes for small patients, i.e. those patients receiving less than one full blood unit. Traditional recommendations have been to administer WB transfusions of 20 ml/kg and RBC transfusions of 10 ml/kg. However, as can be seen in Table 7.7, the amount of an RBC unit that must be given to deliver the same red cell mass as WB 20 ml/kg depends upon the haematocrit of the RBC component and is often more than 10 ml/kg. For RBC concentrates in additive solution, 15 ml/kg should be given in order to assure an adequate haemoglobin increase. For patients with severe malnutrition, who are at increased risk of volume overload, only half these volumes should be given.

Transfusion rate/blood administration

RBC/WB transfusions must be completed within 4 hours of issue of the blood unit from the transfusing facility's blood bank. Recommendations for the transfusion rate are included in Table 7.4. If a patient is unable to tolerate the required volume within this timeframe a diuretic may be administered before transfusion and/or the total amount to be transfused can be divided into separate bags in the blood bank and administered in separate aliquots (following the guidelines mentioned above).

A blood administration set that includes a 170–260-micron filter (or other approved blood transfusion filters of smaller size) must be used. Ideally an infusion pump should be used to ensure the correct infusion rate. The catheter size should be the largest that can be reasonably inserted, at least a 22-gauge.

Drugs should not be administered simultaneously through the same intravenous line as transfusions. Normal saline is compatible with blood and may be simultaneously given if necessary; hypotonic solutions and Ringer's lactate must not be given through the same line as a blood transfusion.

Warming of RBC/WB solutions is not necessary for paediatric patients except when rapidly transfusing large amounts (> 15 ml/kg per hour) of cold blood through a central line. An approved blood warming device should be used.

7.4 Thrombocytopenia and platelet transfusions

The definition of thrombocytopenia is a platelet count (PC) below 140–150 × 10^9/L and is the same for all age groups, both males and females and for all ethnicities, except in the first week of life when the lower limit of normal is approximately 125 × 10^9/L.

Thrombocytopenia occurs frequently in preterm or ill neonates, in neonates with congenital infections and in neonates with perinatal asphyxia. These infants show a poor correlation between the PC and bleeding risk, suggesting that other factors are more important. The possibility of neonatal alloimmune thrombocytopenia (NAIT) should be considered in an otherwise well, term neonate with isolated moderate or severe thrombocytopenia (PC < 75–100 × 10^9/L) and in all other neonates with a PC < 50 × 10^9/L.

The commonest causes of thrombocytopenia in older infants and children are infections (in particular malaria, HIV and other viral infections), critical illness, disseminated intravascular coagulation (DIC), malignant disorders and their treatment, aplastic anaemia and immune thrombocytopenia (ITP). In high-resource settings thrombocytopenia is also common in patients undergoing cardiovascular surgery or on extracorporeal membrane oxygenation (ECMO).

Indications for platelet transfusions

Apart from one study in preterm neonates, published in 2019, there have been no randomized controlled trials of platelet transfusions (PT) specifically addressing indications for PT in paediatric patients (*17, 18*). Thus, guidelines for children are based on evidence from studies in adults (which have sometimes included some children) or, where such evidence is not available, on expert opinion. Generally accepted guidelines for PT in neonates and children are summarized in Box 7.4.

Box 7.4. Indications for platelet transfusions (PT) in neonates and children (*2, 17, 18*)

Neonates[a]

1. Neonatal alloimmune thrombocytopenia (NAIT) or suspected NAIT
   - Give prophylactic PT for a PC ≤ 30×10^9/L.
   - For invasive procedures, surgery or moderate or severe bleeding, use the recommendations for older infants and children as a general guide.
   - Use implicated-antigen-negative platelets where these are readily available, otherwise use random donor platelets; if using maternal platelets, they must be washed and irradiated.

2. Other neonates with thrombocytopenia
   - Give prophylactic PT for a PC ≤ 25×10^9/L
   - For invasive procedures, surgery or bleeding, use the recommendations for older infants and children as a general guide.

Older infants and children

1. Guidelines are based on adult literature and recommendations.

2. Hypoproliferative thrombocytopenia
   - Prophylaxis
     - Stable: PC ≤ 10×10^9/L (for non-reversible hypoproliferative thrombocytopenia consider a lower threshold or only therapeutic PT)
     - Increased bleeding risk (e.g. patient on anticoagulants, laboratory evidence of disseminated intravascular coagulation, sepsis): PC ≤ 20×10^9/L
   - Bleeding (due to or mainly due to thrombocytopenia)
     - minor: PC ≤ 10×10^9/L
     - moderate: PC ≤ 30×10^9/L
     - severe: PC ≤ 50×10^9/L
     - bleeding at a critical site (e.g. central nervous system): PC ≤ 100×10^9/L
   - Invasive procedures/surgery[b]
     - bone marrow aspirate/biopsy – no specific PC required
     - lumbar puncture: PC ≤ 40×10^9/L
     - percutaneous liver biopsy: PC ≤ 50×10^9/L
     - minor surgery at a non-critical site: PC ≤ 20×10^9/L
     - surgery at a critical site (e.g. central nervous system): PC ≤ $75–100 \times 10^9$/L
     - other surgery: PC ≤ 50×10^9/L

3. Immune thrombocytopenias (e.g. ITP, TTP/HUS)
   - Prophylaxis – PT is not indicated.
   - Bleeding – use PT only for severe/life-threatening bleeding.
   - Invasive procedures – decisions are to be made on an individual basis if other treatments not sufficient.

4. Other critically ill children with thrombocytopenia
   - Follow the recommendations in point 2 above as a general guide for PT.

PT, platelet transfusion; PC, platelet count; ITP, immune thrombocytopenia; TTP, thrombotic thrombocytopenia; HUS, haemolytic uraemic syndrome.

[a] Neonates with NAIT or suspected NAIT and neonates with PC < 50×10^9/L should undergo cerebral imaging to rule out the possibility of intracranial haemorrhage.

[b] For insertion and removal of central lines and for renal biopsy, refer to reference (*18*).

Practical aspects

Platelet products

There are three kinds of platelet products:

- platelets prepared from a standard WB donation; approximate volume 50 ml; platelets/unit ≥ 5.5×10^{10} platelets
- buffy coat pool; approximate volume 300–350 ml; platelets/pool ≥ 2.4×10^{11} platelets
- apheresis unit: approximate volume 200–250 ml; platelets/unit ≥ 2.4×10^{11} platelets.

Platelets/unit are an approximation and will vary between jurisdictions.

Usually only one or two platelet products are produced by a blood supplier. Blood suppliers who produce platelets from standard WB donations may pool 4 or 5 units under sterile conditions.

ABO group/Rh type

Ideally platelet units should be of the same ABO group as the recipient. Permissible substitutions are shown in Table 7.8. Whenever possible, group O platelets should be avoided for non-group O infants and children unless they can be volume-reduced (which can only be appropriately performed in specialized centres) or the units have low titres of anti-A/B. Prophylactic use of anti-D may be considered in Rh-negative female patients receiving Rh-positive platelets but this is not generally considered necessary in male patients.

Platelet dosage and transfusion rate

The usual paediatric platelet dosages are:

- neonates: 10–15 ml/kg (up to 50 ml or 1 unit prepared from WB)
- infants 4–10 kg: 5–10 ml/kg (up to 50 ml or 1 unit prepared from WB)
- children and adolescents >10 kg:
  - single units from WB donations: 1 unit per 10 kg (so 1 unit if body weight is 10–19 kg, 2 units if weight is 20–29 kg, etc.) to a maximum of 4–5 units
  - pooled units (buffy coat pool or pool of 4–5 units prepared from WB): 5–10 ml/kg up to 1 pooled unit
  - apheresis unit: 5–10 ml/kg up to 1 unit.

Platelets should be administered at a rate that the patient can safely tolerate (over at least 1 hour, or more slowly to avoid administering a large bolus of cytokines quickly) and in all cases within 4 hours of issue from the transfusing facility's blood bank.

Other practical considerations

In jurisdictions in which only pooled or apheresis platelets are available, partial units may be transfused. They can be prepared using the RBC transfer bags, in which case they should be transfused immediately. If aliquots are withdrawn under sterile conditions, the original unit retains its original expiry date but if prepared non-sterilely the original unit expires in 4 hours. Where available, platelet storage transfer bags should be used; in this case if prepared under sterile conditions and transferring the amount of product indicated by the manufacturer, both the aliquot and the original

unit maintain the original expiry date. If not prepared under sterile conditions both expire in 4 hours. A standard blood administration set with a 170–260-micron filter must be used. Leukoreduction and irradiation of platelet units is discussed in Chapter 3.

7.5 Bleeding disorders other than thrombocytopenia and the transfusion of plasma components

After the neonatal period, the indications for plasma transfusions are the same in children as in adults. Here we discuss only plasma transfusions in neonates, haemorrhagic disease of the newborn and the treatment of children with known or suspected haemophilia A or B when factor concentrates are unavailable.

Plasma transfusion in neonates

Except for von Willebrand factor and Factor VIII, the reference values for coagulation and prothrombotic factors are lower in neonates (including those receiving prophylactic vitamin K) than in adults. The most marked difference is observed in the Factor IX level. Consequently, the reference values for routine coagulation tests, in particular, the activated partial prothrombin time are higher in the neonatal period than later in life. "Adult" levels are reached by about 6 months of age.

There is no good evidence on which to base guidelines on plasma transfusion in the neonate. Plasma transfusions should not be used for volume expansion nor to prevent intraventricular haemorrhage, nor should they be administered to neonates with abnormal coagulation test results, but who are not bleeding (*22*). Plasma should not be used as the infusion fluid in the treatment of polycythemia; saline is a cheaper and safer choice. For bleeding neonates with coagulation test results outside the neonatal reference ranges, decisions should be made on an individual basis, guided by indications for plasma transfusion in older children and adults.

The use of plasma in exchange transfusions is described above.

Haemorrhagic disease of the newborn

A transient decrease in vitamin K-dependent coagulation factors (II, VII, IX, X) occurs normally in neonates within 48–72 hours of birth and can lead to spontaneous bleeding in the first 2–7 days of life. Typically, bleeding is intracranial, intestinal or umbilical. Prophylactic administration of vitamin K – 1 mg intramuscularly at birth (or a repeated oral dosing schedule) – prevents this disorder (known as haemorrhagic disease of the newborn) in most neonates. However, in babies born outside hospitals and/or where systems are not in place to ensure that every newborn receives vitamin K, this still occurs. It is treated with vitamin K, 1–5 mg intravenously. Plasma transfusion is indicated if the bleeding is severe or life-threatening. Infants whose mothers take phenobarbital or phenytoin or certain anti-tuberculosis drugs are at risk later in the neonatal period; bleeding in these infants can be prevented by giving oral vitamin K daily for the first 2 weeks of life.

Treatment of children with known or suspected haemophilia A or B when factor concentrates are unavailable

Ideally all patients with haemophilia A or B should have access to treatment with recombinant or plasma-derived, virally-

inactivated factor concentrates. Where these are unavailable, treatment of active bleeding with plasma components will still be beneficial. Both fresh frozen plasma (FFP, plasma frozen within 8 hours of collection) and plasma frozen within 24 hours of collection (FP24) contain factors VIII and IX, at a concentration of approximately 1 IU/ml. Cryoprecipitate has no Factor IX but each unit should contain at least 80 IU of Factor VIII. If the patient has haemophilia B or a suspected but unconfirmed diagnosis of haemophilia, then plasma should be given. If a diagnosis of haemophilia A is confirmed, cryoprecipitate is preferable to plasma if available. The amounts to be given should be calculated using the recommended number of coagulation factor units for the type of bleeding and then administering the maximum amount/volume that the patient can tolerate.

Practical considerations for plasma transfusions

FFP and FP24 are interchangeable. Ideally FFP/FP24 units should be of the same ABO group as the recipient. Permissible substitutions are shown in Table 7.8. Rh type does not need to be matched.

Partial units, prepared after thawing and using the same transfer bags as for RBC transfusions, may be transfused. If aliquots are withdrawn under non-sterile conditions, the aliquot and the original unit must both be transfused within 24 hours of entry into the original unit. If prepared under sterile conditions, local regulations for permitted length of storage at 2–6 °C must be followed.

If the patient can tolerate the volume, a dose of 20 ml/kg should be given. A standard blood administration set with a 170–260-micron filter must be used. Only normal saline is compatible with FFP/FP24, although co-administration is not recommended.

Practical considerations for cryoprecipitate transfusions

ABO group and Rh type do not need to be matched.

In neonates and small children, a dose of 1–2 units per 10 kg body weight is used; in older children and adolescents the usual dose is 1 unit per 10 kg.

Only normal saline is compatible with cryoprecipitate. Normal saline can be used to dilute the thawed unit if necessary. When more than 1 unit will be given, a pool is usually prepared (see Table 7.8). Following thawing, local regulations for permitted duration of storage at 2–6 °C must be followed. A standard blood administration set with a 170–260-micron filter must be used for infusion.

References

1. Ohls R. Red blood cell transfusions in the newborn. Up-to-date [online] (https://www.uptodate.com/contents/red-blood-cell-transfusions-in-the-newborn?search=neonatal%20transfusion&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1), accessed 31 January 2019).
2. New HV, Berryman J, Bolton-Maggs PHB, Cantwell C, Chalmers EA, Davies T et al. Guidelines for transfusion of fetuses, neonates and older children. Br J Haematol. 2016;175:784–828.
3. American Academy of Pediatrics Clinical Practice Guideline: Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation (https://pediatrics.aappublications.org/content/114/1/297, accessed 31 January 2019).
4. Exchange transfusion guideline for neonates. Barnstaple: Northern Devon Healthcare, NHS Trust; 2018 (https://www.northdevonhealth.nhs.uk/wp-content/uploads/2018/10/Exchange-Transfusion-Guideline-for-Neonates.pdf, accessed 31 January 2019).
5. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Geneva: World Health Organization; 2011 (https://www.who.int/vmnis/indicators/haemoglobin/en/, accessed 10 December 2018).
6. Kasselbaum NJ, Jasrasria R, Naghavi M, Wulf SK, Johns N, Lozano R et al. A systematic analysis of global anemia burden from 1990 to 2010. Blood. 2014;123:615–24.
7. Cheema B, Molyneux EM, Emmanuel JC, M'baya B, Esan M, Kamwendo H et al. Development and evaluation of a new paediatric protocol for Africa. Transf Med 2010;20:140–51.
8. Kiguli S, Maitland K, George EC, Olupot-Olupot P, Opoka RO, Engoru C, et al. Anaemia and blood transfusion in African children presenting to hospital with severe febrile illness. BMC Med. 2015;13:21.
9. The clinical use of blood. Geneva: World Health Organization Blood Transfusion Safety; undated (https://www.who.int/bloodsafety/clinical_use/en/Handbook_EN.pdf, accessed 31 January 2019).
10. Hospital care for children, second edition. Geneva: World Health Organization; 2013 (https://apps.who.int/iris/bitstream/handle/10665/81170/9789241548373_eng.pdf;jsessionid=FF067960883C6566F16CF863965A743F?sequence=1, accessed 31 January 2019).
11. Valentine SL, Bemba MM, Muszynski JA, Cholette JM, Doctor A, Spinella PC et al. Consensus recommendations for RBC transfusion practice in critically ill children from the Paediatric Critical Care and Anemia Expertise Initiative. Pediatr Crit Care Med J. 2018;18:884–98.
12. Evidence-based management of sickle cell disease: Expert Panel Report. Bethesda (MD): National Heart, Lung and Blood Institute; 2014 (https://www.nhlbi.nih.gov/health-topics/evidence-based-management-sickle-cell-disease accessed 31 January 2019).
13. Davis BA, Allard S, Qureshi A, Porter JB, Pancham S, Win N et al. Guidelines on red cell transfusions in sickle cell disease. Part II: Indications for transfusion. Br J Haematol. 2017;176:179-191.
14. Davis BA, Allard S, Qureshi A, Porter JB, Pancham S, Win N et al. Guidelines on red cell transfusions in sickle cell disease. Part I: Principles and laboratory aspects. Br J Haematol. 2017;176:192–209.
15. Aneke J, Barth D, Ward R, Pendergrast J, Cserti-Gazdewich C. The rationale for abandoning sickle cell trait screening of red cell units for patients with sickle cell disease. Transf Med 2019; 29:466-467.
16. Guidelines for the management of transfusion dependent thalassaemia, 3rd edition. Nicosia: Thalassaemia International Federation; 2014 (https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-management-of-transfusion-dependent-thalassaemia-3rd-edition-2014/, accessed 31 January 2019).
17. Cohn CS, Shaz BH. Warming up to cold platelets. Anesthesiology 2020; 133;1161-1162.
18. Fergusson D, Hebert P, Hogan DL et al. Effect of fresh red blood cell transfusions on clinical outcomes in premature, very low-birth-weight infants. JAMA. 2012; 308: 1443–51.
19. Spinella PC, Tucci M, Fergusson DA, Lacroix J, Hébert PC et al. Effect of Fresh vs Standard-issue Red Blood Cell Transfusions on Multiple Organ Dysfunction Syndrome in Critically Ill Pediatric Patients: A Randomized Clinical Trial. JAMA 2019; 322:2179-2190.
20. Curley A, Stanworth SJ, Willoughby K et al. Randomized trial of platelet-transfusion thresholds in neonates. N Engl J Med. 2019; 380: 242–51.
21. Estcourt LJ, Birchell J, Allard S. Guidelines for use of platelet transfusions. Br J Haematol. 2017; 176: 365–94.
22. Keir AK, Stanworth SJ. Neonatal plasma transfusions: an evidence-based review. Transfus Med Rev. 2016: 30: 174–82.

CHAPTER 8

SURGERY AND ANAESTHESIA

Key points

1. Surgical patients benefit from patient blood management (PBM) methods to improve blood utilization. PBM is an evidence-based, multidisciplinary approach to optimizing the care of patients who might need transfusion.

2. Elements of a PBM programme for surgical patients include:
   - management of anaemia and bleeding risks before treatment begins;
   - intraoperative blood recovery, haemostatic pharmacological agents, blood-sparing surgical techniques and evidence-based transfusion guidelines;
   - intensive care units (ICUs) and postoperative strategies to reduce the need for transfusion;
   - education of health care providers.

3. Preoperative anaemia is common. Identifying and treating it before elective surgery is one of the fundamentals of PBM.

4. Encouraging single-unit red blood cell (RBC) transfusions in stable anaemic patients is an effective method of reducing overuse. A Choosing Wisely "Why give 2 when 1 will do?" campaign can substantially reduce overall blood utilization.

5. By practising PBM, perioperative blood conservation is achieved; this reduces the risks and costs of unnecessary transfusions, and conserves blood – a scarce and valuable resource.

8.1 Introduction

Blood transfusions can be life-saving, but are also associated with risks and complications (*1*). Increasing attention by professional associations and health care organizations to the wide variation in transfusion practice and overuse of blood has intensified the need for more appropriate utilization (*2, 3*). Furthermore, blood shortages are common and blood is costly, so any efforts to reduce the need for transfusion add value to patient care. Over the past decade, patient blood management (PBM) has developed into an important and valuable tool to optimize blood utilization. Often described as giving the right product, in the right dose, to the right patient, for the right reason, PBM is an evidence-based, multidisciplinary approach to optimize the care of patients who might need a transfusion. The key components of a strong PBM programme are summarized in Box 8.1.

Box 8.1. Methods for implementing a patient blood management programme

1. Obtain support from health system leadership (business plan).
2. Assemble multidisciplinary team of stakeholders.
3. Educate staff (with emphasis on the available randomized controlled trials supporting restrictive transfusion).
4. Ensure hospital-wide adoption of transfusion guidelines.
5. Conduct transfusion guideline compliance audits with feedback (reports) to providers.
6. Consider methods to improve blood utilization:
   - evidence-based transfusion triggers
   - "Why give 2 when 1 will do" Choosing Wisely® campaign for red blood cells
   - preoperative anaemia management
   - antifibrinolytics (e.g. aminocaproic acid, tranexamic acid)
   - intraoperative autologous cell salvage (cell saver®) when available
   - anaesthetic management (autologous normovolaemic haemodilution, controlled hypotension, normothermia)
   - surgical methods (newer cautery methods, topical haemostatics and sealants)
   - reduce phlebotomy blood loss (smaller tubes, eliminate unnecessary testing)
   - point-of-care testing (for rapid turnaround times).

Although PBM applies to both medical and surgical patients, this chapter will describe how PBM concepts can be used in anaesthesia and surgery to improve perioperative care for surgical patients.

Learning outcomes

After studying this chapter, the reader should be able to:

- understand how to identify and manage anaemia and bleeding risks before surgery
- be aware of methods to reduce intraoperative bleeding
- understand how to:
  - practise evidence-based fluid and blood administration
  - use the patient's own (autologous) blood to reduce the need for allogeneic transfusions
  - optimize postoperative care to improve blood utilization.

8.2 Patient selection and preparation: detection and correction of preoperative anaemia

Preoperative anaemia – diagnosis and treatment

One important and especially challenging aspect of PBM is the timely diagnosis and treatment of preoperative anaemia. Treatment is particularly important for patients who are undergoing elective surgery, as bringing such patients to the operating room with untreated anaemia represents suboptimal care. Anaemia has been shown to be an independent predictor of increased perioperative morbidity and mortality. It should therefore be considered a modifiable risk factor and elective surgery should be delayed when possible to allow for diagnosis and adequate treatment.

First, it is important to determine the cause of anaemia. Simple iron deficiency can be treated with either oral or intravenous iron. Patient adherence to oral iron treatment can be problematic owing to significant gastrointestinal side-effects. Moreover, since oral iron is both poorly and slowly absorbed, many experts in the field advocate intravenous iron therapy to allow for more rapid resolution of anaemia. The newer compounds can be administered in one or two high doses for complete iron repletion. They are also associated with a lower incidence of adverse events than the older iron compounds such as high-molecular-weight iron dextran. For specific patients, erythropoietic-stimulating agents (ESAs) may be indicated for treating preoperative anaemia. Two concerns about the use of ESAs are the costs, and apparent risk of thrombotic events and promotion of tumour growth. Use of pharmacological therapy such as low-molecular-weight heparin for venous thrombosis prophylaxis may decrease the risk of thrombosis in postoperative patients. However, ESAs should be used with caution in patients with a history of thrombosis, ischaemic stroke, uncontrolled hypertension, seizures or cancer. With this in mind, the risk–benefit ratio must be carefully considered when prescribing ESAs.

One of the most challenging aspects of diagnosing and treating preoperative anaemia is having enough time before surgery to achieve the goals. Often, preoperative laboratory tests are ordered only days before the surgery date, leaving little or no time to do what is best for the patient. Clearly, for semi-urgent surgeries the options are limited, but for truly elective cases, the preoperative lab tests should ideally be done four or more weeks before the surgery date. This allows adequate time for proper diagnosis and treatment of anaemia (*4*). Additionally, when appropriate, providers should rule out other medical causes of anaemia, for example, a gastrointestinal malignancy, when iron deficiency anaemia is detected. Most patients will respond well to intravenous iron within 3–4 weeks, but they will respond even more dramatically and rapidly when ESAs are given together with the iron.

Maximum surgical blood order schedule

The concept of the maximum surgical blood order schedule (MSBOS) was first developed in the mid-1970s to prevent the over-ordering of blood before surgery – thus the term "maximum" surgical blood order schedule. The main concern is that many institutions have an outdated MSBOS that is based on consensus opinions rather than on actual blood utilization data for specific surgical procedures. Using an algorithm that includes three variables – the percentage of patients receiving transfusions, the median estimated blood loss, and the average number of units transfused per patient – the authors described methods for creating an institution-specific MSBOS (*5*). The actual document, created as a guide for preoperative blood orders, includes 135 types of surgical procedures and the associated recommended blood order for each (Fig. 8.1, which is derived from Johns Hopkins Hospital blood utilization data).

Figure 8.1. An institution-specific maximum surgical blood order schedule (MSBOS) derived from blood utilization data at the Johns Hopkins Hospital (*5*).

SURGICAL BLOOD ORDER SCHEDULE

Cardiac surgery	Rec.
Heart or lung transplant	T/C 4U
Minimally invasive valve	T/C 4U
Revision sternotomy	T/C 4U
CABG/valve	T/C 4U
Open heart surgery	T/C 4U
Assist device	T/C 4U
Cardiac/major vascular	T/C 4U
Open ventricle	T/C 4U
CABG	T/C 2U
Cardiac wound surgery	T/C 2U
Percutaneous cardiac	T/C 2U
Pericardium	T/C 2U
Lead extraction	T/C 2U
AICD/pacemaker placement	T/S

General surgery	Rec.
AP resection	T/C 2U
Intra-abdominal GI	T/C 2U
Whipple or pancreatic	T/C 2U
Liver resection	T/C 2U
Retroperitoneal	T/C 2U
Substernal	T/C 2U
Bone marrow harvest	T/S
Hernia – ventral/incisional	T/S
Hernia – inguinal/umbilical	No sample
Appendectomy	No sample
Abdomen/chest/soft tissue	No sample
Lap. or open cholecystectomy	No sample
Thyroid/parathyroid	No sample
Central venous access	No sample
Any breast – except w/flaps	No sample

Gynecological surgery	Rec.
Uterus open	T/C 2U
Open pelvic	T/C 2U
Uterus/ovary	T/S
Total vaginal hysterectomy	T/S
Cystectomy robotic-assisted	T/S
Cystoscopy	No sample
External genitalia	No sample
GYN cervix	No sample
Hysteroscopy	No sample
Superficial wound	No sample

Neurosurgery	Rec.
Thoracic/lumbar/sacral fusion	T/C 4U
Spine tumor	T/C 2U
Posterior cervical spine fusion	T/C 2U
Spine incision and drainage	T/C 2U
Intracranial tumor/aneurysm	T/C 2U
Laminectomy/discectomy	T/S
Spine hardware removal/biopsy	T/S
ACDF	T/S
Extracranial	No sample
Nerve procedure	No sample
CSF/shunt procedure	No sample

Orthopedic surgery	Rec.
Thoracic/lumbar/sacral fusion	T/C 4U
Pelvic orthopedic	T/C 4U
Open hip	T/C 2U
Femur open	T/C 2U
Above/below knee amputation	T/C 2U
Humerus open	T/S
Fasciotomy	T/S
Shoulder incision and drainage	T/S
Tibial/fibular	T/S
Total knee replacement	T/S
Shoulder open	T/S
Knee open	T/S
Thigh soft tissue	No sample
Ortho external fixation	No sample
Peripheral nerve/tendon	No sample
Lower extremity I&D	No sample
Hand orthopedic	No sample
Upper extremity arthroscopy	No sample
Upper extremity open	No sample
Podiatry/foot	No sample
Hip closed/percutaneous	No sample
Lower extremity arthroscopic	No sample
Shoulder closed	No sample
Tibial/fibular closed	No sample

Otolaryngology surgery	Rec.
Laryngectomy	T/C 2U
Facial reconstruction	T/C 2U
Cranial surgery	T/C 2U
Radical neck dissection	T/C 2U
Carotid body tumor	T/C 2U
Mandibular surgery	T/S
Neck dissection	T/S
Mastoidectomy	No sample
Parotidectomy	No sample
Facial plastic	No sample
Oral surgery	No sample
Sinus surgery	No sample
Thyroid/parathyroidectomy	No sample
Suspension laryngoscopy	No sample
Bronchoscopy	No sample
Cochlear implant	No sample
EGD	No sample
External ear	No sample
Inner ear	No sample
Tonsillectomy/adenoidectomy	No sample
Tympanomastoid	No sample

Thoracic surgery	Rec.
Esophageal open	T/C 2U
Sternal procedure	T/C 2U
Chest wall	T/C 2U
Thoracotomy	T/C 2U
Pectus repair	T/C 2U
VATS	T/S
Mediastinoscopy	T/S
EGD/FOB	No sample
Central venous access	No sample

Urology	Rec.
Cystoprostatectomy	T/C 2U
Urology open	T/C 2U
Nephrectomy	T/C 2U
Lap kidney/adrenal	T/S
RRP	T/S
Robotic RRP/kidney/adrenal	T/S
Percutaneous nephrolithotomy	No sample
External genitalia	No sample
TURP	No sample
Cysto/ureter/urethra	No sample
TURBT	No sample

Vascular/Transplant surgery	Rec.
Liver transplant	T/C 15U
Thoracoabdominal aortic	T/C 15U
Major liver resection	T/C 4U
Major vascular	T/C 4U
Exploratory lap. vascular	T/C 4U
Kidney pancreas transplant	T/C 2U
Major endovascular	T/C 2U
Above/below knee amputation	T/C 2U
Nephrectomy/kidney transplant	T/C 2U
Organ procurement	T/C 2U
Peripheral vascular	T/C 2U
Vascular wound I and D	T/C 2U
Carotid vascular	T/S
AV fistula	T/S
Peripheral endovascular	T/S
Angio/Arteriogram	No sample
Peripheral wound I&D	No sample
First rib resection/thoracic outlet	No sample
Superficial or skin	No sample
Vascular foot amputation/debride	No sample
Central venous access	No sample

If the procedure you are looking for is not on this list, then choose the procedure that most closely resembles that procedure.

Emergency release blood is avaiable for ALL cases, and carries a risk of minor transfusion reaction of 1 in 1,000 cases.

This list specifies recommended preoperative blood orders for 135 different types of surgical procedures.
T/C, type and crossmatch; T/S, type and screen; U, unit.
Source: Reproduction with permission from Frank et al. Anesthesiology, 2013 (*5*).

A data-driven MSBOS not only improves the blood ordering process, but can also decrease costs by reducing unnecessary blood orders (*6*). The crossmatch-to-transfusion ratio, a classic measure of blood ordering efficiency, can be improved (decreased) by using an accurate MSBOS. For those procedures during which transfusions are rarely or never given, no preoperative blood orders are needed. In the case of unexpected bleeding, the backup plan is emergency release, uncrossmatched (type O) blood, which is much safer than many clinicians believe (*7*).

The other benefits of having an accurate, up-to-date MSBOS are that over-ordering of preoperative crossmatches and setting aside RBC units leads to potential outdating and wastage. At the other extreme, in cases where there is a genuine need for prepared blood, blood units are more likely to be ready when they are needed.

Optimizing coagulation

An important aspect of reducing blood loss and unnecessary transfusions is to optimize coagulation before surgery. For example, vitamin K antagonists (such as warfarin) usually require discontinuation 3–5 days before surgery to normalize coagulation. Vitamin K (0.5–mg intravenously) can be given if surgery can wait for 6 or more hours, otherwise plasma (up to 15 ml/kg) can be given to correct the international normalized ratio (INR) to be < 2.0. Other drugs such as P2Y12 inhibitors (for example, clopidogrel) should be discontinued, if possible, in time for their effect to subside before elective surgery. Often, a cardiac surgery patient needs 2–5 days off the medication for coagulation to normalize before surgery. Aspirin and other non- steroidal anti-inflammatory drugs (NSAIDs) have less impact on coagulation, and for most surgeries do not have to be discontinued. However, for brain, spine or eye surgery, where bleeding into a closed anatomical space can be harmful, these drugs should be discontinued (i.e. aspirin 7 days and others 24 hours prior to surgery). Subcutaneous heparin, at least when administered in twice a day doses, does not require discontinuation, but three times a day dosing may induce a greater coagulation deficiency.

Preoperative autologous blood donation

Historically, preoperative autologous blood donation (PAD) was often used in an attempt to avoid use of allogeneic blood. However, over the past decade, preoperative autologous blood collection has been decreasing. In 2015, only 25,000 units were collected in the United States, representing approximately 0.2% of the total allogeneic RBC/whole blood collection and 60% fewer units than were collected in 2013. Major factors contributing to this decline include the increased safety of and public confidence in the blood supply, adoption of intraoperative blood-conserving techniques, high wastage of PAD blood (>45% discarded), and a higher risk for preoperative anaemia after donation. Errors related to production and handling, delays in receipt of the units at the designated hospital, and increasing acquisition costs also contributed to the decrease in PAD. There may also be additional cost to the patient due to lost time from work required for the donation.

Despite these concerns about efficacy, PAD can be a reasonable option for patients with rare blood types or multiple red cell alloantibodies. In these situations, advance planning and patient evaluation are crucial before PAD is attempted. To mitigate the anaemia induced by PAD and avoid allogeneic transfusions, efforts should focus on:

- timing of collections to allow 3–4 weeks between the last donation and planned surgery;
- collecting the minimal amount; and
- prescribing iron-replacement therapy with or without an ESA before donation.

8.3 Techniques to reduce operative blood loss

Minimally invasive surgical approaches

In the past two decades, new surgical approaches have been introduced, including laparoscopic techniques, which have dramatically reduced blood use. For instance, at the author's institution, only 1 in 800 patients undergoing laparoscopic/robotic prostatectomy received an intraoperative transfusion, whereas historically, the vast majority of open prostatectomy patients were given transfusions (*5*). A similar situation has also been seen with laparoscopic and robotic methods of gynaecological surgery, for example hysterectomy and myomectomy procedures. At first, robotic and other minimally invasive procedures were marketed as reducing pain and length of hospital stay and enabling an earlier return to work. However, these approaches have also dramatically reduced the need for transfusion.

Maintaining normothermia, controlled hypotension, avoiding excessive haemodilution

Another strategy for reducing transfusions is centred around decreasing intraoperative blood loss. Reducing intraoperative blood loss begins with meticulous surgical technique, but other strategies to reduce bleeding have also been developed (Table 8.1). Simply maintaining normothermia by warming IV fluids and the patient directly (for example, forced-air warming) will reduce bleeding. Even mild hypothermia (35 °C) increases bleeding by about 20% by inhibiting platelet function and the clotting cascade.

Another simple method of reducing intraoperative blood loss is controlled hypotension, which is especially effective in orthopaedic and spine surgery. With increased depth of anaesthesia, and/or administration of potent vasodilators, the blood pressure can be carefully decreased while maintaining vital organ perfusion with a mean arterial blood pressure above the autoregulation threshold.

Avoiding excess crystalloid is also helpful as this leads to decreased haemoglobin levels resulting from haemodilution. This can be accomplished with administration of colloid to expand intravascular volume (for example, albumin), and/or low-dose vasoconstrictors (for example, phenylephrine) to treat anaesthetic-induced hypotension.

Topical haemostatics, sealants and other methods to reduce intraoperative bleeding

Topical haemostatic agents, such as fibrin, thrombin, gelatin, collagen and bone wax have been shown to aid in haemostasis in some settings. Some commercially available combination products contain gelatin and thrombin in the appropriate ratio to optimize haemostasis. Newer cauterization methods, such as a saline-irrigated bipolar cautery, or the harmonic scalpel, which cauterizes vessels as it cuts are also effective in reducing intraoperative bleeding. There is some evidence that neuraxial anaesthesia (spinal or epidural) may reduce bleeding by about 20%, perhaps through reduction of venous and/or arterial blood pressures.

Antifibrinolytic medications

Antifibrinolytic medications such as tranexamic acid or aminocaproic acid were introduced almost 50 years ago, but only in the past decade have they gained popularity as a means for reducing perioperative blood loss and the need for transfusion. Tranexamic acid, in particular, has been called a "game changer" and is quickly becoming the standard

of care for certain procedures, even though using these drugs to reduce surgical bleeding is considered "off-label" use. Multiple studies have shown that their use has reduced bleeding, transfusion and cost associated with spine surgery, hip and knee arthroplasty, and cardiac surgery. Overall, the studies collectively show that, compared to placebo, tranexamic acid reduces blood loss and transfusion requirements by about 30%. The drug is thought to stabilize a clot that has already formed, by preventing its breakdown (fibrinolysis). The risk of deep venous thrombotic events does not appear to increase with use of these drugs, even in the three largest clinical trials with placebo control groups.

Two studies with 20,000 patients in each, one in haemorrhaging trauma patients (the CRASH-2 Trial) (*8*), and the other in women with postpartum haemorrhage (the WOMAN Trial) (*9*) showed a reduction in mortality when tranexamic acid was given within 3 hours of the bleeding onset. However, no benefit was seen after this 3-hour window. The CRASH-2 study showed a 9% reduction in overall mortality and a 15% reduction in mortality from haemorrhage. In the WOMAN Trial, there was a 19% reduction in overall mortality and a 31% reduction in mortality from haemorrhage. A single loading dose of 1 g is now common for adult patients who are having total joint surgeries, and this dose was also used in the two above-mentioned trials. For longer surgical procedures, for example the larger spine cases, this loading dose is often followed by a continuous infusion, but the ideal dose has not yet been determined. Recent findings suggest that 3–5 mg/kg per hour may provide a steady state and an efficacious therapeutic level. The contraindications to systemic tranexamic acid include uncontrolled seizures or an active thrombotic event, but a history of these conditions is not thought to be a contraindication.

Point-of-care testing

When turnaround times for laboratory test results are long, it is likely that during the waiting period, the clinician will decide to administer a transfusion to the patient rather than wait for the test results. Haemoglobin and some coagulation measurements can be done at the bedside with a drop of blood, in which case it is quicker and easier to get results, and an unnecessary transfusion can be avoided based on the quick turnaround time. Undoubtedly, point-of-care testing is an important component in a PBM programme and can reduce unnecessary transfusions.

8.4 Fluid replacement and transfusion

Volume expanders

Dilutional anaemia from excessive intravenous fluids is common in hospitalized patients and can lead to unnecessary transfusions. In this scenario, the total red cell mass can be normal, but the haemoglobin concentration will be low. To avoid this, many centres have reduced crystalloid administration in surgical patients, and some have substituted colloids for crystalloids. Starch solutions, or in the United States more commonly albumin, have become popular as volume expanders. Haemodilution still occurs with colloids, but probably to a lesser extent since lower volumes are required to treat hypovolaemia. Whether outcomes differ between crystalloid and colloid therapies is still an ongoing debate; however, there is less evidence for harm (for example, renal dysfunction) with albumin than with starch solutions.

Transfusion guidelines

A patient's response to anaemia is highly individualized and depends on ability to maintain adequate oxygen delivery to tissues. Tolerance depends on the patient's volume status, physiological reserve (including cardiac, pulmonary and renal function), and the dynamics of the anaemia. Patients with chronic anaemia due to chronic renal failure, slow gastrointestinal bleeding or menorrhagia often physiologically adapt to a lower haemoglobin level by increasing

cardiac output, heart rate or stroke volume. However, rapid blood loss from surgical bleeding or trauma often results in haemodynamic instability, shock and other symptoms that require more rapid volume replacement. Thus, chronic anaemia seems to be better tolerated than acute anaemia.

As discussed previously, and according to the studies shown in Table 8.1, there is strong evidence supporting a restrictive transfusion strategy, using lower haemoglobin thresholds than were used historically (7–8 g/dl instead of 10 g/dl). However, evidence is lacking to support applying a restrictive threshold in patients with active bleeding, or ongoing cardiac or cerebral ischaemia. More importantly, an arbitrary haemoglobin level or "trigger" should not be the sole driver for transfusion. Transfusion decisions should be individualized and based not only on the haemoglobin level but also on the patient's clinical signs and symptoms of anaemia and ability to tolerate and compensate for the anaemia (*10*). More simply stated, we should treat the whole patient and not just their laboratory values.

The general methods used to implement and sustain a strong PBM programme are outlined in Table 8.1. It is intuitively apparent that education is perhaps the most important component of any quality improvement effort. Even educated clinicians are unlikely to familiar with all of the large randomized trials that have been published, all in support of a restrictive RBC transfusion strategy with haemoglobin thresholds lower than those traditionally employed (Table 8.1).

Table 8.1. Large prospective randomized trials on red blood cell transfusion thresholds

Clinical trial (number of participants)	Patient population	Restrictive strategy (Hb trigger – target)	Liberal strategy (Hb trigger – target)	Reduction in blood utilization	Primary outcome			
					Event	Restrictive (incidence)	Liberal (incidence)	*P* value
Hebert, et al. (1999) (*11*) (n=838)	Critically ill (adults)	7 to 8.5 g/dl	10 to 10.7 g/dl	54% fewer RBC units transfused	30-day mortality	18.7%	23.3%	0.11
Hajjar, et al. (2010) (*12*) (n=502)	Cardiac surgery (adults)	8 to 9.1 g/dl	10 to 10.5 g/dl	58% fewer RBC units transfused	Composite end-point	11%	10%	0.85
					30-day mortality	6%	5%	0.93
					Cardiogenic shock	9%	6%	0.42
					ARDS	2%	1%	0.99
					Acute renal injury requiring dialysis	4%	5%	0.99
Carson et al. (2011) (*13*) (n=2,016)	Femur fracture (elderly adults)	8.0 to 9.5 g/dl	10.0 to 11.0 g/dl	65% fewer RBC units transfused	Composite end-point	34.7%	35.2%	NS
					60-day mortality	28.1%	27.6%	NS
					60-day Inability to walk	6.6%	7.6%	NS
Villanueva et al. (2013) (*14*) (n=921)	Gastrointestinal bleeding (adults)	7 to 9.2 g/dl	9 to 10.1 g/dl	59% fewer RBC units transfused	45-day all-cause mortality	5%	9%	0.02
Holst et al. (2014) (*15*) (n=998)	Septic shock (adults)	7 to 7.5 g/dl	9 to 9.5 g/dl	50% fewer RBC units transfused	90-day all-cause mortality	43.0%	45.0%	0.44
Robertson et al. (2014) (*16*) (n=200)	Traumatic brain injury (adults)	7 to 9.7 g/dl	9.5 to 11.4 g/dl	74% fewer RBC units transfused	Glascow outcome scale score (favourable)	42.5%	33%	0.28
Lacroix et al. (2007) (*17*) (n=637)	Critically ill (paediatric)	7 to 8.7 g/dl	9.5 to 10.8 g/dl	44% fewer RBC units transfused	Multiorgan dysfunction score (MODS)	12%	12%	NS
Murphy et al. (2015) (*18*) (n=2,007)	Cardiac surgery (adults)	7.5 to 9 g/dl	9.0 to 10 g/dl	40% fewer RBC units transfused	Serious infections or ischaemic event at 90 days	35.1%	33.0%	0.30
Mazer et al. (2017) (*19*) (n=5243)	Cardiac surgery (adults)	7.5 to 9 g/dl	9.5 to 10 g/dl	33% fewer RBC units transfused	Death, MI, stroke or renal failure w/ dialysis by day 28	11.4%	12.5%	NS

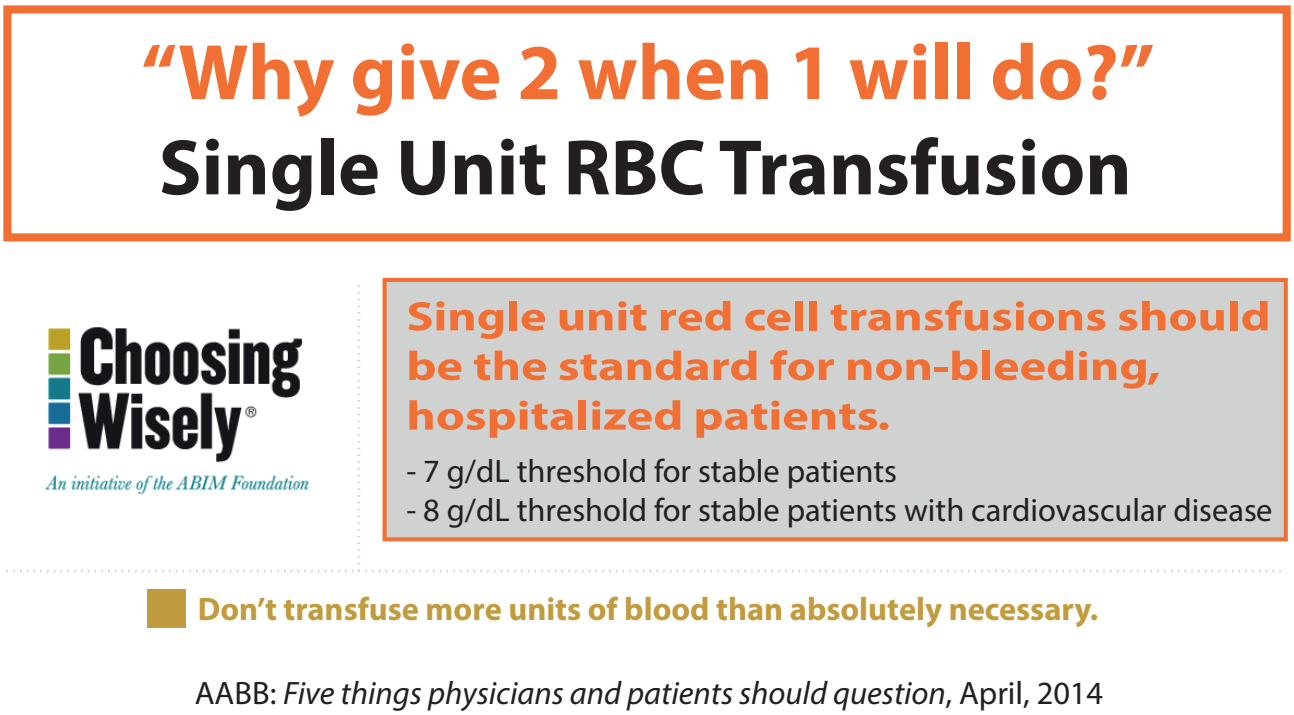
ARDS, acute respiratory distress syndrome; Hb, haemoglobin; MODS, multiple organ dysfunction syndrome; MI, myocardial infarction; NS, not significant; RBC, red blood cell.

Single-unit RBC transfusions

Traditionally, physicians were strongly encouraged to order two-unit RBC transfusions, a practice that evolved several decades ago when single-unit transfusions were extensively criticized. A unit of blood can have varying effects on haemoglobin and haematocrit, depending on the patient's total blood volume and fluid shifts. Often a single RBC unit provides an adequate response and relieves symptoms. In 2014, the AABB Choosing Wisely campaign was launched and its first aim was "Don't transfuse more units of blood than absolutely necessary" (*20*). This included a recommendation for, in a non-bleeding hospitalized patient, a single-unit RBC transfusion followed by clinical reassessment before additional units were given. The impact of implementing a single-unit transfusion policy can be significant and may have an even greater impact on reducing overall blood utilization than monitoring haemoglobin thresholds.

The Johns Hopkins Health System launched a "Why Give 2 When 1 Will Do?" campaign resulting in a 50% decrease in double-unit RBC transfusion orders, and an overall 20% decrease in RBC utilization (*12*). One effective method of encouraging single-unit RBC orders was a custom-designed message displayed in hospital newsletters (Fig. 8.2).

Figure 8.2. Image used for a "Why Give 2 When 1 Will Do?" campaign to emphasize the importance of single-unit red blood cell (RBC) transfusions in haemodynamically stable, nonbleeding patients.



Source: The image was published in newsletters and displayed across the health system. This message is backed by the AABB Choosing Wisely guidelines (*20*).

8.5 Autologous blood transfusion, acute normovolaemic haemodilution and cell salvage

Acute normovolaemic haemodilution

Acute normovolaemic haemodilution (ANH) is a technique that involves phlebotomy (collection of blood into anticoagulant-containing blood bags), of usually from one to four units of whole blood before the blood-loss portion of the surgery and intentional haemodilution with crystalloid and/or colloid. Because this process creates a state of intraoperative anaemia, the shed blood contains fewer RBCs. Near the end of the procedure, when most of the anticipated blood loss is complete, the phlebotomized blood is reinfused. Although it may seem that this method would be effective in reducing transfusion requirements, the value provided by ANH requires all three of the following conditions to be met:

- The preoperative haematocrit must be sufficiently high that the patient can tolerate the phlebotomy and haemodilution.
- The blood loss during surgery must be substantial enough to obtain the benefits.
- The volume of phlebotomized blood must be great enough to make a difference.

Because these three conditions are not always met, there is controversy about whether the ANH technique reliably reduces the need for allogeneic transfusion. ANH may be most useful for patients who benefit most from receiving fresh coagulation factors and platelets in the whole blood that is reinfused. This may be of potential use in major procedures such as cardiac surgery, where the whole blood is not subjected to cooling and may also help reduce damage to platelets by the cardiopulmonary by-pass machine.

Autologous blood salvage (cell saver)

Although not available in all hospitals, intraoperative autologous blood salvage, one of the earliest blood conservation methods, was developed in the late 1970s (*22*). Using a specialized bowl to collect and wash debris from the shed blood, the "cell saver" was conveniently introduced just before the outbreak of HIV. This method of blood conservation became very popular in the 1980s, when patients strongly preferred to have their own blood rather than banked allogeneic blood for transfusion, primarily to avoid transfusion-transmitted infections. In this procedure, shed blood is washed in a cone or cylindrical-shaped centrifuge bowl that concentrates the RBCs, which are then immediately transfused back to the patient. The resulting product has a haematocrit similar to that of RBCs from the blood bank, and is devoid of plasma and platelets. If enough salvaged blood is administered (about five or more units), the patient will begin to develop a dilutional coagulopathy. Nonetheless, for vascular, transplant, orthopaedic and cardiac procedures, autologous salvaged blood has become a standard of care for blood conservation in many countries.

A primary limitation of blood salvage is that a pooled cavity is needed for optimal collection and recovery of shed blood. There are also concerns about potential contamination of the shed blood, such as in cases of infection or tumours, and with amniotic fluid if used during caesarean section. Use of washing and leukocyte depletion filters have been shown to significantly reduce risk of contaminating cells, however, and the currently available literature does not show worse outcomes when salvaged blood is used in these cases.

The use of autologous blood salvage has several advantages. Evidence shows that where one or more units are returned to the patient, intraoperative blood salvage adds economic value. Additionally, salvaged RBCs are likely to be of higher quality than stored (banked) RBCs.

Because salvaged RBCs for immediate reinfusion do not suffer from "storage lesions", red cell membrane deformability and 2,3-diphosphoglycerate levels are near normal, whereas both of these parameters are decreased in stored blood. Use of autologous blood also eliminates the risk for viral transmission and alloimmunization. For all of these reasons, salvaged RBCs are usually preferred over allogeneic stored RBCs.

Cell salvage can be used in both elective and emergency procedures, provided it is activated promptly when bleeding is a concern. Trained staff and appropriate equipment and consumables are required, along with careful attention to all quality aspects to ensure proper collection and reinfusion of shed blood using the cell saver. Clinical audit programs should include the appropriate utilization of blood salvage.

8.6 Care in the postoperative period

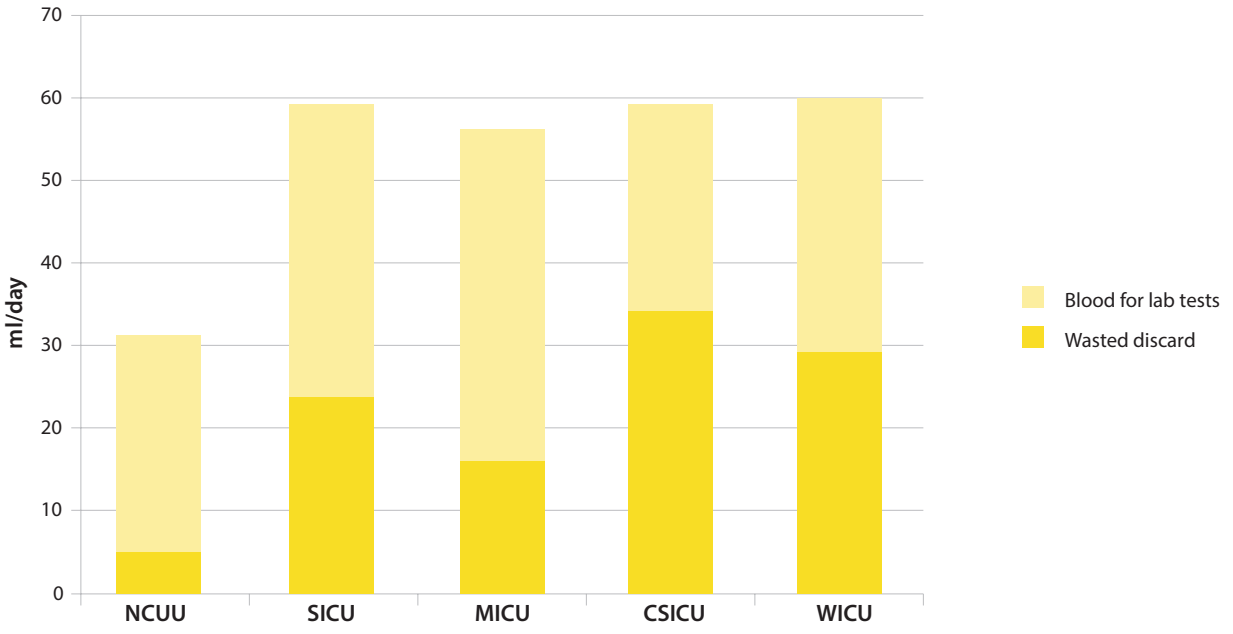
Postoperative blood recovery

Postoperative blood recovery involves collecting and reinfusing blood from surgical drains and/or wounds. Adequate amounts of blood need to be collected and processed for this to be effective. Thus, it is used mainly in trauma, vascular, cardiac and complex orthopaedic surgical cases where the shed blood volume can be significant (≥ 500 ml). Postoperative recovered blood can be unwashed or washed. When unwashed, shed blood is collected and filtered in a device until sufficient volume is reached; then it is transferred to an infusion bag for reinfusion. For the washed product, once sufficient shed blood is collected, it is processed by washing and then transferred to a bag for reinfusion. In the past, reinfusion of unwashed shed blood was popular as a blood conservation technique in joint replacement surgery. However, the growing use of antifibrinolytics has led to a decrease in surgical bleeding, making postoperative blood recovery less relevant. In addition, unwashed shed blood is less desirable because it has a haematocrit of 20–30% and contains activated clotting and complement factors, inflammatory mediators, cytokines and fat particles that can increase the risk for febrile reactions.

Reducing phlebotomy blood loss

It is well-recognized that patients are prone to iatrogenic blood loss as a result of laboratory testing, especially when they are in the ICU, where more frequent lab tests are ordered. In addition, easy access to blood draws when arterial and central venous catheters are present predisposes these ICU patients to lose approximately 1% or more of their circulating blood volume per day to samples for laboratory testing. About half the blood is lost when lines are cleared to draw an undiluted sample, and the rest is blood sent to the laboratory. Fig. 8.3 shows unpublished data on the average amount of blood lost per day in ICU patients from laboratory testing in five different adult ICUs at Johns Hopkins Hospital. Smaller phlebotomy tubes are useful to reduce blood loss, and in-line devices that return blood that would otherwise be wasted, in a sterile fashion, are also helpful. One ICU, the neurocritical care unit, was able to decrease blood loss by half by using an in-line return device (Fig. 8.3). Simply eliminating unnecessary laboratory tests is also important. In some cardiac surgery patients, up to one or two units of blood can be lost due to phlebotomy alone during longer ICU stays.

Figure 8.3. Graph illustrating the average volume of blood that patients lose as a result of laboratory testing in the five different adult intensive care units (ICUs) at the Johns Hopkins Hospital



NCCU: neurocritical care unit | **SICU**: surgical intensive care unit | **MICU**: medical intensive care unit
CSICU: cardiac surgical intensive care unit | **WICU**: Weinberg intensive care unit (primarily surgical oncology patients)

Summary

Successfully implementing a PBM programme requires planning, education and teamwork. A PBM programme is an important patient safety and quality measure that can also lead to improved blood utilization and cost savings. Focus on education and evidence-based transfusion guidelines can be effective in encouraging good practice and reducing unnecessary transfusions.

PBM guidance is available from various professional organizations, including the AABB (formerly the American Association of Blood Banks), SABM (Society for the Advancement of Blood Management) and the International Society of Blood Transfusion (ISBT). With a successful PBM programme, we can reduce risk, improve outcomes and reduce cost, which in combination, can increase the value of health care we deliver.

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References

1. Carson JL, Triulzi DJ, Ness PM. Indications for and adverse effects of red-cell transfusion. N Engl J Med. 2017;377:1261–72.
2. Frank SM, Savage WJ, Rothschild JA, Rivers RJ, Ness PM, Paul SL. Variability in blood and blood component utilization as assessed by an anesthesia information management system. Anesthesiology. 2012;117:99–106.
3. Joint Commission Overuse Summit 2012: https://www.jointcommission.org/assets/1/6/National_Summit_Overuse.pdf; accessed 9/20/2018.
4. Shander A. Preoperative anemia and its management. Transfus Apher Sci. 2014;50:13-5.
5. Frank SM, Rothschild JA, Masear CG, Rivers RJ, Merritt WT, Savage WJ et al. Optimizing preoperative blood ordering with data acquired from an anesthesia information management system. Anesthesiology. 2013;118:1286–97.

6. Frank SM, Oleyar MJ, Ness PM, Tobian AA. Reducing unnecessary preoperative blood orders and costs by implementing an updated institution-specific maximum surgical blood order schedule and a remote electronic blood release system. Anesthesiology. 2014;121:501–9.
7. Dutton RP, Shih D, Edelman BB, Hess J, Scalea TM. Safety of uncrossmatched type-O red cells for resuscitation from hemorrhagic shock. J Trauma. 2005;59:1445–9.
8. Roberts I, Shakur H, Afolabi A, Brohi K, Coats T, Dewan Y et al. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. Lancet. 2011;377:1096-101, 101 e1–2.
9. WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. Lancet. 2017;389:2105–16.
10. Carson JL, Guyatt G, Heddle NM, Grossman BJ, Cohn CS, Fung MK et al. Clinical Practice Guidelines From the AABB: Red Blood Cell Transfusion Thresholds and Storage. JAMA. 2016;316:2025–35.
11. Hebert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med. 1999;340:409–17.
12. Hajjar LA, Vincent JL, Galas FR, Nakamura RE, Silva CM, Santos MH et al. Transfusion requirements after cardiac surgery: The TRACS randomized controlled trial. JAMA. 2010;304:1559–67.
13. Carson JL, Terrin ML, Noveck H, Sanders DW, Chaitman BR, Rhoads GG et al. Liberal or restrictive transfusion in high-risk patients after hip surgery. N Engl J Med. 2011;365:2453–62.
14. Villanueva C, Colomo A, Bosch A, Concepcion M, Hernandez-Gea V, Aracil C et al. Transfusion strategies for acute upper gastrointestinal bleeding. New Engl J Med. 2013;368:11– 21.
15. Holst LB, Haase N, Wetterslev J, Wernerman J, Guttormsen AB, Karlsson S et al. Lower versus higher hemoglobin threshold for transfusion in septic shock. N Engl J Med. 2014;371:1381–91.
16. Robertson CS, Hannay HJ, Yamal JM, Gopinath S, Goodman JC, Tilley BC et al. Effect of erythropoietin and transfusion threshold on neurological recovery after traumatic brain injury: A randomized clinical trial. JAMA. 2014;312:36–47.
17. Lacroix J, Hebert PC, Hutchison JS, Hume HA, Tucci M, Ducruet T et al. Transfusion strategies for patients in pediatric intensive care units. N Engl J Med. 2007;356:1609–19.
18. Murphy GJ, Pike K, Rogers CA, Wordsworth S, Stokes EA, Angelini GD et al. Liberal or restrictive transfusion after cardiac surgery. N Engl J Med. 2015;372:997–1008.
19. Mazer CD, Whitlock RP, Fergusson DA, Hall J, Belley-Cote E, Connolly K et al. Restrictive or liberal red-cell transfusion for cardiac surgery. N Engl J Med. 2017;377:2133–44.
20. Callum JL, Waters JH, Shaz BH, Sloan SR, Murphy MF. The AABB recommendations for the Choosing Wisely campaign of the American Board of Internal Medicine. Transfusion. 2014;54:2344–52.
21. Frank SM, Thakkar RN, Podlasek SJ, Ken Lee KH, Wintermeyer TL, Yang WW et al. Implementing a health system-wide patient blood management program with a clinical community approach. Anesthesiology. 2017;127:754–64.
22. Waters JH. Indications and contraindications of cell salvage. Transfusion. 2004;44:40S–4S.

Suggested reading

Review articles

Carson JL, Triulzi DJ, Ness PM. Indications for and adverse effects of red-cell transfusion. N Engl J Med. 2017;377:1261–72.

Shander A. Preoperative anemia and its management. Transfus Apher Sci. 2014;50:13–5.

Auerbach M. Intravenous iron in the perioperative setting. Am J Hematol 2014;89:933.

Vassallo R, Goldman M, Germain M, Lozano M, Collaborative B. Preoperative autologous blood donation: Waning indications in an era of improved blood safety. Transfus Med Rev. 2015;29:268–75.

Esper SA, Waters JH. Intra-operative cell salvage: A fresh look at the indications and contraindications. Blood Transfus. 2011;9:139–47.

Sikorski RA, Rizkalla NA, Yang WW, Frank SM. Autologous blood salvage in the era of patient blood management. Vox Sang. 2017;112:499–510.

Resar LM, Wick EC, Almasri TN, Dackiw EA, Ness PM, Frank SM. Bloodless medicine: Current strategies and emerging treatment paradigms. Transfusion. 2016;56:2637–47.

Guidelines

Carson JL, Guyatt G, Heddle NM, Grossman BJ, Cohn CS, Fung MK et al. Clinical Practice Guidelines From the AABB: Red Blood Cell Transfusion Thresholds and Storage. JAMA. 2016;316:2025–35.

Roback JD, Caldwell S, Carson J, Davenport R, Drew MJ, Eder A et al. Evidence-based practice guidelines for plasma transfusion. Transfusion. 2010;50:1227–39.

Kaufman RM, Djulbegovic B, Gernsheimer T, Kleinman S, Tinmouth AT, Capocelli KE, et al.

Platelet transfusion: A clinical practice guideline from the AABB. Ann Intern Med. 2015;162:205–13.

Randomized trials

Red blood cell transfusion

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

Hajjar LA, Vincent JL, Galas FR, Nakamura RE, Silva CM, Santos MH et al. Transfusion requirements after cardiac surgery: The TRACS randomized controlled trial. JAMA.

2010;304:1559–67.

Hebert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med. 1999;340:409–17.

Lacroix J, Hebert PC, Hutchison JS, Hume HA, Tucci M, Ducruet T et al. Transfusion strategies for patients in pediatric intensive care units. N Engl J Med. 2007;356:1609–19.

Robertson CS, Hannay HJ, Yamal JM, Gopinath S, Goodman JC, Tilley BC et al. Effect of erythropoietin and transfusion threshold on neurological recovery after traumatic brain injury: A randomized clinical trial. JAMA. 2014;312:36–47.

Villanueva C, Colomo A, Bosch A, Concepcion M, Hernandez-Gea V, Aracil C et al. Transfusion strategies for acute upper gastrointestinal bleeding. New Engl J Med. 2013;368:11–21.

Murphy GJ, Pike K, Rogers CA, Wordsworth S, Stokes EA, Angelini GD et al. Liberal or restrictive transfusion after cardiac surgery. N Engl J Med. 2015;372:997–1008.

Holst LB, Haase N, Wetterslev J, Wernerman J, Guttormsen AB, Karlsson S et al. Lower versus higher hemoglobin threshold for transfusion in septic shock. N Engl J Med. 2014;371:1381–91.

Mazer CD, Whitlock RP, Fergusson DA, Hall J, Belley-Cote E, Connolly K et al. Restrictive or liberal red-cell transfusion for cardiac surgery. N Engl J Med. 2017;377:2133–44.

Platelet transfusion

Slichter SJ, Kaufman RM, Assmann SF, McCullough J, Triulzi DJ, Strauss RG et al. Dose of prophylactic platelet transfusions and prevention of hemorrhage. N Engl J Med. 2010;362:600– 13.

Useful websites

AABB: https://www.aabb.org/news-resources/resources/patient-blood-management, accessed 13 June 2021
ISBT: https://www.isbtweb.org/working-parties/clinical-transfusion, SABM: https://sabm.org, accessed 13 June 2021

CHAPTER 9

IMPLEMENTING A HOSPITAL-BASED PATIENT BLOOD MANAGEMENT PROGRAMME

Key points

1. Patient blood management (PBM) involves the implementation of evidence-based transfusion guidelines to reduce variability in transfusion practice.

2. Patient safety is at the heart of transfusion practice and PBM.

3. PBM aims to improve clinical outcomes by avoiding unnecessary exposure to blood components.

4. PBM requires a multidisciplinary team approach to study, implement and monitor activities that can impact the use of blood and blood components.

5. PBM has many different strands and allows clinicians to focus on strategies that work for their patients within their transfusion environment.

9.1 Introduction

There is increasing awareness of the limited clinical efficacy of blood transfusion, concerns regarding its safety and the rising costs of providing blood products. Patient blood management (PBM) programmes are a solution to these problems. The practice of PBM involves the implementation of evidence-based transfusion guidelines to reduce variability in transfusion practice, and the establishment of multidisciplinary teams to study, implement and monitor activities that can impact the use of blood and blood components. PBM also aims to improve clinical outcomes by avoiding unnecessary exposure to blood components and a number of different models are described in the literature. Institutions are advised to review the available models and adapt one that works within their health care setting.

Learning outcomes

The goal of this chapter is to provide information on PBM and give readers a structure to implement this within their own clinical setting. Specifically, the reader should be able to:

- Devise a plan for using PBM strategies within their transfusion practice
- Consider which members of the multidisciplinary team are required to implement PBM, including the role of the Transfusion Practitioner
- Understand the importance of audit as both a tool for baseline assessment and for reviewing the impact of changes made
- Develop a strategy for the roll-out of safe transfusion practice education and information for all those involved in blood transfusion

9.2 Where do I start and how do I develop a plan of action?

John Kotter, a Harvard Business School professor, has outlined a strategy of change management (*1*). This strategy can be used to develop a plan of action for building a PBM programme. The place to start is that a crisis needs to be created. This crisis can relate to the availability of allogeneic blood; it can relate to the safety of the available blood; or, it can relate to the cost of acquiring a unit of blood.

Once the crisis has been recognized, a coalition of individuals needs to be created. These individuals need to be leaders who can implement and force change. They must have the power and resources to create change. A business plan then needs to be developed.

A strategy to optimize blood utilization and perioperative blood management is outlined in Table 9.1. An easy place to start is to make sure that clinicians are using blood appropriately and see where the best available evidence demonstrates benefit. Hospitals information systems should be set up to provide prospective auditing data on appropriate blood use. If prospective data collection is not possible, then retrospective auditing will need to be performed where blood use is reviewed by a team of experts to determine if use was appropriate. If use was inappropriate, this is then conveyed to the provider. This communication is ideally performed in a non-threatening, educational way.

Table 9.1. A strategy to optimize blood utilization and perioperative blood management

Transfusion practice	Leverage solutions to push evidence-based transfusion practice
Autotransfusion	Follow national or professional society intraoperative blood recovery and reinfusion (cell salvage, normovolaemic haemodilution, component therapy) standards*
Anaemia management	Implement a preoperative haemoglobin optimization programme
Reduce wastage related to blood product use	Reduce wastage as it relates to transfusion practice by reducing phlebotomy loss, eliminating preoperative autologous donation and reducing allogeneic blood wastage due to mishandling
Surgical technique	Minimize iatrogenic blood loss through meticulous surgical technique, limit sampling practice, use point-of-care testing
Reporting	Enhance physicians' awareness through education and auditing of blood utilization practice

* For example, available at: AABB: https://www.aabb.org/news-resources/resources/patient-blood-management

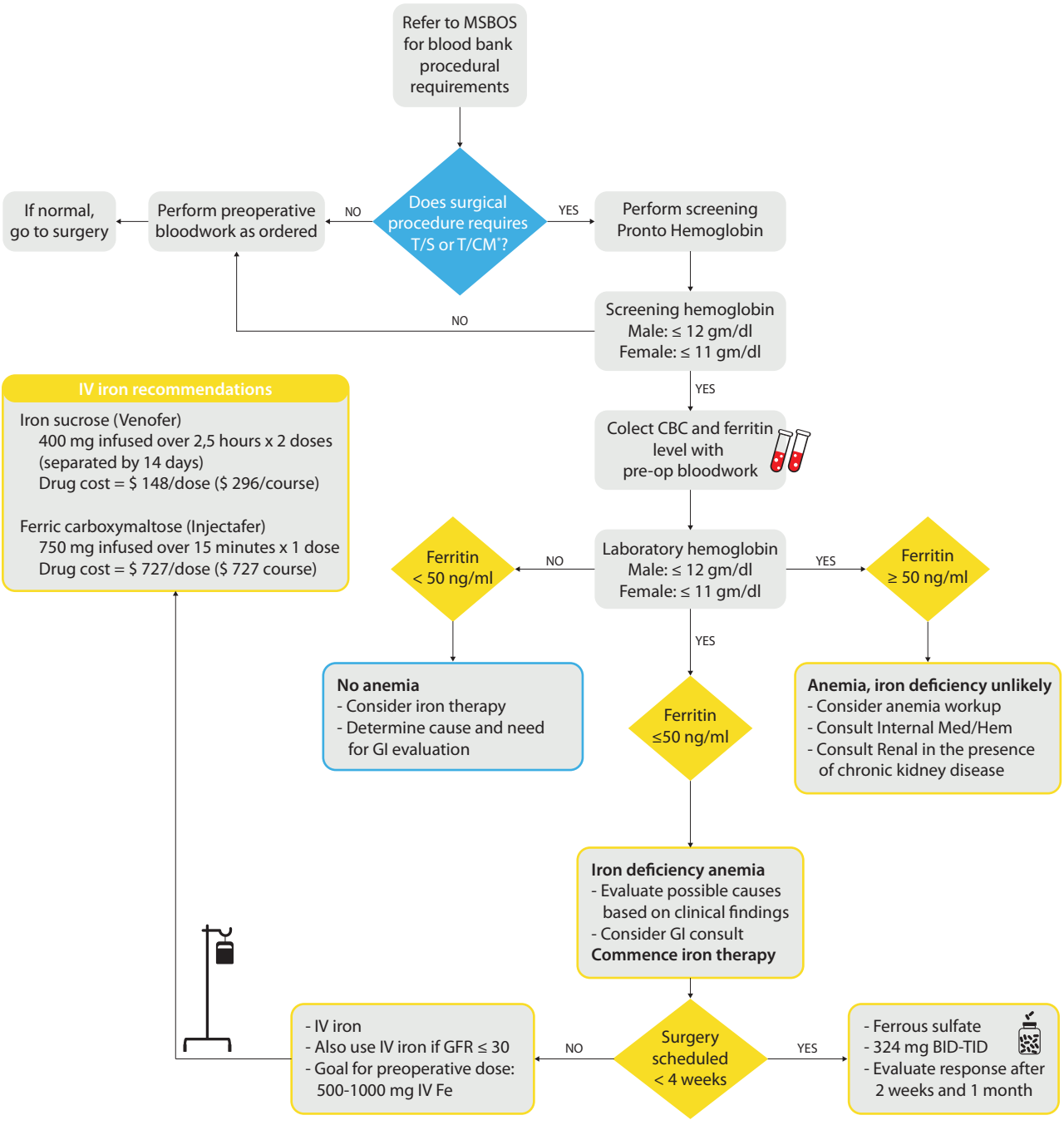
Another focus is on anaemia management. Preoperative anaemia is associated with increases in perioperative morbidity and mortality. The prevalence of anaemia worldwide is staggering. A structure should therefore be in place for identifying and managing preoperative anaemia. Fig. 9.1 shows a treatment algorithm for this purpose. Additionally, in hospitalized patients, phlebotomy blood loss can be extensive, especially in critically ill patients from whom frequent blood samples are taken. Such patients tend to have bone marrow suppression in association with their illness, so regenerating a red cell mass is difficult when phlebotomy loss is repetitive.

To minimize phlebotomy loss, the following could be considered:

- Point-of-care testing devices could be used (if available), which use microlitre quantities of blood to obtain laboratory information.
- Routine blood draws scheduled at set times should be limited.
- The use of paediatric samples with smaller volumes should be considered.
- Consideration should be given to "waste" volumes taken at the beginning of the phlebotomy process to minimize the amount of discarded blood.

One of the most effective techniques for managing surgical blood loss is through the use of autotransfusion, sometimes called cell salvage or intraoperative cell salvage, where shed surgical blood is collected, processed and reinfused (see Chapter 8, section 8.5). In many parts of the world, blood is simply collected, filtered and reinfused. Many blood volumes can be returned to a patient via autotransfusion. However, if this blood is not managed appropriately, injury to a patient can occur. A common danger is from using sterile water to wash the shed blood and causing massive red cell lysis. Another danger comes from connecting a primary reinfusion bag directly to a patient's intravenous line and causing an air embolism. Thus, a robust quality control system needs to be established to ensure that the technician operating the equipment is appropriately educated and trained, is aware of these dangers and monitors the blood processing appropriately. In addition, quality assurance testing of the machines should be performed at regular intervals to make sure that they are working appropriately.

Figure 9.1. Algorithm for managing patients who are anaemic and who have been identified as being at high risk of needing a transfusion during a surgical procedure



* T/S: Type and Screen
T/CM: Type and Cross-Match
Source: Reproduced with permission from UPMC patient blood management program.

9.3 Oversight of transfusion practice in the hospital

Oversight of transfusion practice in the hospital should cover hospital transfusion service senior management structure and responsibilities, engaging clinicians and patients, and the structure and function of the Hospital Transfusion Committee.

Every hospital should have some mechanism for overseeing the use of blood. Traditionally, this has taken the form of the Transfusion Committee. Typically, this committee will review blood product and component use, adverse events associated with blood, the crossmatch to transfusion ratio, and changes in the management of blood products and components. This traditional committee can evolve to become a Patient Blood Management Committee, which performs the traditional activities of a Transfusion Committee as well as taking responsibility for quality improvement activities. These activities can include:

- review of the phlebotomy practice;
- implementation of preoperative anaemia management;
- implementation of point-of-care testing;
- development of a bloodless medicine programme for the care of patients who refuse blood; and
- guidelines for the use of adjuncts such as tranexamic acid.

When this committee is established, it is important to have representatives of services that use blood such as surgeons, anaesthetists, haematologists, renal physicians and obstetricians; members of the supply chain who negotiate contracts for blood and related services; members who understand the legal challenges associated with the provision of blood; transfusion medicine specialists, scientists and nurses.

9.4 Clinical practice audit, performance and quality metrics

Auditing should start with a basic understanding of where a hospital's blood resources are being utilized. For instance, if a hospital uses 1000 units of blood per year, it would be useful to know which services and which physicians use this blood. This knowledge would facilitate any quality improvement practices that might be undertaken. Once a basic understanding is achieved, developing volume-adjusted metrics is valuable to separate changes in blood product use from changes in hospital admission rates or in surgical volume. So, if 1000 units of blood per year are being provided for 1000 surgical procedures, a metric of 1 unit per surgical procedure can be used to compare performance if the surgical cases expanded to 1200 or decreased to 800. Fig. 9.2 and Table 9.2 show examples of reports looking at blood utilization. Table 9.2 is a report with volume-adjusted blood use by inpatient admissions and surgical procedures, and Fig. 9.2 looks at blood usage in hip surgery.

Once a basic understanding of where blood is being used has been achieved, reports comparing physicians across similar domains are valuable. A useful example is comparing surgeons who perform total joint replacement surgery. If a hospital finds that one surgeon is doing a total knee replacement without transfusing any blood while another surgeon is administering transfusions to 40% of his or her patients, an opportunity would exist for performance improvement. In total joint replacement, variability can arise from different surgical approaches, different thrombosis prophylaxis, different transfusion thresholds and differences in placement of surgical drains, among others.

Figure 9.2. Blood product use for a single surgical procedure, total hip replacement, which is performed frequently

	2009 Q 3	2009 Q 4	2010 Q 1	2010 Q 2	2010 Q 3
Discharges	376	442	432	411	409
Total receiving blood	153	179	138	175	151
% Total that receive	40.7%	40.5%	31.9%	42.6%	36.9%
Average units per case	1.97	1.93	1.87	2.22	1.87
ALOS w blood	3.8	3.4	3.3	3.4	3.6
ALOS w/o blood	3.5	3.3	3.1	3.1	3.1
Ave charges w blood	$ 90,965	$ 81,021	$ 82,873	$ 78,380	$ 79,704
Ave charges w/o blood	$ 65,493	$ 63,276	$ 62,018	$ 65,165	$ 68,276
% Autologus	12.4%	10.1%	8.0%	9.1%	12.6%
Home discharge %	71.5%	70.4%	83.1%	73.5%	69.9%
Facility discharge %	28.5%	29.6%	16.9%	26.5%	30.1%

Note: The table at the top of the figure shows average blood product use, whereas the bullet graph at the bottom shows where individual surgeons fall. Each bullet represents a single surgeon and the size of the bullet represents the number of surgeries that he or she performed in a reporting period. The x-axis shows the average number of patients who were transfused with erythrocytes during the reporting period whereas the y-axis shows the average number of units transfused during a transfusion episode. The variability in transfusion results from different transfusion triggers, different surgical approaches to replacing the hip, and differing deep vein thrombosis prophylaxis.

Source: Reproduced with permission from UPMC patient blood management program.

Table 9.2. Blood product use with volume adjustment for total surgical cases and for inpatient admissions

	Total products used				Total products used by total surgical cases				Total products used by total inpatient acute admissions			
Blood product	July 2011 – May 2012	July 2012 – May 2013	Variance	Percentage variance	July 2011 – May 2012 (212 258 cases)	July 2012 – May 2013 (221 993 cases)	Variance	Percentage variance	July 2011 – May 2012 (151 311 cases)	July 2012 – May 2013 (164 980 cases)	Variance	Percentage variance
Whole blood	4	0	4	–100.0	0.00	0.00	0.00	–100.0	0.00	0.00	0.00	–100.0
Packed cells	78 397	68 586	9 811	–12.5	0.37	0.31	0.06	–16.4	0.52	0.42	0.10	–19.8
Leukoreduced red cell product	32 924	29 191	3 733	–11.3	0.16	0.13	0.02	–15.2	0.22	0.18	0.04	–18.7
Red blood cells, divided	3 192	2 587	605	–19.0	0.02	0.01	0.00	–22.5	0.02	0.02	0.01	–25.7
Washed/frozen cells	136	296	(160)	117.6	0.00	0.00	(0.00)	108.1	0.00	0.00	(0.00)	99.6
FFP/thawed plasma	41 419	38 142	3 277	–7.9	0.20	0.17	0.02	–12.0	0.27	0.23	0.04	–15.5
Cryo-poor plasma	1 793	1 967	(174)	9.7	0.01	0.01	(0.00)	4.9	0.01	0.01	(0.00)	0.6
Platelets	71 969	60 707	11 262	–15.6	0.34	0.27	0.07	–19.3	0.48	0.37	0.11	–22.6
Cryoprecipitate	11 435	9 272	2 163	–18.9	0.05	0.04	0.01	–22.5	0.08	0.06	0.02	–25.6
Platelet pheresis	2 113	1 915	198	–9.4	0.01	0.01	0.00	–13.3	0.01	0.01	0.00	–16.9
Granulocytes	23	36	(13)	56.5	0.00	0.00	(0.00)	49.7	0.00	0.00	(0.00)	43.6
Total	210 481	183 508	26 973	–12.8	0.99	0.83	0.16	–16.6	1.39	1.11	0.28	–20.0

Note: When total blood products are evaluated in this chart, a –12.8% reduction in products is seen; however, when adjusted for changing volumes the reductions look much larger. For instance, if blood product use is volume-adjusted based on the total inpatient admissions, then the reduction looks dramatically larger at –20.0%.

Source: Reproduced with permission from UPMC patient blood management program.

Another report can cover the inappropriate use of blood. A hospital would need to define what is considered appropriate or inappropriate use of blood in association with laboratory criteria and evidence-based guidelines on best practice. The reporting of inappropriate blood use allows for targeted education of providers who use blood inappropriately. It also provides an opportunity to develop some cost-saving metrics. This allows clinicians and their teams to see the positive financial impact of appropriate blood use and the financial savings could potentially be directed to other health care initiatives.

Clinical audits should also cover quality and safety activities such as storage and handling of the blood products, administration practices and compliance with hospital policies and procedures. Useful resources for blood transfusion audits include:

- National Comparative Audit of Blood Transfusion (http://hospital.blood.co.uk/audits/national-comparative-audit/).
- Audit Reports (https://www2.health.vic.gov.au/hospitals-and-health-services/patient-care/speciality-diagnostics-therapeutics/blood-matters/transfusion-audits).

9.5 Guidelines on the clinical use of blood including maximum surgical blood ordering schedules (MSBOS)

In the 1970s, MSBOS were developed to prevent patients from arriving in the operating room without adequate blood being available. The MSBOS were generated by surveys performed by surgeons to determine the anticipated need for blood for their particular surgery. Surveys were repeated annually in an attempt to maintain a current MSBOS. Several investigators have suggested that using electronic tools to provide data on actual blood product need is a more effective system. But even though MSBOS have become a slightly archaic tool for supporting the most up-to-date surgical techniques, they are a good starting point for those who wish to begin reviewing their blood ordering and usage and have not yet implemented electronic systems within their health care system.

Health care providers manage surgical blood ordering in different ways. At the University of Pittsburgh, United States, the recommendations are stratified according to three groups:

- patients needing no preoperative blood screening;
- patients who should have a type and screen performed; and
- patients who should be screened and crossmatched.

These categories would reflect historical blood need of less than 5%, 5–25%, and greater than 25%, respectively.

9.6 Education and training on the clinical use of blood

For patients to receive a safe and appropriate blood transfusion, it is essential that all those involved in the blood transfusion process are provided with information and training. This requires the implementation of a comprehensive

education programme that includes the latest evidence-based information, uses a range of learning techniques, and allows easy access and flexibility to ensure compliance.

When current clinical practice is understood (which can be achieved using audits or surveys), this can be compared with any guidelines or standard operating procedures (SOPs) that are in place. If no guidelines or SOPs are available, comparisons can be made with national guidelines from other countries such as the British Society for Haematology (BSH) or the AABB (formerly the American Association of Blood Banks). When developing transfusion guidelines, it is important that:

- They are evidence-based, wherever possible (noting ongoing evidence gaps in many areas of clinical transfusion practice).
- They are based on local practice.
- They take into account what is feasible within the institution.
- A collaborative approach is taken involving representatives in the process, with a group chair.
- Clinical staff can read them easily and they guide them on how to manage the patient undergoing a transfusion.
- Education can be delivered based on the guidelines.

When the standards of appropriate use of blood are in place, this helps to provide a framework for the education of clinical staff.

Consider the transfusion process as a framework for education as shown in Table 9.3.

Table 9.3. Components of a framework for education

Decision to transfuse	Appropriate use of blood
	Use of blood components
	Review of transfusion triggers
	Consideration of alternatives
Blood administration	Collecting blood safely from the laboratory
	Checking of blood at the patient's bedside
	Monitoring of the patient during the transfusion
	Monitoring of blood wastage
Management of adverse events	Management of transfusion reactions
	Management of unexpected events (e.g. transfusion errors)
Patient blood management	Consideration of preoperative management strategies (e.g. iron therapy)
	Hospital-wide initiatives (e.g. iatrogenic anaemia review)
	Quality programme associated with autotransfusion

A number of different approaches are available for educating and training clinical staff on the clinical use of blood (Table 9.4).

Table 9.4. Possible approaches for educating and training clinical staff on the clinical use of blood

Type of approach	Advantages and disadvantages
PowerPoint presentations	Can be given in the classroom setting
	Easy to update when information changes
	Information can be delivered to a large number of people at one time
	Information retention by those listening is not guaranteed
E-learning	Can be undertaken whenever the learner is ready
	Information retention can be monitored by the use of assessments
	Requires access to the internet
	Programmes from other countries can be considered
	Difficult to update as software program writers are required
Workshops	Learners can be taught in small groups
	Specific topics can be covered
	Understanding of information can be assessed through feedback activities Activities require facilitation
	Participants need to be released from duties to attend
Informal ward-based teaching	Session times can be set when clinical areas are less busy with staff performing patient-related duties (e.g. 08:00 or afternoons)
	Staff are close to the session
	Sessions can be tailored according to clinical area (e.g. surgery or obstetrics)
	Activities risk being cancelled if the ward becomes busy, or the trainer cannot deliver the session
For all sessions	
• Know the audience (e.g. senior clinicians, doctors in training, registered nurses) • Understand the learning needs of the group to enable trainers to decide which information is more relevant to a particular group • Ensure the information given is accurate and current • Where possible, obtain feedback from participants to assist in improving future sessions	
Other useful resources	Patient information leaflets so staff can become familiar with them
	Posters for clinical areas to promote safe transfusion messages
	Bookmarks that staff can take away
	If available, use smart phone apps with information that can be referred to once the session is over

9.7 Patient blood management: haemovigilance structures and reporting

WHO recognizes the importance of haemovigilance to identify and prevent occurrence or recurrence of transfusion-related adverse events, and to increase the safety, efficacy and efficiency of blood transfusion, covering all activities of the transfusion chain from donor to recipient (Box 9.1) (*2*).

Box 9.1. Definition of haemovigilance

What is haemovigilance?

Haemovigilance is a set of surveillance procedures covering the entire transfusion chain, from the donation and processing of blood and its components, to their provision and transfusion to patients and their follow-up. It includes the monitoring, reporting, investigation and analysis of adverse events related to the donation, processing and transfusion of blood, and taking actions to prevent their occurrence or recurrence.

Source: reference (*2*).

Patient safety is at the heart of transfusion practice and PBM. Reporting systems play a fundamental role in enhancing patient safety by enabling learning from failures and potential failures, and then putting systems in place to prevent them from recurring. Many health care providers have established the Haemovigilance Officer role, with the responsibility for investigating and reporting transfusion reactions, adverse events and near-misses both internally and externally to national haemovigilance schemes.

Investigating these events ideally includes communicating directly with the staff and patients involved to collect all the essential details about the event and the factors that led to it. This information will help determine the final conclusion (type of reaction), and recommendations for future transfusion plans for the patient, and/or the implementation of corrective and preventive measures.

Haemovigilance is often part of the Transfusion Practitioner role (see section 9.7), or it could be allocated as a key task to a member of staff such as a senior nurse, a senior scientist or a clinician, if no Haemovigilance Officer or Transfusion Practitioner roles are in place.

Surveillance through audits can help to identify current clinical practice, understand the transfusion processes and any gaps or potential risks that may be present. Review and assessment of staff knowledge can help to guide what education is needed and these activities all contribute to quality improvement (*3*).

Haemovigilance is also linked to the donation side of the transfusion process with the monitoring and recording of serious adverse events associated with donation. Although donation is safe for most donors, a small proportion may suffer an adverse event and surveillance of these events helps improve donor and overall transfusion safety (*4*).

Haemovigilance is the responsibility of everyone who is involved in the transfusion process, including the patient. It should be part of the quality cycle of transfusion that works towards safe transfusion practice.

9.8 Patient blood management and the Transfusion Practitioner (TP)

The term TP is often used to describe roles related to safety and appropriate use of blood, including activities to reduce use and provide alternatives. TPs come from a number of different health care backgrounds, although they are predominantly nursing or biomedical scientists. They are regarded as an important link, bridging the gap between the laboratory and clinical areas, nursing staff, medical teams and support staff (*5*). Other terms that are used to describe the role include:

- transfusion nurses
- transfusion safety officers
- haemovigilance officers
- PBM practitioners
- PBM officers.

As PBM requires a multidisciplinary approach, the primary role of the TP is to promote safe and appropriate use of blood or appropriate alternatives to a wide range of clinical colleagues across health care establishments. They play a role in engaging and educating scientific, medical and nursing colleagues, pulling together available resources, collecting and sharing data and evaluating activities intended to improve patient outcomes. They may do this by sourcing information and resources from clinical colleagues in other health care establishments.

An example of a PBM strategy that the TP might wish to lead is to examine if patients are going into surgery with anaemia that could be managed before surgery. The TP could use audits to demonstrate the need for anaemia management. With these data, and in conjunction with the PBM team, the TP could develop a process, suited to the organization, to address the need and to improve patient outcomes. If organizations do not have a TP, elements of the role could be incorporated within other clinical roles, whether this is medical, nursing or scientific staff, there are projects that can be undertaken to promote PBM.

The incumbent of the TP role is uniquely placed to work with all teams bridging the transfusion gap and ensuring that the patient remains at the centre of the transfusion process. TPs are expert practitioners in transfusion medicine including blood administration, appropriate use and laboratory practices. They ensure that clinical staff have access to the most up-to-date transfusion training and policies and, as a result, patients and families are given the right transfusion information.

References

1. Kotter JP. Leading change. Boston (MA): Harvard Business Review Press; 2012.
2. A guide to establishing a national haemovigilance system. Geneva: World Health Organization: 2016 (http://www.who.int/bloodsafety/haemovigilance/haemovigilance-guide/en/, accessed 1 February 2021).
3. Wood EM, Stevenson L, Bielby L, Wiersum-Osselton JC. Haemovigilance: concepts and frameworks. ISBT Science Series 2014;9:86–90.
4. Serious Hazards of Transfusion (SHOT). SHOT Annual Reports 1996–2017 [online]. https://www.shotuk.org/ accessed 3 December 2018).
5. Bielby L, Moss R. Patient blood management and the importance of the Transfusion Practitioner role to embed this into practice. Transfus Med. 2018;28:98–106.

Suggested reading

International Society of Blood Transfusion [online]: (www.isbtweb.org/working-parties/clinical-transfusion and links from this page to ISBT PBM resources, accessed 13 June 2021)

Patient blood management [online]. Bethesda (MD): AABB (http://www.aabb.org/pbm/Pages/default.aspx, accessed 1 February 2021).

Patient blood management guidelines [online]. Canberra: Australian National Blood Authority (https://www.blood.gov.au/pbm-guidelines, accessed 1 February 2021).

Implementing the PBM Guidelines [online]. Canberra: Australian National Blood Authority (https://www.blood.gov.au/implementing-pbm, accessed 1 February 2021).

Consumers, Health, Agriculture and Food Executive Agency. Building national programmes on Patient Blood Management (PBM) in the EU A guide for health authorities. Brussels: Publications Office of the EU; 2017 (https://publications.europa.eu/en/publication-detail/-/publication/5ec54745-1a8c-11e7-808e-01aa75ed71a1/language-en, accessed 1 February 2021).

European Commission. Supporting patient blood management in the EU. A practical implementation guide for hospitals. Brussels: Directorate-General for Health and Food Safety Health Programme, European Commission; 2017 (https://ec.europa.eu/health/sites/health/files/blood_tissues_organs/docs/2017_eupbm_hospitals_en.pdf, accessed 1 February 2021).

Patient blood management. National Health Service Blood & Transplant [online] (http://hospital.blood.co.uk/patient-services/patient-blood-management/, accessed 1 February 2021).

United Kingdom Transfusion Guidelines [online]. Joint United Kingdom Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (https://www.transfusionguidelines.org/uk-transfusion-committees/national-blood-transfusion-committee/patient-blood-management, accessed 1 February 2021).

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